A Randomized Clinical Trial Application of Honey versus Ketoconazole 2% Shampoo for the Treatment of Seborrheic Dermatitis

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INTRODUCTION

Seborrheic dermatitis (SD) is a common chronic relapsing inflammatory skin disorder clinically characterized by poorly defined erythematous patches and scaling. SD primarily affects sebum rich areas, including scalp, face, upper chest and back.[1] Less commonly involved sites include interscapular, umbilical, perineum, and the anogenital crease.[2] The dermatitis presents with pink to erythematous, superficial patches and plaques with a yellow, branny and sometimes greasy scale.[3]

The prevalence of adult SD is estimated at 5%.[4] This condition is more common in males than in females. Among adults, the peak incidence is in the third and fourth decades of life. In the Jose R. Reyes Memorial Medical Center Department of Dermatology, it is one of the most commonly seen cases in the outpatient department with a total of 390 cases seen last 2014. Although the exact cause of SD has yet to fully elucidated, Malassezia yeasts, hormones (androgens), sebum levels and immune response are known to play important roles in its etiopathogenesis.[5] Some researchers propose a pivotal role for Malassezia yeasts (formerly called Pityrosporum ovale) in seborrheic dermatitis.[6] Antifungal therapy leads to decreased colonization with Malassezia spp. and concomitant disappearance of skin lesions, which is probably the strongest evidence that Malassezia spp. Have momentous role in the development of SD.[7] Other therapeutic options include corticosteroids, immunomodulators and antibiotics.

Honey is a by-product of flower nectar and the upper aero-digestive tract of the honey bee, which is concentrated through a dehydration process inside the beehive. Honey has a very complex chemical composition that varies depending on the botanical source. It has been used both as food and medicine since ancient times. Human use of honey is traced to some 8000 years ago as depicted by Stone Age paintings. In addition to important role of natural honey in the traditional medicine, during the past few decades, it was subjected to laboratory and clinical investigations by several research groups and it has found a place in modern medicine. Honey has been reported to have an inhibitory effect on around 60 species of bacteria, some species of fungi and viruses. Antioxidant capacity of honey is important in many disease conditions and is due to a wide range of compounds including phenolics, peptides, organic acids, enzymes, and Maillard reaction products. Honey has also been used in some gastrointestinal, cardiovascular, inflammatory and neoplastic states.[8]

The mainstay management of seborrheic dermatitis includes topical corticosteroids, antifungals, coal tar, metronidazole and topical calcineurin inhibitors. Several studies had shown ketoconazole as an effective treatment for seborrheic dermatitis[9,10]. Most medications for seborrheic dermatitis, however, are expensive, inaccessible, and some are associated with adverse side effects. Hence, it is important to find a cost-effective alternative treatment especially for use in a developing country such as the Philippines.

An open label pilot study was done in Jose R Reyes Memorial Medical Center on 2016 by the primary investigator and Dr. Zharlah Gulmatico-Flores, M.D, F.P.D.S which showed significant improvement from the patients treated using diluted honey.

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METHODOLOGY

This study started upon receiving the approval from the Institutional Review Board and Institutional Ethics Committee of Jose R. Reyes Memorial Medical Center. The nature and purpose of the study were described to potential subjects. Comprehensible verbal and written (English and Tagalog) instructions were given in detail. All patients who were voluntarily willing to participate were asked to sign a written informed consent before admission to the study. Eligible patients were initially seen and examined by the primary investigator. The skin was gently cleansed with hypoallergenic soap prior to measurement of erythema index using Mexameter®. The sites measured were indicated in the data sheet and were the same throughout the course of the study. Subjects for both honey group as well as ketoconazole group were instructed to apply the (dilution 1:1) solution once every other day on the lesions with gentle rubbing for 2-3 minutes. For the honey group, honey was rinsed with warm water after three hours. While for the ketoconazole group, the solution was rinsed with water after 10 minutes. No soap or cleanser needed. The patients were monitored for changes in color, itching and scaling by the primary investigator with two other co-residents during the treatment period every two weeks until 4 weeks. Firm instruction was given not to apply any other creams, lotions, or powders to areas under active treatment.

