A prospective, randomized, double-blind, comparative study on the efficacy and safety of 2% enzymatic virgin coconut oil monoglyceride cream versus 5% benzoyl peroxide cream in the treatment of mild to moderate acne vulgaris

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Background: Acne vulgaris is a common dermatologic disorder caused by follicular colonization of Propionibacterium acnes leading to inflammation. Enzymatic virgin coconut oil monoglyceride has been shown to have anti-inflammatory effects and antimicrobial activity against Propionibacterium acnes.

Objectives: To compare the efficacy and safety of enzymatic virgin coconut oil monoglyceride (EVCO) 2% cream versus benzoyl peroxide (BPO) 5% cream in the treatment of mild to moderate acne vulgaris.

Methods: 100 participants with mild to moderate acne or a rating of 2 or 3 in the Investigator’s Global Assessment (IGA) for acne were randomized to receive either EVCO 2% cream or BPO 5% cream applied on the face twice daily over an 8-week period. Primary outcomes measured in the study were clearance rate graded as “clear” or “almost clear” (rating of 0 or 1) based on the IGA and adverse reaction rate.

Results: At week 8, the clearance rate was achieved in 56% (28/50) of participants in the BPO group and 46% (23/50) in the EVCO group. The difference between the two groups was not statistically significant (p=0.319). Adverse reactions observed in the BPO group were erythema (16%), pruritus (14%), scaling (12%), dryness (6%) and burning/stinging (6%) and while in the EVCO group only burning/stinging (2%) was noted; however, this was not statistically significant (p=0.1806).

Conclusion: EVCO 2% cream is an efficacious and safe alternative treatment for acne vulgaris.

Keywords: acne vulgaris, enzymatic virgin coconut oil, benzoyl peroxide

INTRODUCTION

Acne vulgaris is a common dermatologic disorder that affects individuals of all races and ethnicities.1 There are four factors in the pathophysiology of acne: increase and alteration of androgen-dependent sebum production, alteration in keratinization leading to the comedone formation, follicular colonization of Propionibacterium acnes and inflammation due to the release of pro-inflammatory mediators.2,3 Acne is common in adolescents. However, it can occur in all age groups. It affects approximately 85% of young people between ages 12 to 24 years.3,5 To some degree, this disease may persist into adulthood particularly in women.3 Acne was reported in 8% of adults aged 25 to 34 years and 3% of adults aged 35 to 44 years.5 In 2015, the Philippine Dermatological Society (PDS)-Health Information System (HIS) ranked acne vulgaris as the most common consult among the 11 training institutions accredited by the PDS.6

Due to its prevalence, it is often mistaken as physiologic. Individuals with acne can be affected psychologically with an increased likelihood of social isolation, depression and even suicidal ideation.4 Though this skin disease may be self-limiting, it can cause permanent physical, emotional and psychological scars unless provided with an effective long-term treatment.3,8 Medications for acne should target the multiple factors causing the disease. It should be able to eradicate existing lesions, prevent the development of new ones and avoid the long-term effects of scarring.4,7 Topical therapy, which includes comedolytics, anti-inflammatory agents and antibiotics, is the recommended first-line management of mild to moderate acne. Examples of common topical medications for acne include topical retinoids and benzoyl peroxide.4 Benzoyl peroxide is a potent bactericidal agent with a mild comedolytic property that reduces the number of P. acnes within the hair follicle.4,5 It is safe and effective even for those who are pregnant and those planning to be pregnant.8 Its safety profile and anti-acne ability justify its use as a first-line treatment in mild to moderate acne.2 However, benzoyl peroxide can cause bleaching or discoloration of clothes and beddings.8 It may also cause local irritation or allergy in 1% of patients.4,5,9

The coconut (Cocos nucifera L.) is referred to as the “tree of life” due to its many uses, ranging from biofuel to food.10 The coconut oil has been traditionally used by different cultures for ritualistic practices as well as for treatment of ailments including...
Virgin coconut oil (VCO) is extracted from the fresh and mature kernel of the coconut, and obtained via mechanical and natural means, with or without the use of heat as long as the properties of the oil are not modified. Lauric acid is a medium chain fatty acid which comprises 50% of the fatty acids in virgin coconut oil. It is considered the critical antibacterial component against *P. acnes*.

The virgin coconut oil extracted utilizing a no-heat enzymatic process is otherwise known as enzymatic virgin coconut oil monoglyceride (EVCO). It yields a higher content of lauric acid of 76% compared to the 50% lauric acid content from virgin coconut oil produced by other methods. EVCO is mainly used for dermatological studies and laboratory use. Treatment derived from botanical sources are often considered as therapeutic alternatives. A relatively increasing portion of dermatologic patients is looking for botanical products as an alternative to the existing therapy or as adjunctive therapy. These treatments provide cheaper therapeutic options especially for patients belonging to the lower socio-economic classes.

According to the Philippine National Standard for VCO, virgin coconut oil consists of medium chain fatty acids, saturated fatty acids, and natural vitamin E. VCO contains the highest amount of medium chain fatty acid (MCFA) of about 64% compared to other oil products. The fatty acids in VCO includes lauric acid ranging from 47 to 53% to other oil products. The fatty acids in VCO includes lauric acid ranging from 47 to 53% compared to other oil products. The fatty acids in VCO includes lauric acid ranging from 47 to 53% depending on the coconut variety and the extraction method. Lauric acid is the most active antimicrobial free fatty acid, known to have bactericidal and anti-inflammatory properties.

Monolaurin is the monoglyceride form of lauric acid, known to have antibacterial and antiviral properties. In humans, the ingestion of lauric acid would lead to a systemic breakdown of VCO into monolaurin.

