A double-blind randomized controlled trial on the efficacy and safety of metformin as an adjunct to lymecycline and topical adapalene plus benzoyl peroxide gel in the treatment of moderate to severe acne vulgaris

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ABSTRACT

Introduction: Acne vulgaris has multifactorial causes. Prolonged systemic antibiotics are often necessary because relapse of lesions occurs upon its discontinuation. Currently, antimicrobial resistance is a growing concern. Androgen inhibitors like metformin may decrease need for antibiotics and maintain adequate control of the disease.

Objective: To determine the efficacy and safety of metformin versus placebo as an adjunct to lymecycline and adapalene+benzoyl peroxide gel in the treatment of moderate to severe acne vulgaris

Methods: Patients with moderate to severe acne vulgaris received either metformin or placebo tablets, together with lymecycline and adapalene+benzoyl peroxide gel. Lymecycline was taken for six weeks. The rest were given for 18 weeks. Evaluation was done biweekly using the mean reduction rates of non-inflammatory, inflammatory and total lesion count, modified global severity score, subjective self-assessment score, Dermatology life quality index (DLQI) score, and cutaneous and systemic adverse events.

Results: Forty patients were selected for the trial. Mean reduction rates of the non-inflammatory lesion counts of the two groups were comparable ($p>0.05$). Mean reduction rates of the inflammatory and total lesion count in the metformin group were higher than the placebo group ($p<0.05$). The mean modified global severity score of the metformin group was lower than the placebo group ($p=0.034$). Mean DLQI scores decreased in both groups ($p<0.0001$). Subjective self-assessment scores improved in both groups with comparable results. Cutaneous adverse events (erythema, pain, scaling, and dryness) were tolerable. Systemic adverse events (diarrhea, flatulence, headache, and epigastric pain) were self-limited.

Conclusion: Metformin is an effective and safe adjunct in the treatment of moderate to severe acne vulgaris.

Keywords: acne vulgaris, metformin, lymecycline

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INTRODUCTION

Acne vulgaris is a chronic inflammatory condition of the pilosebaceous unit, characterized by the formation of the non-inflammatory (comedones) and inflammatory papules, pustules, nodules and cysts. It is one of the most common inflammatory skin conditions that affect 85-100% of the world's population.[1] In 2013, it ranked as the first among the top 10 diseases most commonly seen in the clinics of the Philippine Dermatological Society training institutions with a prevalence of 16.79%.[2] Patients having this condition are greatly affected in terms of the physical and psychosocial aspects of their well-being, leading to anxiety, depression, social withdrawal, lower self esteem, and unemployment.[3]

The four main factors involved in the pathogenesis of acne are: (1) androgen-stimulated increase in sebum production; (2) hyperproliferation and abnormal desquamation of the intrafollicular epithelium leading to the precursor microcomedo lesion; (3) proliferation of the anaerobic bacteria, *Propionibacterium acnes*, within the sebaceous follicles; and (4) inflammation resulting from the release of proinflammatory cytokines by *P. acnes* or from rupture of the microcomedo, explaining the inflammatory papules, pustules, and nodulocystic lesions.[1]

No single treatment can directly target all of these four pathogenic mechanisms. Combination therapy is used to tackle the different factors, making it the gold standard for acne therapy.[4]

The fixed-dose combination of topical adapalene and benzoyl peroxide has a dual advantage of treating both the non-inflammatory and the inflammatory acne lesions. Adapalene, one of the topical retinoids, modulates cell proliferation and keratinization, thus preventing the comedone formation.[5] It also blocks the release of inflammatory cytokines and inhibits cellular inflammation.[6] Benzoyl peroxide has antimicrobial property because it generates reactive oxygen species (ROS) which oxidizes protein in the bacterial cell membranes, leading to the elimination of *P. acnes*.[7] Its mechanism of action does not involve ribosomal synthesis unlike antibiotics, thus explaining the findings that it prevents and eliminates *P. acnes* resistance.[8] Its anti-inflammatory effect has been shown to be enhanced upon combination with retinoids[9] such as adapalene.