Materials

Pure honey was obtained from a honeybee farm "Ilog Maria" in Tagaytay. Virgin honey is produced by Italian honeybees from floral nectar collected in the cool and clean highlands of Silang, Cavite. Nectar was gathered from profuse blooms of sunflower, avocado, mango, coffee, citrus, fruit trees, wild vines and wildflowers. Honey was authenticated by the Institute of Biological Sciences, College of Arts and Science at the University of Philippines Los Baños. Ketoconazole 2% shampoo was obtained from a pharmaceutical company.

STUDY SUBJECTS

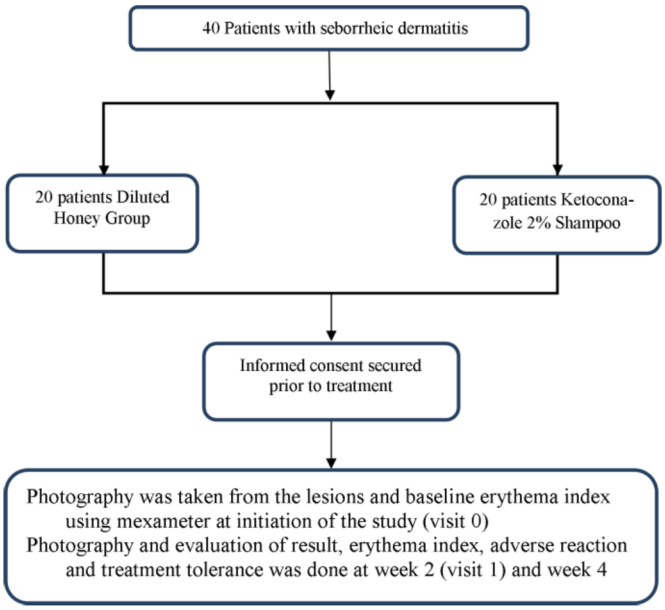
Inclusion criteria:

1. Aged over 18 years old of any gender and race
2. With stable or exacerbating seborrheic dermatitis of the face.
3. Patients without previous treatment or with more than 5 days without any topical or systemic treatment.
4. Patient's written acceptance to participate in the study.

Exclusion criteria:

1. Patients with: decompensated diabetes mellitus, cancer in advanced stage, severe septic stage, hepatopathy, nephropathy, pregnancy.
2. Hypersensitivity to the medications.
3. Patients who receive concomitant topical treatments of the scalp/face or any non-systemic treatments with antifungal agents, corticosteroids, retinoids, erythromycin, tetracycline or derivatives, trimethoprim and/or sulfamethoxazole, or cytostatic or immunomodulating drugs for 4 weeks before the start of treatment.
4. Other medical conditions that prevent compliance with the protocol.
5. Those who are immunocompromised.

Conceptual Flowchart



STATISTICAL ANALYSIS

Statistical analysis was done using SPSS 16.0 to evaluate the comparison between honey and ketoconazole. Descriptive analysis was done by computing the frequency and central tendency measures of demographic variables. Both tests were used to determine the normality of the data. ANOVA of repeated measures was done to determine the difference between means on baseline, day 14 and day 28. A post-hoc comparison test (Tukey) was also done if the p-value from ANOVA was <0.05.

OUTCOME MEASURES

Primary outcome measures are the clinical assessment and erythema index from baseline to end of treatment at the end of visit (week 4). Secondary outcome measure are the presence or absence of adverse reactions and subjective treatment tolerance.
Primary outcome: Clinical assessment on resolution of lesion

1. Color of lesion: change color from erythema to normal skin color was noted. Scoring was given in following manner: 0=absent, 1=mild, 2=moderate, 3=severe
2. Scaling of lesion: scoring was given in following manner: 0=absent, 1=mild, 2=moderate, 3=severe
3. Itching: scoring was given in the following manner: 0=no itching, 1=itching not affecting daily activities, 2=moderate itching affecting daily activities, 3=severe itching disturbing the sleep

Clinical clearing of lesions was assessed by the primary investigator and two co-residents on each visit. The scores were added together and averaged in order to obtain a clinical score. Clinical cure was considered if there is a reduction of ≥2 points from the mean baseline score at the end of the study.

Global physician assessment was assessed by the primary investigator and two co-residents at the end of 4 weeks of the study on each subject using a four-point scale of 4 to 0 (4=clear, 3=almost clear, 2=no change, 1=worse, 0=much worse). A score ≥3 regard as effective, scores ≤2 indicted not effective.