In a study done by Nakatsuji et al., the antimicrobial property and anti-inflammatory effect of lauric acid for acne vulgaris were examined. They found that the minimum inhibitory concentration (MIC) of lauric acid to prevent growth against *Propionibacterium acnes* is 1.95 μg/ml. Lauric acid has growth-inhibiting activity on common skin bacteria such as *P. acnes*, *S. aureus*, and *S. epidermidis* at a concentration that is 15 times lower than that of benzoyl peroxide. This suggests that lauric acid has a much stronger antimicrobial effect than benzoyl peroxide. Also, *P. acnes* was the most sensitive to lauric acid among the tested common skin organisms. It is estimated that the minimum bactericidal concentration (MBC) of lauric acid is 60-100 μg/ml. In this study, sebocytes were incubated with lauric acid for 18 hours, and lauric acid proved to be non-cytotoxic to sebocytes at concentrations exerting an antimicrobial effect. Sebocytes are cells in the skin with an activity that contributes to the pathophysiology of acne. Taken together, the lauric acid may exert its antimicrobial effect by disrupting the bacterial membranes only and not the mammalian cell membranes.

An in vivo study was done where the antimicrobial activity of lauric acid against *P. acnes* was evaluated. *P. acnes* with 1 × 10^7 colony forming unit (CFU) was intradermally injected into the ears of the mice. The *P. acnes*-injected site was then injected with lauric acid (2 μg) the following day. The sites injected with lauric acid had significantly reduced swelling and number of *P. acnes* colony count. It was also demonstrated by tissue section to produce a decreased granulomatous response to *P. acnes* with an injection of lauric acid when compared to injection of only the vehicle.

The therapeutic potential of lauric acid by epicutaneous application for acne therapy was demonstrated by application of lauric acid (150 μg) in petroleum base applied epicutaneously on a rabbit’s ear injected with *P. acnes* (1 ± 10^5 CFU). Epicutaneous application of lauric acid for one day noticeably reduced the swelling and the number of colonies within the ear. The tissue sample was obtained, and the TUNEL assay was done to detect possible DNA fragmentation that resulted from apoptosis. The results showed that application of lauric acid epicutaneously did not lead to an apoptotic response of differentiated keratinocytes. This suggests that application of lauric acid epicutaneously can effectively decrease *P. acnes*-induced inflammatory response without injuring skin cells.

A clinical study was done by Haris et al. to evaluate the efficacy and safety of an enzymatically extracted activated virgin coconut oil, prepared as a topical gel in the treatment of acne. It was an open, single-centric, non-comparative clinical trial consisting of 21 participants with the once daily application of the gel over the lesions for a duration of 8 weeks with follow-up of every two weeks. The exact percentage of the activated virgin coconut oil used in the gel formulation was not mentioned in the study. Baseline assessment was done with clinical grading and was compared at the end of the study period. From baseline to 8 weeks’ follow-up, there was a significant reduction in the acne grading from 1.50 to 0.77 (p < 0.001). There was also a significant reduction in the papule (from 12.52 to 5.24) and pustule (from 5.38 to 1.33) count (p < 0.001). There were no adverse outcomes, or irritancy noted, and the study concluded that the activated virgin coconut oil gel has an anti-acne activity which can be effective and safe for external use for patients with acne vulgaris.

In the Philippines, Pineda-DLS and Verallo-Rowell did an open-label study on monolaurin 2% gel for mild to moderate acne vulgaris. Monolaurin was extracted from lauric acid found in enzymatic virgin coconut oil. After extraction, 2% monolaurin was dissolved in 40% alcohol and was made into a gel. The exact formulation or preparation of the gel was not mentioned in the study. The study consisted of 17 participants with a study duration of 6 weeks and followed up of every two weeks. Among the participants, 10 had treatment success defined as a decrease in 50% of the lesion count from baseline. The study reported that there were no associated adverse reactions nor irritancy.

Another study by Verallo-Rowell et al. was done to compare monolaurin 2% gel versus the gel vehicle alone. It was a randomized, double-blind clinical trial consisting of 24 participants.
in the monolaurin group and another 20 in the plain gel vehicle group with a study duration of 8 weeks, and follow up of every two weeks. The monolaurin group showed it could clear acne cysts by 58.8%. They found that the control group was also effective and lead to the clearance of acne. The difference between the two groups was not statistically significant compared to the control group. There was no peeling, stinging, itching or redness among the participants in the monolaurin group. The study recommended that further studies should be undertaken with a bigger sample size. The authors concluded that monolaurin 2% gel preparation is effective and safe in the treatment of acne.22

Thus based on the recommendation of the aforementioned studies, this study was conceptualized with a bigger sample size using the enzymatic virgin coconut oil monoglyceride (EVCO) that contains both monolaurin and lauric acid.10,11,13,15

Research Question
Using a randomized controlled trial, what is the efficacy of enzymatic virgin coconut oil monoglyceride (EVCO) 2% cream in producing clinical remission in patients with mild to moderate acne vulgaris?

The significance of the Study
The results of this study will be of benefit to the following:
To individuals affected with acne vulgaris, this will aid in providing another treatment option that is more cost-effective, non-irritating as well as readily available to the public.

Acne is a dermatologic condition which needs long-term maintenance therapy to prevent its recurrence. Additionally, a wide scope of therapeutic options is available but are noted to be expensive. The cumulative expense of maintenance medications may be a financial burden to patients. Furthermore, acne medications are often noted to cause discomfort since it can be irritating to the skin.5, 20

This study will also aid other dermatologists to provide an alternative treatment that caters to a wider scheme of socio-economic groups and provide a more readily available product. This will provide additional information in the field of medicine where non-chemical remedies are embraced and promoted.

To future researchers, this study can be used as a source of related literature should they wish to conduct a similar study with other alternative remedies, and for continuing studies. This double-blind study has a larger sample size and compares enzymatic virgin coconut oil monoglyceride to a standard anti-acne medication which is benzoyl peroxide.