The standard of care for moderate to severe acne and treatment-resistant forms of inflammatory acne is the use of systemic antibiotics.[10] Lymecycline, a second generation semisynthetic tetracycline, ameliorates symptoms of acne vulgaris by blocking the 30S ribosomal subunit, inhibiting translation during bacterial protein synthesis.[11,12] This indirectly results in the inhibition of bacterial lipases produced by *P. acnes*, causing a subsequent decrease in the formation of inflammatory papules, pustules, and nodulocystic lesions. Tetracyclines are also known to have anti-inflammatory/ immunomodulatory effect.[13]

Acne vulgaris has a prolonged course characterized by a slow onset with acute outbreaks. Upon discontinuation of any therapy, relapse or recurrence can occur. It is now considered as a chronic disease needing long-term treatment. Despite the possibility of increased side effects, prolonged usage of systemic antibiotics is usually given to acne patients, even up to three months. However, the appropriate time point at which to assess response to this treatment is at six to eight weeks.[14] Currently, bacterial resistance to antibiotics is a growing concern and has been an issue in acne treatment.[15] Antibiotic courses of three months are highly likely to result in the formation of resistant strains of *P. acnes*.[12] Recently, there are also findings indicating the possibility of resistance spreading between organisms with the emergence of antimicrobial resistance of microorganisms such as *Staphylococcus epidermis* and *Streptococcus pyogenes* among acne patients,[16-18] their close family contacts, and even the doctors treating them.[19] There is therefore, a need to search for an adjunct treatment, which may help shorten the course of antibiotic use and still maintain the improvement in the patient after discontinuation of oral antibiotics.

The role of androgen in the pathophysiology of acne vulgaris is well known. An increase in androgen levels results in an abnormal hyperkeratinization, leading to retention hyperkeratosis that blocks the outward flow of sebum secretion. This results in the occlusion of the follicular infundibulum and subsequent development of the comedone. The trapped sebum provides an optimal milieu for the growth of *P. acnes*. With the recruitment of proinflammatory cytokines, inflammatory lesions of acne occur.[20]

Several clinical studies have proposed different mechanisms on how hyperandrogenemia can cause acne vulgaris. One mechanism can be explained at the level of the genomic regulation. A recent hypothesis suggests that a nuclear deficiency of the metabolic transcription factor Fox01, which is an important regulator of androgen receptor, cell proliferation, apoptosis, and lipogenesis, contributes to the pathogenesis of acne. Several factors such as growth factor (GH), insulin, and insulin growth factor-1 (IGF-1) are all integrated at the level of the phosphoinositol-3 kinase (PI3K). With the aid of the activated kinase Akt, phosphorylation of the nuclear Fox01 protein occurs, exporting Fox01 protein into the cell's cytoplasm. This process activates target genes and nuclear androgen receptors.[21] When androgens bind with the nuclear androgen receptors, these androgen-receptor complexes will further interact with the deoxyribonucleic acid (DNA) in the sebaceous cells' nuclei, resulting in the regulation of the genes involved in cell proliferation leading to comedogenesis, lipogenesis causing hyperseborrhea, and inflammation thru the activation of interleukins, prostaglandins, matrix metalloproteinase, and T cell proliferation.[22]

Metformin is an agent commonly used for the treatment of non insulin-dependent diabetes mellitus. It has been used in patients with polycystic ovarian syndrome resulting in improvement of the skin manifestations of hyperandrogenemia. In a study by Kolodziejczyk et al.,[23] the administration of 500 mg of metformin three times a day for three months resulted in a reduction of acne score by 14%. It has been shown to significantly decrease insulin levels and hyperandrogenism.[24] A decrease in androgen levels will inhibit seborrhea, lipogenesis, and follicular hyperkeratinization, subsequently decreasing the formation of acne lesions. Prolonged intake of metformin is tolerated well by many patients with minimal side effects. It is, therefore, valuable to determine if it can serve as an adjunct treatment in patients with moderate to severe acne vulgaris to help limit the duration of the intake of oral antibiotics and avoid quick relapse upon discontinuation of these antibiotics. Its efficacy as an adjunct may ultimately contribute to lessen the possibility of the development of antimicrobial resistance.

The primary objective of this study was to determine the efficacy and safety of metformin versus a placebo in combination with lymecycline and adapalene 0.1% + benzoyl peroxide 2.5% gel in the treatment of moderate to severe acne vulgaris.