Subjective assessment for overall satisfaction using 5 point scale (5=greatly improved, 4=somewhat improve, 3=no change, 2=somewhat worse, 1=much worse)

Secondary Outcome: clinical and subjective assessment of adverse reaction

Erythema	0 = Absent (no difference with surrounding skin)
	1 = mild (just perceptible erythema without defined borders)
	2 = moderate (uniform erythema with sharply defined borders)
	3 = severe (bright red color and pronounced induration (edema) raised above the surrounding skin)
Itching	0 = Absent (no episode of itching)
	1 = mild (episodic itching, not disturbing daily activity
	2 = moderate (mild continuous itching, slight disturbing daily activity such as sleeping)
	3 = severe (continued itching, very disturbing daily activity, such as sleeping)
Burning	0 = Absent (no episode of burning sensation)
	1 = mild (episodic burning, not disturbing daily activity)
	2 = moderate (mild continuous burning, slight disturbing daily activity such as sleeping)
	3 = severe (continuous burning, very disturbing daily activity, such as sleeping)

A mean score of ≤1 indicated tolerability of the agent.

RESULT

Demographic Profile

Forty patients were included in the study. Majority of the patients enrolled in the study were male 22/40 (55%). The demographic profile of patients is seen in Table 1.

Variable	Honey	2% Ketoconazole	p-value
Age in Year (Mean + SD)	42.3±16.28	45.75±11.63	0.475
Gender M: F	14 (70%): 6(30%)	8 (40%): 12 (60%)	0.058

Table 1. Demographic profile (mean score)

Primary Outcomes

The clinical cure of both groups at baseline (mean of 5.32± 1.286) compared to day 28 (mean of 0.97± 0.830) showed a significantly remarkable

improvement with p-value of < 0.0001. The clinical cure between day 14 and day 28 for both honey and ketoconazole showed significant improvement with p - value of < 0.0001 for honey and 0.009 for ketoconazole. While day 14 and day 28 of treatment for both ketoconazole and honey group showed no significant different with p-value of 0.873 (day 14) and 1 (day 28). A post hoc comparison test was done which showed that as early as day 14 (p < 0.0001), there was a remarkable improvement.

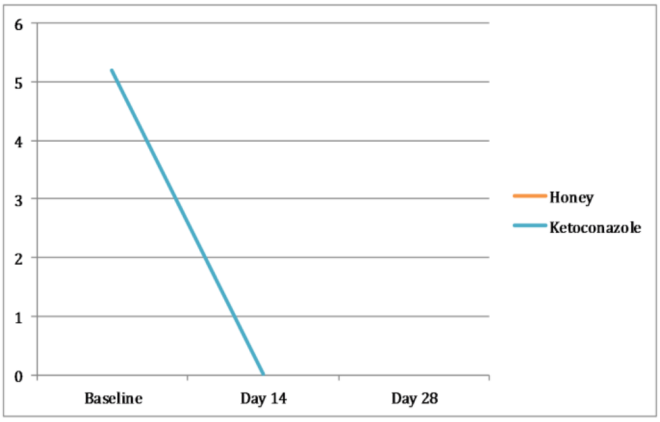


Figure 1. Clinical cure

The mexameter results, which reflects the erythema index in both groups were significantly different (p= 0.342). A post hoc comparison test was done which showed that as early as day 14, there was significant difference in terms of erythema among both groups. However, the improvement observed in between days 14 and 28 were not statistically different (p= 0.342).