Objectives
The general objective of this study was to compare the efficacy and safety of enzymatic virgin coconut oil monoglyceride (EVCO) 2% cream versus benzoyl peroxide (BPO) 5% cream in the treatment of mild to moderate acne vulgaris.

This study specifically aimed to:
1. To compare the efficacy of EVCO 2% cream versus BPO 5% cream in achieving clearance using Investigator’s Global Assessment (IGA) for acne score
2. To compare the efficacy of EVCO 2% cream versus BPO 5% cream in achieving clinical response based on the total number of inflammatory and non-inflammatory lesions by at least 50%
3. To determine the number of weeks, it will take for the intervention to achieve 50% improvement of acne
4. To determine any adverse reactions with topical application of EVCO 2% cream
5. To determine patients’ overall assessment of treatment satisfaction

METHODS
Study Design
This is a prospective, double-blinded, randomized controlled trial comparing the efficacy and safety of EVCO 2% cream versus BPO 5% cream in the treatment of mild to moderate acne vulgaris.
including acne surgery, intralesional glucocorticoids, phototherapy or lasers.

5. The participant and/or parent/legal guardian is willin and able to comply with the study protocol

6. The participant or parent/legal guardian, as applicable, has given written informed, dated consent to participate in the study

**Exclusion Criteria**

1. Participants diagnosed with severe or nodulocystic acne with a rating of 4 or 5 in the IGA for acne vulgaris

2. Allergy to active ingredients of both drugs

3. Participants who exhibited other facial dermatological conditions that could hinder or obstruct clinical assessments

4. Participants who needed to use another non-acne topical medication that could interfere with study treatment

5. Participants with any serious and/or uncontrolled cutaneous problems, systemic disease, or comorbidities such as hypertension, diabetes, AIDS, pulmonary, renal, heart disease, cancer or mental illness

6. Participants who did not comply with the topical or systemic washout criteria

**Setting**

This study was approved by the Hospital Research and Ethics Committee and conducted at the out-patient section in a tertiary hospital between May 2015 to February 2016.

**Sampling procedure**

Patients from the out-patient section in a tertiary hospital, diagnosed to have mild to moderate acne vulgaris with IGA score of 2 or 3, were included in the study.

**Interventions and Comparisons**

The study interventions were EVCO 2% cream and BPO 5% cream. The EVCO was obtained from O’Mark Enterprises, which is a known developer of virgin coconut oil, approved by the Food and Drug Administration (FDA) of the Philippines. The EVCO was compounded and prepared by an industrial pharmacist into a 2% cream. The formulation of the cream includes EVCO 2.0 ml; stearic acid triple pressed 20 g, isopropyl myristate 5.0 ml, triethanolamine 2.0 ml, propylene glycol 3.0 mL and purified water 68.0 ml.

In studies done by Pineda-DLS and Verallo-Rowell, EVCO was further extracted to obtain monolaurin and was formulated into a 2% gel which was found to be effective and safe for acne vulgaris.21,22 The EVCO, 2% cream, was submitted for microbiological studies, and no growth of organisms was found. The standard - benzoyl peroxide 5% cream was obtained from a pharmaceutical company.

The treatment cream and standard cream were placed in identical 10-gram pre-coded jars. Both creams were identical in color and consistency. Participants were provided with transparent and odorless soap for facial washing before application of either drug. After rinsing the skin thoroughly and patting dry, participants were instructed to wait 10 minutes to allow the skin to dry completely before applying the medication provided. They were instructed to apply the provided medication evenly on the face twice daily for eight weeks avoiding the areas around the eyes and lips. The participants were asked to follow up on the 2nd, 4th, 6th and 8th week. The assignment of the medications was unknown to both the participant and the investigator.

The Investigator’s Global Assessment (IGA) for acne vulgaris was used for severity classification and outcome measurement. The IGA is one of the global assessment scales for acne and is considered as a measure of efficacy because it incorporates the totality of the clinical presentation into a single category of severity. The severity scale also correlates with inflammatory and non-inflammatory lesion counts. It was proposed by Allen and Smith Jr. and has been the template for global assessment in many acne trials attesting to its greater clinical relevance than lesion counts alone and it is recommended by the US FDA for the development of new anti-acne products.23 Drug safety and treatment satisfaction assessment were measured and recorded using international methods utilized by published large-scale randomized controlled trials on acne vulgaris.

**Outcome Measure**

**Primary Outcome Measures**

- Clearance rate is defined as "clear" or "almost clear" (score 0 or 1) based on the Investigator’s Global Assessment (IGA) after eight weeks of treatment. Treatment failure is defined as IGA acne score same as a baseline (IGA 2 or 3) or an increase in the baseline IGA.

- Adverse reaction rate or the percentage of participants by treatment group in which irritation or any adverse skin reaction occurred during the treatment period

**Secondary Outcome Measures**

- The clinical response rate is defined as an improvement of total lesion count by at least 50% from baseline. Treatment failure is no improvement of total lesion count by at least 50% from baseline.

- Mean percentage reduction of the total lesion count per treatment group at week 8. Total lesion count was the number of non-inflammatory (open and closed comedones) and inflammatory (papules and pustules) lesions on the participants’ faces.

- Number of weeks it took for each intervention to achieve a reduction of lesion count by 50% from baseline.

- Number and percentage of participants in either group who had grade 1 (mild) and grade 2 (moderate) adverse reactions.

**Sample Size Computation**

The sample size for this randomized controlled trial was computed using the software Minitab. The computation utilizes the assumption that EVCO produces 73% reduction of acne from a study done by Haris et al.20 Calculation was done for the study to detect a 30% difference in clearance rate between the two intervention groups as statistically significant. In a statistical test for comparison of two proportions, a sample size of 42 per group
were instructed to come back for a follow-up at the end of the study was also provided. Both the primary investigator and the participants should and should not do while participating in the treatment intervention. The research assistant gave the application instructions and schedules for follow-up. A list of what the participants to either EVCO 2% cream or BPO 5% cream using a computer-based randomization list downloaded from www.randomization.com.