Acne vulgaris is a chronic inflammatory condition of the pilosebaceous unit, characterized by the formation of the non-inflammatory (comedones) and inflammatory papules, pustules, nodules and cysts. It is one of the most common inflammatory skin conditions that affect 85-100% of the world's population.[1] In 2013, it ranked as the first among the top 10 diseases most commonly seen in the clinics of the Philippine Dermatological Society training institutions with a prevalence of 16.79%.[2] Patients having this condition are greatly affected in terms of the physical and psychosocial aspects of their well-being, leading to anxiety, depression, social withdrawal, lower self esteem, and unemployment.[3]

Specifically, it aimed to determine and compare the improvement of acne lesions in both treatment groups through the evaluation of the following:

1. The mean reduction rate of the non-inflammatory, inflammatory, and total lesion count, based on the Leeds Acne Lesion Counting System. (Appendix A)
2. The improvement of the modified global severity score. (Appendix B)
3. The improvement in severity as reported by the patient during each follow-up visits using the subjective self-assessment score of change. (Appendix C)
4. The improvement in the quality of life as reported by the patient using the Dermatology Life Quality Index (DLQI) scores before and after treatment. (Appendix D and E)
5. The grading of cutaneous adverse events (erythema, pain, scaling, and dryness) reported by the patient and/or observed by the investigator.
6. Incidence and frequency of systemic adverse events reported by the patient such as allergy, diarrhea, nausea, vomiting, abdominal pain, and others.

METHODOLOGY

A. Study Design

This double-blind, randomized, controlled trial was conducted from December 2013 to August 2014 at the dermatology outpatient department of the University of Santo Tomas Hospital.

B. Patient Selection and Recruitment

Patients selected for this study were males and females, aged 16 to 45 years old, diagnosed with moderate to severe acne by the primary investigator, with a modified global severity score of 2 to 4. (Appendix B)

Patients with history of hypersensitivity to tetracycline, metformin, benzoyl peroxide or adapalene, diabetes mellitus, renal, cardiac and hepatic diseases, alcoholism, serious infection, severe diarrhea or vomiting, fever, poor oral intake, conditions predisposing to tissue anoxia, and females with pregnancy or polycystic ovaries were excluded from the study. Wash-out periods for topical treatment on the face were observed as follows: two weeks for corticosteroids, antibiotics, antibacterials, antiseptics, retinoids, and other anti-inflammatory drugs or other acne treatments; and one week for phototherapy devices for acne and cosmetic procedures. For systemic treatment, wash-out periods were observed as follows: four weeks for antibiotics, six months for other acne treatments, six months for oral contraceptive pills, and three months for antiandrogens such as spironolactone/drospirenone.

C. Randomization and Blinding

Subjects were randomized using the block randomization technique. Patients were randomly assigned a study number in the order that they were recruited, and then assigned to either the metformin (M) group or the placebo (P) group by a secondary investigator. The patients, as well as the primary investigator who assessed them at baseline and during their follow-up visits, were blinded to the treatment being given.

D. Intervention and Data Collection

Eligible participants who fulfilled all the inclusion criteria were recruited. The nature of the study was explained to the patients using the information sheet (Appendix F) and they were requested to sign the informed consent (Appendix G). The legal representatives of those aged 18 and below were asked to sign the consent form as well.

Baseline fasting blood glucose and serum creatinine were acquired prior to the beginning of treatment. Female patients underwent a pregnancy test and a transvaginal/ transrectal ultrasound done by a licensed OB-Gynecology sonologist to rule out pregnancy and polycystic ovaries. Patients with abnormal fasting blood glucose or serum creatinine, pregnancy, or polycystic ovaries, were excluded from the study and referred to a medical internist or an obstetrician-gynecologist, respectively, for appropriate management.

Demographic profiles and the following baseline data were recorded: weight (kg), height (cm), body