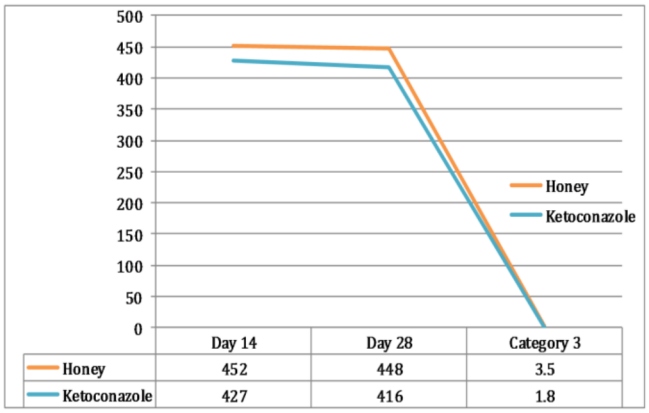


Figure 1. Mexameter results

The parameters such as erythema, scaling and pruritus are shown in Figure 3-5. Erythema, scaling and pruritus in both groups were significantly different (p <0.0001, 0.002, 0.014 respectively). A post hoc comparison test was done which showed that as early as day 14 (p <0.0001), there was a significant improvement in these parameters. However, improvement in erythema observed in between days 14 and 28 were statistically different (p=0.004) in contrast to scaling and pruritus, which showed insignificant improvement from day 14 to day 28 (p= 0.069 and 0.707, respectively).

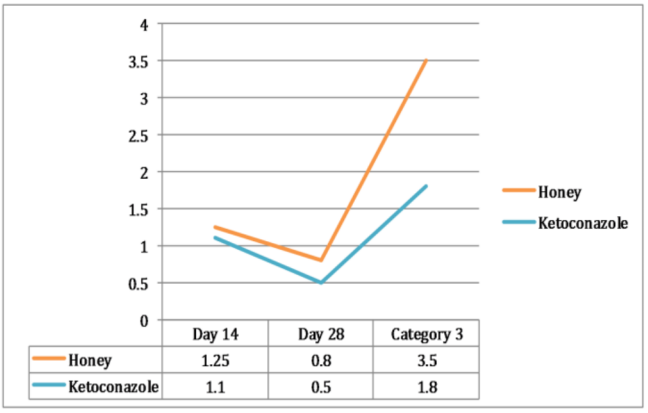


Figure 3. Erythema scores on day 14 and day 28.

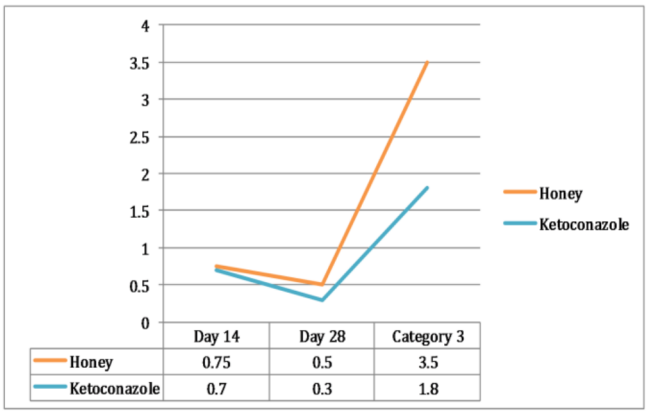


Figure 4. Scaling scores on day 14 and day 28.

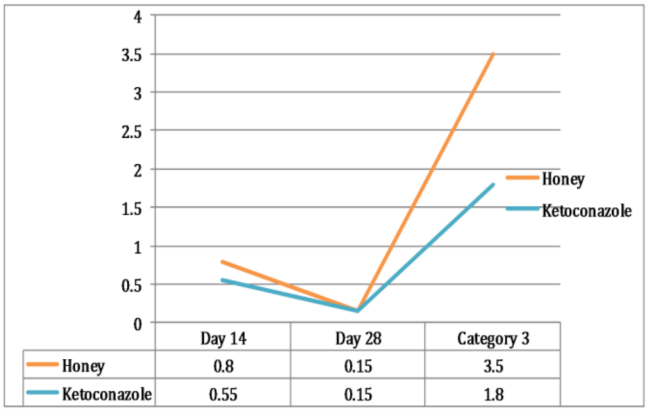


Figure 5. Pruritus scores on day 14 and day 28.

Global Physician Assessment (GPA)

For Global Physician Assessment (GPA), the GPA scores of the honey group are statistically insignificant both on the 2nd and 4th week from the ketoconazole group. GPA scores on the 2nd week showed 19 (95%) subjects who have ≥3 GPA scores in the ketoconazole group and 14 (70%) subjects in the honey group (p=0.059). GPA scores on the 4th week showed 20 (100%) subjects who have ≥3 GPA scores in the ketoconazole group and 20 (100%) subjects in the honey group (p=0.763). *Figures 5* shows difference in GPA score.