A research assistant was tasked to keep all the list of code numbers assigned to each participant in a sealed envelope and also dispensed the allocated treatment to each participant. Prefilled treatment jars good for the whole duration of the study per participant were stored in a zip locked plastic envelope labeled with the code number of the participant. The research assistant also gave the instructions regarding the application of the medication and medications upon follow-up.

Data Gathering

Participants diagnosed with mild to moderate acne vulgaris defined as having the score of 2 or 3 based on the IGA for acne vulgaris (Table 1) and fulfilled the inclusion criteria were included in the study.

### Table 1. Investigator’s Global Assessment (IGA) for acne vulgaris

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Clear</td>
</tr>
<tr>
<td>1</td>
<td>Almost clear</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
</tr>
<tr>
<td>5</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

Residual hyperpigmentation and erythema may be present
A few scattered comedones and a few (<5) small papules
Easily recognizable; less than half the face involved; many comedones and many papules and pustules.
More than half of the face is involved; numerous comedones, papules, and pustules.
Entire face is involved; covered with comedones, numerous papules, and pustules, and a few nodules and cysts.
Highly inflammatory acne covering the face with nodules and cysts.

Before the enrollment in the study, acne and its causation, currently available treatments, possible side effects, as well as the intent of the study were discussed with the subject. An informed consent form was given to the participant, and significant points were explained. If the participant was a minor, an assent form was accomplished together with a parent consent form.

Upon enrollment, participant information was gathered using the data extraction form. The baseline lesion count was taken which included the actual count of inflammatory lesions (comedones and pustules), non-inflammatory (open and closed comedones) and total lesion count. Photo documentation was also done. The participants were then randomly assigned to the treatment intervention. The research assistant gave the application instructions and schedules for follow-up. A list of what the participants should and should not do while participating in the study was also provided. Both the primary investigator and participants of the study were blinded.

The duration of the study was eight weeks. Participants were instructed to come back for a follow-up at the end of the 2nd, 4th, 6th and 8th week of treatment. The participants were reminded via phone call or text message a few days before the expected date of follow-up so they will comply with their follow-up schedule. Photo documentation was done on all follow-up visits. Safety and tolerability were assessed at each visit by grading the occurrence of erythema, scaling, dryness, pruritus, stinging and/or burning on a scale ranging from 0 (none), 1 (mild), 2 (moderate), and 3 (severe). The average score among these five parameters should be below 1. Participants with a grade of 1 (mild) or 2 (moderate) were to continue the study with every other day application of the assigned medication. A grade of 3 (severe) will be dropped from the study. Medications for any adverse event were given for free. These included topical steroids for erythema, emollients for dryness and scaling, antihistamines for pruritus and pain relievers for stinging and/or burning sensation.

On the final follow-up (8th week), participants were asked to answer a questionnaire regarding their satisfaction with the treatment. The satisfaction questionnaire was adapted from the study by Delima et al.7, 24, 25

Treatment failure was defined as IGA acne score same as a baseline (rating of 2 or 3) or an increase in the baseline IGA.7

At the end of the study period, participants who were considered as treatment failure were given the standard treatment. Treatment allocation was disclosed by the research assistant. The transportation expenses were reimbursed by the investigator.

**Independent Variable**

Independent variables included the treatment allocation such as enzymatic virgin coconut oil monoglyceride (EVCO) 2% cream and benzoyl peroxide (BPO) 5% cream applied for eight weeks.

**Dependent Variable**

Dependent variables included the Investigator’s Global Assessment for acne vulgaris scores, the inflammatory and non-inflammatory lesion count and adverse reaction from either the treatment or the control group.

**Statistical methods**

The data gathered were encoded into computer software, Microsoft Excel. Independent t-test was used for the parametric comparison. Chi-square was used to compare the clearance rate, clinical response and adverse reactions of both treatment groups both at the endpoint of the study and per week comparison. The means, standard deviations, and percentages were used to compare the weekly reduction of lesions in both groups. Survival analysis was used to compare time (in weeks) to clinical response and adverse reactions of both treatment groups. Fischer’s Exact test was used to compare the adverse effects in both groups.

The primary analysis for this study was carried out using the intention-to-treat (ITT) principle. All participants who were randomized were included in the ITT analysis. A separate analysis excluding patients lost to follow up (LTFU) was done in the per-protocol (PP) analysis. Sensitivity analysis with three scenarios was done to test the robustness of the primary analysis (Table 2).

**RESULTS**
A total of 100 participants were recruited and randomized from May 2015 to February 2016 (Figure 1). Eighty-five participants completed the study and 15 participants, 7 in the EVCO 2% cream group and 8 in the BPO 5% cream group, were lost to follow-up and considered as drop-outs. Reasons for dropping out were not identified since the participants opted not to follow-up.

Table 2. Sensitivity analysis done in the study

<table>
<thead>
<tr>
<th>Sensitivity Analysis</th>
<th>LTFU in BPO group</th>
<th>LTFU in EVCO group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Clearance rate</td>
<td>Clearance rate</td>
</tr>
<tr>
<td>2</td>
<td>Clearance rate</td>
<td>Treatment failure</td>
</tr>
<tr>
<td>3</td>
<td>Treatment failure</td>
<td>Clearance rate</td>
</tr>
</tbody>
</table>

Clearance rate = IGA 0-1 (clear/almost clear)
Treatment failure = IGA 2-3 (mild/moderate)

Demographics and clinical profile

Statistical analysis showed that there was no significant difference between the two treatment groups by sex, age, duration of lesions, a previous treatment used, baseline clinical severity based on IGA scores and number of lesions (p > 0.05). This signifies the comparability of both treatment groups at baseline (Table 3).