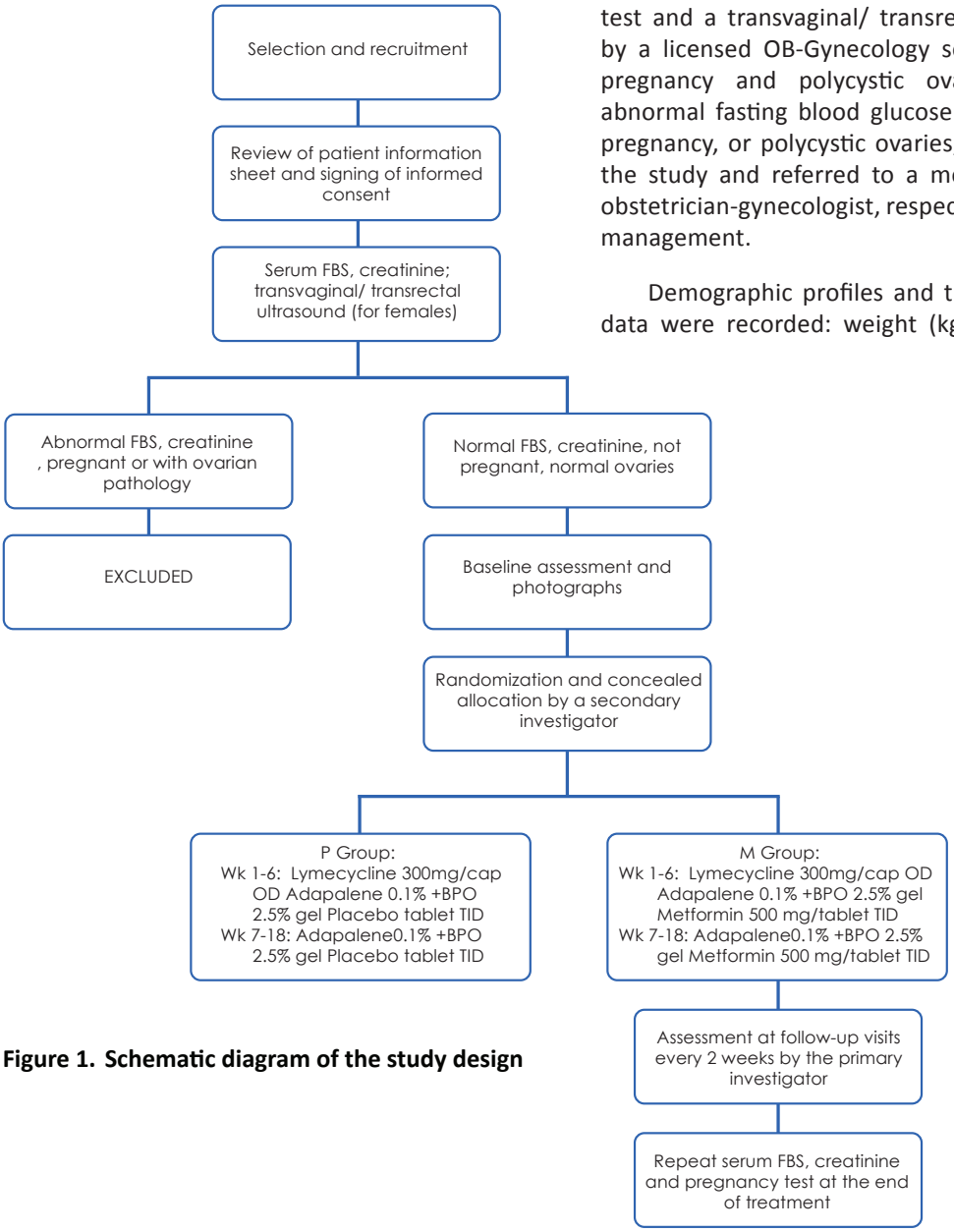


Figure 1. Schematic diagram of the study design

mass index (BMI), non-inflammatory, inflammatory, and total lesion count using the Leeds Acne Lesion Count System[25-27] (Appendix A), and the corresponding modified global severity score[25,27] (Appendix B), fasting blood glucose (FBS) level, serum creatinine level, results of the transvaginal/ transrectal ultrasound and pregnancy test (for female patients), and DLQI[28] scores.

Photographs were taken at baseline, a foot away from the subject, using a Canon EOS camera (Model 60D, macro mode setting). Full anterior, right, and left views of the face were photographed.

Sealed envelopes, prepared and given to the patients by the secondary investigator, were labeled according to the week that these are supposed to be opened. Patients were instructed to open a designated envelope for each week, and to take the capsules one hour before meals or two hours after meals and the tablets immediately after meals. To lessen the gastrointestinal side effects of metformin,[29] titration of this drug was done as follows: One 500 mg tablet of metformin was initially given on the first day. On the second day, the dose was increased to one tablet every 12 hours. The full dose of 1500 mg (1 tablet every 8 hours) was given on the third day until the end of the treatment period. The placebo tablets given to the P group were titrated the same way. The placebo tablets were manufactured by the same company as the metformin brand used in this study. Both metformin and placebo tablets looked similar, except that the placebo tablets do not contain any active ingredient.