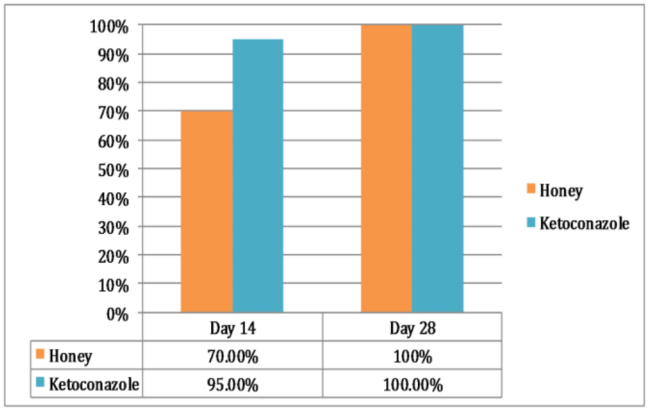


Figure 6. Global physician assessment on day 14 and day 28.

Subjective Assessment

Based on subjective assessment, mean score of honey in 4th week monitoring is 4.6±0.53, while those in ketoconazole group is 4.3±0.47. Using Paired t-test, there is insignificant difference in subjective assessment scores between honey and ketoconazole group, p=0.055.

DISCUSSION

Similar to other studies, the demographic profile of the study participants shows a male predominance with disease occurring mostly during the fourth decade of life.[36] This pattern of prevalence in men may be attributed to the androgen-modulated sebaceous gland activity. Seborrheic dermatitis is usually a chronic disease with different patterns of disease recurrence.[36-37]

The clinical trial of once every other day application of diluted honey compared to ketoconazole showed statistically significant improvement in the clinical cure rate. The decrease in clinical parameters of erythema, scaling and pruritus may be attributable not only to the antifungal effect of honey but also to its anti-inflammatory effect. The antifungal activity of honey is also derived from the osmotic effect of its high sugar content and low moisture content. Honey is characteristically acidic because of gluconic acid, its pH being between 3.2 and 4.5 which is enough to be inhibitory to many animal and fungal pathogens.[38] Another major factor that account for inhibition of honey has been found to be due to hydrogen peroxide produced enzymatically in the honey. Several chemical with antifungal activity has been identified in honey by various researchers. These include pinocembrin, terpenes, benzyl alcohol, 3, 4-dimethoxy-4-hydroxybenzoic acid (syringic acid).[39]

Erythema is an indicator of inflammation. This inflammation is said to be due to *Malassezia* lipases acting on sebaceous triglycerides resulting to the release of inflammatory unsaturated fatty acids. Other factors that affect inflammation are elevation of cytokines IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, TNF-α anf IFN-γ; neutrophil infiltration; leukocyte infiltration by major histocompatibility complex (MHC) positive lymphocytes and natural killer (NK) cells; and increase in histamine levels. The degree of inflammation was evaluated by means of assessing the erythema index in different facial regions using the mexameter. The results of the study showed significant difference in erythema in both groups as early as the second week among both

groups. However, the improvement observed in between days 14 and 28 were not statistically different.

No significant side effects were recorded in the 40 patients included in the study.

CONCLUSION

Diluted honey exhibited comparable efficacy in the clinical improvement in the signs and symptoms of seborrheic dermatitis and is a safe and cost-effective alternative in clearing the lesions of seborrheic dermatitis. There was noted improvement as early as 14 days of treatment. The degree of erythema as measured by using a mexameter and the erythema scores were significantly improved with diluted honey noted as early as 14 days. However, both groups were comparable in terms of improvement during days 14 to 28. Erythema, scaling and pruritus in both groups were significantly different. As early as day 14, there was a significant improvement in these parameters. However, improvement in erythema observed in between days 14 and 28 were statistically different in contrast to scaling and pruritus, which showed insignificant improvement from day 14 to day 28. Both groups were similar in terms of safety.

RECOMMENDATION

The authors recommend future larger randomized clinical trials using a more frequent dosing, higher concentration or longer treatment duration of diluted honey to determine if a more favorable result may be achieved with this agent. We would also recommend to use other species of honey from other regions of the country which may possibly exhibit higher potency against microorganism. Fungal cultures may also be performed to determine the etiologic agents susceptible to and resistant to honey.

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