Table 3. Baseline demographic and clinical characteristics of treatment groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BPO 5% cream (n=50)</th>
<th>EVCO 2% cream (n=50)</th>
<th>Total (n=100)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex distribution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21, 55%</td>
<td>17, 45%</td>
<td>38, 38%</td>
<td>0.314</td>
</tr>
<tr>
<td>Female</td>
<td>29, 47%</td>
<td>33, 53%</td>
<td>62, 62%</td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>20.9 ± 6.1</td>
<td>21.4 ± 6</td>
<td>21.1 ± 6.1</td>
<td>0.621</td>
</tr>
<tr>
<td>10-19 years old</td>
<td>17, 47%</td>
<td>19, 53%</td>
<td>36, 36%</td>
<td></td>
</tr>
<tr>
<td>20-29 years old</td>
<td>25, 48%</td>
<td>27, 52%</td>
<td>52, 52%</td>
<td></td>
</tr>
<tr>
<td>30-39 years old</td>
<td>7, 88%</td>
<td>1, 13%</td>
<td>8, 8%</td>
<td></td>
</tr>
<tr>
<td>&gt; 40 years old</td>
<td>1, 25%</td>
<td>3, 75%</td>
<td>4, 4%</td>
<td></td>
</tr>
<tr>
<td>Duration of lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>3.3 ± 3.2</td>
<td>3.8 ± 4.1</td>
<td>3.6 ± 3.6</td>
<td></td>
</tr>
<tr>
<td>0-5 years</td>
<td>33, 47%</td>
<td>37, 53%</td>
<td>70, 70%</td>
<td>0.541</td>
</tr>
<tr>
<td>6-10 years</td>
<td>15, 68%</td>
<td>7, 32%</td>
<td>22, 22%</td>
<td></td>
</tr>
<tr>
<td>11-15 years</td>
<td>2, 40%</td>
<td>3, 60%</td>
<td>5, 5%</td>
<td></td>
</tr>
<tr>
<td>16-20 years</td>
<td>0, 0%</td>
<td>2, 100%</td>
<td>2, 2%</td>
<td></td>
</tr>
</tbody>
</table>

Previous treatment used

None    13, 50%     13, 50%   26, 26%   0.704
Topical 34, 49%   35, 51%   69, 69%  
Topical + Oral 3, 60%   2, 40%   5, 5%  

Clinical severity based on IGA scores

Mild 14, 56%   11, 44%   25, 25%  0.541
Moderate 36, 48%   39, 52%   75, 75%  

Number of lesions, mean ± SD

<table>
<thead>
<tr>
<th>Total lesions</th>
<th>mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>59.5 ± 66.7</td>
</tr>
<tr>
<td></td>
<td>56.2 ± 66.7</td>
</tr>
<tr>
<td></td>
<td>57.8 ± 66.7</td>
</tr>
<tr>
<td>Non-inflammatory</td>
<td>18.8 ± 17.1</td>
</tr>
<tr>
<td></td>
<td>17.1 ± 17.1</td>
</tr>
<tr>
<td></td>
<td>17.7 ± 17.7</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>36.7 ± 34.3</td>
</tr>
<tr>
<td></td>
<td>31.6 ± 34.3</td>
</tr>
<tr>
<td></td>
<td>32.4 ± 34.3</td>
</tr>
<tr>
<td>IGA-Investigator’s Global Assessment</td>
<td>17.5 ± 34.3</td>
</tr>
</tbody>
</table>

Majority of the participants were female (62%). The mean age was 20.9 years old (SD ± 6.1) and 21.4 years old (SD ± 6.1) in the BPO and EVCO group respectively. Majority of the participants belonged to the age group of 20-29 years old (52%). The mean duration of the lesions of the participants in both groups was 3.6 years (SD ± 3.6). Seventy percent of study participants reported having lesions for less than one year to 5 years. Majority of the participants (69%) had topical medications as the previous treatment to treat their acne, and only 26% claimed to have no previous treatments used.

Outcome analysis

Clearance rate

The primary outcome of the study is the clearance rate which is defined as the percentage of participants in each group who were graded “clear” or “almost clear” (score 0 or 1) based on IGA after eight weeks of treatment.

Per-protocol analysis at week 8

Using per-protocol analysis, all lost to follow up (LTFU) were not included. At week 8, BPO 5% cream group had 66.7% (28/42) clearance rate compared to the EVCO group with a...
clearance rate of 53.5% (23/43). The difference between the two groups regarding achieving clearance rate based on the IGA scores at week 8 was not statistically significant (Table 4A).

Table 4A. Clearance rate based on IGA scores at week 8 (Per-protocol analysis)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BPO 5% cream</th>
<th>EVCO 2% cream</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance rate</td>
<td>28 66.7</td>
<td>23 53.5</td>
<td>0.361</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>14 33.3</td>
<td>20 46.5</td>
<td></td>
</tr>
</tbody>
</table>

Clearance rate = IGA score 0 or 1
Treatment failure = IGA score 2 or 3 or an increase in baseline
Chi-square test

An intention-to-treat analysis at week 8
Using intention-to-treat analysis, all LTFU were included. At week 8, BPO 5% cream group had 56% (28/50) clearance rate compared to the EVCO group with 46% (23/50). The difference between the two groups concerning achieving clearance rate based on the IGA scores at week 8 was not statistically significant (Table 4B).

Table 4B. Clearance rate based on IGA scores at week 8 (Intention-to-treat analysis)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BPO 5% cream</th>
<th>EVCO 2% cream</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance rate</td>
<td>28 56</td>
<td>23 46</td>
<td>0.319</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>22 44</td>
<td>27 54</td>
<td></td>
</tr>
</tbody>
</table>

Clearance rate = IGA score 0 or 1
Treatment failure = IGA score 2 or 3 or an increase in baseline
Chi-square test

Sensitivity Analysis
Sensitivity analysis was done to test for the robustness of the primary analysis. Three case scenarios were in this analysis.

The 1st case assumed that all LTFU from both groups had achieved a clearance rate with an IGA score of 0-1 (clear/almost clear) (Table 5A). At eight weeks follow-up, the BPO group had a clearance rate of 72% (36/50) compared to 60% (30/50) of EVCO group. The difference between the two groups was not statistically significant (p = 0.206).

Table 5A. Clearance rate case: sensitivity analysis 1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BPO 5% cream</th>
<th>EVCO 2% cream</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance rate</td>
<td>36 72</td>
<td>30 60</td>
<td>0.206</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>14 28</td>
<td>20 40</td>
<td></td>
</tr>
</tbody>
</table>

Clearance rate = IGA 0-1
Treatment failure = IGA 2-3
Chi-square test

In the 2nd case, it was assumed that all LTFU from the BPO group had treatment failure with an IGA grade of 2-3 (mild/moderate) and all LTFU from EVCO group achieved clearance rate with an IGA score of 0-1 (clear/almost clear) (Table 5C). At eight weeks follow-up, the BPO group had a clearance rate of 56% (28/50) compared to 60% (30/50) of EVCO group. The difference between the two groups was not statistically significant (p = 0.685).

Table 5C. Clearance rate case: sensitivity analysis 3

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BPO 5% cream</th>
<th>EVCO 2% cream</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance rate</td>
<td>28 56</td>
<td>30 60</td>
<td>0.685</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>22 44</td>
<td>20 40</td>
<td></td>
</tr>
</tbody>
</table>

Clearance rate = IGA 0-1
Treatment failure = IGA 2-3
Chi-square test

Adverse reaction rate
In the BPO group, most common adverse reactions include erythema (16%), followed by pruritus (14%), scaling (12%), dryness (6%) and burning/stinging (6%). In the EVCO group, only one patient (2%) had an adverse reaction which was burning/stinging (Table 6).
Table 6. Adverse reaction on both treatment group

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>BPO 5% cream</th>
<th>EVCO 2% cream</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Erythema</td>
<td>8</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Scaling</td>
<td>6</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Dryness</td>
<td>3</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Burning/Stinging</td>
<td>3</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

Clinical response rate
The clinical response rate was defined as an improvement of total lesion count by at least 50% from baseline.

Per-protocol analysis at week 8
Using per-protocol analysis, the BPO group had 100% (42/42) clinical response rate while EVCO group had 97.7% (42/43). The difference between the two groups was not statistically significant (Table 7A).

Table 7A. Comparison of clinical response at week 8 (Per-protocol analysis)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BPO 5% cream</th>
<th>EVCO 2% cream</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Clinical response</td>
<td>42</td>
<td>100</td>
<td>42</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Clinical response = reduction of lesions at least 50% from baseline
Treatment failure= no reduction of lesions by at least 50% from baseline
Chi-square test

Mean percentage reduction of lesion count per treatment group
Total lesion
Figure 2 shows that the total number of lesions in the participants receiving BPO 5% cream gradually declined from the baseline number of 59.5 lesions (SD ± 21.4) to 15 lesions (SD ± 12.8) at the end of the study period. The same decline was noted in the participants receiving EVCO 2% cream from baseline total lesion count of 56.2 lesions (SD ± 20.7) to 15.4 lesions (SD ± 12.4). The percentage reduction from baseline was 75% for the BPO group and 73% for EVCO group. There was no statistical difference between the two groups in the total number of lesions counted at weeks 2, 4, 6 and 8 (p > 0.05).

Figure 2. Mean number of total lesions counted at weeks 0, 2, 4, 6 and 8 (p > 0.05).

Non-inflammatory lesions
Figure 3 shows that the mean number of non-inflammatory lesions declined in both treatment groups from baseline count to the end of the study period. The percent reduction was initially higher for BPO 5% cream (22%) compared
to EVCO 2% cream (13%) on the 1st follow-up (2nd week). However, the overall percentage reduction from baseline noted at the end of the study period (8 weeks) was almost the same in both groups (61% for BPO and 62% for EVCO). In all weeks of follow-up, there was no statistical difference between the two groups in reducing the number of non-inflammatory lesions (p-value > 0.05).

Figure 3. Mean number of non-inflammatory lesions counted at weeks 0, 2, 4, 6 and 8 (p > 0.05).

Inflammatory lesions

Figure 4 shows that the mean number of inflammatory lesions declined in both treatment groups from baseline count to the end of the study period. The percent reduction was higher for BPO 5% cream than EVCO 2% cream throughout the duration of the study (week 2 = 18% compared to 12%; week 4 = 40% compared to 34%). However, the overall percentage reduction at the end of the study period was almost the same for both groups (76% for BPO group and 72% for EVCO group). In all weeks of follow-up, there were no statistical differences between the two groups in reducing the number of non-inflammatory lesions (p > 0.05).

Figure 4. Mean number of inflammatory lesions counted at weeks 0, 2, 4, 6 and 8 (p > 0.05).

Number of weeks in achieving clinical response

Figures 5A, 5B and 5C, show the number of weeks it took for the clinical response to be achieved. Participants who did not achieve the clinical response or had dropped out were assigned as censored observations.

Figure 5A showed that it took four weeks for the BPO group to achieve the clinical response in the mean total lesion count, while it took six weeks for the EVCO group (p=0.074). Figure 5B showed that it took six weeks for both groups to achieve the clinical response in the mean non-inflammatory lesion count (p=0.133). Figure 5C showed that it took six weeks for both groups to achieve the clinical response in the mean inflammatory lesion count (p= 0.411). These measures indicated that the two treatment groups were comparable in achieving clinical response or reduction of at least 50% in acne lesion count.

Overall Comparisons

<table>
<thead>
<tr>
<th>Test of equality of survival distributions for the different levels of treatment</th>
<th>Chi-Square</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>0.074</td>
<td>1</td>
<td>0.785</td>
</tr>
</tbody>
</table>

Figure 5A. Number of weeks it took to achieve reduction of total lesion count by 50% from baseline.

Overall Comparisons

<table>
<thead>
<tr>
<th>Test of equality of survival distributions for the different levels of treatment</th>
<th>Chi-Square</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>0.133</td>
<td>1</td>
<td>0.715</td>
</tr>
</tbody>
</table>

Test of equality of survival distributions for the different levels of treatment
Participants with tapered treatment

Tapering was done if the total adverse reaction score during each visit reached a grade of 1 (mild) 2 (moderate) among the five adverse reaction parameters which were erythema, scaling, dryness, pruritus and stinging or burning. No participants were tapered from treatment since the adverse reaction scores did not reach 1.

Treatment satisfaction

After completing the 8-week study period, the participants were tasked to fulfill a questionnaire focusing on treatment satisfaction. The following five aspects were evaluated: 1) treatment effectiveness, 2) cosmetic properties of the drug, 3) overall satisfaction with treatment, 4) treatment side effects and 5) answering the question: “how do you feel about yourself?” (Table 8).

With regards to treatment effectiveness, 71.4% of participants from the BPO group and 51.2% of the participants from the EVCO group responded that they were “very satisfied” with the treatment’s effect. Regarding the cosmetic properties of the drug, 52.4% of participants from the BPO group and 41.9% of participants from the EVCO group responded as “very satisfied.” For the overall satisfaction with treatment, 54.8% of the participants from the BPO group and 41.9% of those belonging to the EVCO group rated that they were “very satisfied.” For the treatment side effects, 97.6% from the BPO group and 95.3% of the EVCO group were “not bothered.” Lastly, the participants were asked to evaluate themselves by answering the question “how do you feel about yourself?” where it was noted that 52.4% from the BPO group and 48.8% from the EVCO group felt “much better” after treatment. Although 7.1% from the BPO group and 16.3% from the EVCO group felt “no better” after treatment, for both treatment groups, there were no significant differences in the five aspects evaluated with the questionnaire (p > 0.05).

Below are the representative pictures of participants treated with enzymatic virgin coconut oil monoglyceride 2% cream and benzoyl peroxide 5% cream (Figure 6 and 7).

![Figure 5B](image)

**Figure 5B.** Number of weeks it took to achieve reduction of non-inflammatory lesion count by 50% from baseline.

<table>
<thead>
<tr>
<th>Overall Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-Square</td>
</tr>
<tr>
<td>Log Rank (Mantel-Cox)</td>
</tr>
</tbody>
</table>

Test of equality of survival distributions for the different levels of treatment

![Figure 5C](image)

**Figure 5C.** Number of weeks it took to achieve reduction of inflammatory lesion count by 50% from baseline.
DISCUSSION
Limitations
The duration of the study could have been extended to a more extended period. Some topical agents for the treatment of acne vulgaris may take a longer duration to achieve complete resolution of acne lesions as seen in some studies such as that of Schmidt et al. and Gold et al.1,26
The study participants were all Southeast Asians, and different skin types among races have different skin characteristics that might lead to the different effect of the drug. This study was also limited by the use of monotherapy of the study drug and cannot predict the possible interactions with other anti-acne medications which is essential in clinical practice since the current treatment approach to acne vulgaris is combination therapy.

Interpretation
The study evaluated the efficacy and safety of twice-daily application of enzymatic virgin coconut oil monoglyceride 2% cream in the treatment of mild to moderate acne vulgaris by comparing it to benzoyl peroxide 5% cream applied in the same frequency as the control drug.

The US FDA Guidance for Industry on the development of drugs for acne vulgaris recommended that efficacy evaluation is carried out using intention-to-treat analysis and also recommended that a supportive analysis using the per-protocol analysis be done.23

Using the intention-to-treat analysis, all LTFU in either group were considered as treatment failure. The clearance rate after eight weeks in the BPO group was higher (56%) compared with EVCO group (46%) however, the difference was not statistically significant (p = 0.319).

Per-protocol analysis was also done which did not include LTFUs in both groups for supportive analysis. The BPO group had a higher clearance rate (66.7%) compared to EVCO group (53.5%). The difference between the two groups was not statistically significant (p = 0.361). In both intention-to-treat analysis and per-protocol analysis of the clearance rate, statistical results showed no significance between the two treatment groups (p = 0.319, 0.361 respectively). These would indicate that the treatment group (EVCO) is comparable with the control group (BPO) in achieving clearance rate.

At eight weeks, both treatment groups had clinical response or improvement of lesion count by at least 50% from baseline. Using intention-to-treat analysis, the clinical response of BPO and EVCO were the same at 84%. Using per-protocol analysis, the clinical response of BPO was a little higher (100%) compared to EVCO (97.7%). In both analyses, the clinical response in both groups was not statistically significant (p = 0.779, 0.462, respectively). This would again indicate that the treatment group is comparable with the control group in achieving clinical response.

The clearance rate of EVCO 2% cream in both intention-to-treat and per-protocol analysis (46% and 53% respectively) were a little lower compared to the result of the study done by Verallo-Rowell on VCO monoglyceride, wherein the treatment success was 58.8% among study participants.22 On the other hand, the results for the control drug BPO were comparable with the findings of previously published studies.7,27,28,29,30

In this study, we wanted to assess if the LTFU on both groups were substantial enough to affect the results. Sensitivity analysis was done using the worst case-best case scenario. In the 1st case, we assumed that all LTFU on both groups achieved clearance rate after eight weeks, the difference between the two groups was not statistically significant (p = 0.206).

The 2nd case was the worst-case scenario, and we assumed that after eight weeks, all LTFU of BPO group achieved clearance rate while all LTFU of EVCO group had treatment failure. This was assigned as the worst-case scenario because the best possible score was assigned to all LTFU on the BPO group and the worst score was assigned to all LTFU on the EVCO group.23 In this worst-case scenario, the difference between 2 groups was significant (p = 0.008).

The 3rd case was the best-case scenario, and we assumed that after eight weeks, all LTFU of the BPO group were treatment failure and all LTFU from the EVCO group achieved clearance rate after eight weeks. The difference between the two groups was not statistically significant (p = 0.685).

The best-case and worst-case analysis are done to create scenarios in which factors are set within a realistic range, it can either be favorable (best-case) or unfavorable (worst-case). These scenarios were designed to reflect the extremes of realistic range.31,32

So in this case, looking at the worst case scenario the difference between the two groups was statistically significant. Therefore, we can assume that the possible dropouts in the EVCO group can significantly alter our conclusion.

Regarding the observed adverse reactions, the BPO group had more reactions compared to the EVCO group, although the difference was not statistically significant. According to published literature, benzoyl peroxide causes skin irritation that can manifest as erythema, pruritus, stinging/burning, dryness, and scaling.2,3,4,7 This was supported by a study done by Gold et al. that revealed that application of benzoyl peroxide caused few transient adverse skin reactions during treatment.26 In addition, the adverse effects of BPO were also recorded in the study done by Delima et. al.7 With regards to EVCO and its derivatives; published literature showed an excellent safety profile of the drug as reflected by the study done by Haris et al. and the studies of Verallo-Rowell that recorded no adverse reactions.20,22

Tapering was not done because the adverse reaction score during each visit did not reach a grade of 1 (mild) or a grade of 2 (moderate). These were based on the average score among the five adverse reaction parameters which were erythema, scaling, dryness, pruritus and stinging or burning. In a study done by Gold et al., which employed the same safety evaluation method, benzoyl peroxide had a few adverse reactions. However, the mean worst-case scores for all tolerability signs and symptoms were all below grade 1 (mild).26

It took six weeks in both study groups to achieve clinical response. Although the standard drug for acne – benzoyl peroxide group, achieved the clinical response at four weeks. Based on the number of weeks, the BPO group had a slightly faster effect regarding clinical response when compared with EVCO. Thus clinically it would translate that EVCO needs to be applied longer compared to BPO, but it is still useful in achieving clinical response. The results in our study were consistent with the study of Haris et
al., wherein it also took six weeks for the EVCO group to achieve 50% or more reduction in lesional counts.¹⁰

Enzymatic virgin coconut oil monoglyceride (EVCO) is known to yield more lauric acid compared with other oils.¹⁴ Lauric acid is known to have an antibacterial effect against P. acnes and also anti-inflammatory effect.¹³ In our study, we also assessed the lesion reduction from baseline until eight weeks. The inflammatory lesion (papules and pustules) reduction on BPO group was 76% compared to 72% of EVCO. This finding was consistent with the mentioned properties of EVCO. However, we also found that the non-inflammatory lesion (open and closed comedones) reduction on BPO group was 61% compared with EVCO of 62%. The results for BPO were already expected since it is known to have mild comedolytic properties.⁹ For EVCO, the findings could suggest that it has comedolytic effects. In this study, both groups took six weeks to achieve a clinical response in non-inflammatory and inflammatory lesions.

Upon completion of the study period, the participants were asked to fill up a satisfaction survey. The difference in the satisfaction of the participants between the two groups was not statistically significant. All of these would indicate that participants from both treatment groups had comparable levels of satisfaction.

The satisfaction rating was adapted from the study by Thiboutot et al. and was also used in the acne study using sweet basil done by Delima and colleagues.⁷,²⁴ Satisfaction rating results for the control drug (benzoyl peroxide) were comparable with the previous studies.²⁰,²⁴ However, this is the first study to have used this satisfaction survey questionnaire for the EVCO 2% cream.

Comparing the costs of both treatment modalities, 15-grams of enzymatic virgin coconut oil monoglyceride 2% cream is Php 21.60 which is significantly cheaper compared to 15-grams of over-the-counter benzoyl peroxide 5% which costs Php 329.00. The difference in the price range is a good basis to consider in choosing EVCO as an alternative treatment for mild to moderate acne vulgaris.

**Recommendations**

This study recommends the use of enzymatic virgin coconut oil monoglyceride for acne vulgaris be carried out for a longer duration to further evaluate its efficacy and safety and to accurately assess the length of time needed to achieve complete resolution of lesions, compare the anti-acne effect of the test drug using different bases to determine the most appropriate formulation, conduct a study on different skin types, and combine the test drug with other anti-acne medications to evaluate possible synergistic effects that might lead to faster clinical remission.

**CONCLUSION**

EVCO 2% cream had comparable clearance rate with BPO 5% cream in the treatment of mild to moderate acne vulgaris. The EVCO, 2% cream, took six weeks to achieve 50% or more decrease in total acne lesion count from baseline, and this was comparable to BPO 5% cream in achieving this reduction. Notably, only 2% of the participants in the EVCO 2% cream group experienced burning/stinging. The satisfaction survey revealed that more than half of the study participants (51.2%) in the EVCO group were “satisfied” and as much as 41.9% of the study participants were “very satisfied” with this treatment.

The raw materials of the test drug are indigenous to our locality and readily accessible even in remote areas. Hence, enzymatic virgin coconut oil monoglyceride 2% cream is an efficacious and safe alternative treatment for acne vulgaris.

**REFERENCES**


31. Riegelman RK. Studying a Study and Testing a Test: Reading Evidence-Based Health Research. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2012