The sealed envelopes given to the M (metformin) group contained the following:

Weeks 1-6:

Day 1:	1	tablet of metformin, 500mg/tablet;
	1	capsule of lymecycline, 300mg/capsule
Day 2:	2	tablets of metformin, 500mg/tablet;
	1	capsule of lymecycline, 300mg/capsule
Days 3-42:	3	tablets of metformin. 500mg/tablet;
	1	capsule lymecycline, 300mg/capsule

Weeks 7-18[25]:

Days 43-126:	3	tablets of metformin 500mg/tablet

The sealed envelopes given to the P (placebo) group contained the following:

Weeks 1-6:

Day 1:	1	placebo tablet;
	1	capsule of lymecycline, 300mg/capsule
Day 2:	2	placebo tablets;
	1	capsule of lymecycline, 300mg/capsule,
Days 3-42:	3	placebo tablets;
	1	capsule of lymecycline, 300mg/capsule,

Weeks 7-18:

Days 43-126:	3	placebo tablets

In addition, for both treatment groups, adapalene 0.1%+ benzoyl peroxide 2.5% gel was applied thinly over the entire face nightly, and a mild facial soap was used twice daily. Patients were advised to to buy the same brand of mild white soap. Adapalene 0.1% + benzoyl peroxide 2.5% gel was provided by the investigator.

The following data were recorded at every follow-up visit, scheduled at weeks 2, 4, 6, 8, 10,12, 14, 16, and 18 from the beginning of treatment:

1. Weight in kg.
2. Body Mass Index (BMI)
3. Number of non-inflammatory, inflammatory, and total lesion count using the Leeds Acne Lesion Count System and the corresponding modified global severity score.
4. Subjective Self-Assessment Score of Change in Acne Severity as reported by the patient, and graded as (0) worsened, (1) no change, (2) mild improvement, (3) moderate improvement, or (4) marked improvement.

5. Systemic adverse events to treatment as reported by the patient.

6. Cutaneous adverse events of erythema, pain, scaling, and dryness over the face,[30,31] reported by the patient and observed by the clinical investigator, assessed as none (0), mild (1), moderate (2), and severe (3).

7. DLQI scores before and after treatment.

Photographs were also taken at every follow-up visit.

Patients were instructed to contact the primary investigator immediately if any adverse events were experienced during the course of treatment.

Serum fasting blood sugar, creatinine, and pregnancy test for females were repeated upon the completion of the treatment.

E. Assessment

Primary efficacy end points were evaluated through the mean reduction rates of non-inflammatory, inflammatory, and total acne lesion counts at each follow-up visit until the end of treatment. Secondary efficacy end points included the modified global severity score and subjective self-assessment score of change in acne severity at each follow-up visit, and the DLQI, before and after treatment.

Safety end points were the comparison between the two treatment groups of the following parameters: (1) mean grades of the cutaneous side effects of erythema, pain, scaling, and dryness at each follow-up visit and (2) the incidence and frequency of systemic adverse events as reported by the patient (e.g. diarrhea, nausea, vomiting, and abdominal pain).

F. Statistical considerations and data analysis

I. Sample size and statistical power

The sample size was computed based on the mean difference in total number of lesions from a previous study,[32] reported as 75.21, and a mean difference estimated at 135 for the current study. Seventeen (17) subjects were needed to be included in each group to detect a statistically significant clinical response between lesion counts, with a power of 80% and α=0.05 level of significance.

II. Data Analysis

Descriptive analysis for the variables of age and body mass index was done using central tendency measures, means, and standard deviation. For the variable of gender, the Pearson chi-square test was used. The Shapiro-Wilk test for normality was used in order to determine homogeneity and whether parametric and non-parametric tests were indicated.

The Student's t test was used to analyze the differences between groups for the mean age, FBS, and BMI at baseline and at the end of treatment. The Wilcoxon signed rank test was used to determine the difference between groups for DLQI at baseline and at the end of treatment.

The mean reduction rates from baseline to each follow-up visit of the non-inflammatory, inflammatory, and total lesion counts for each group were compared using the Mann-Whitney U test to determine if a statistically significant difference was demonstrated. For the comparison of the mean reduction rates from baseline to each follow-up visit within each group, the Wilcoxon signed rank test was used. The mean of modified global severity and subjective self-assessment scores for every follow-up visit were analyzed using the Mann-Whitney U test as well.

For the comparison of the cutaneous adverse events such as erythema, pain, scaling, and dryness, as well as the incidence and frequency of the systemic adverse events between the two groups, the Fisher's exact test was used.

All results were expressed as the mean standard deviation. A p value of <0.05 was considered statistically significant.

An intent-to-treat analysis was performed, with the study population defined as those who were assigned to their respective treatment arms and those who received the medications, regardless of outcome, whether the subjects completed the study or not. For missing data and withdrawals, it was assumed that there was no change or improvement in the variable of interest after the period of non-compliance so the last values of the variables of interest were carried out until the end of the treatment period.

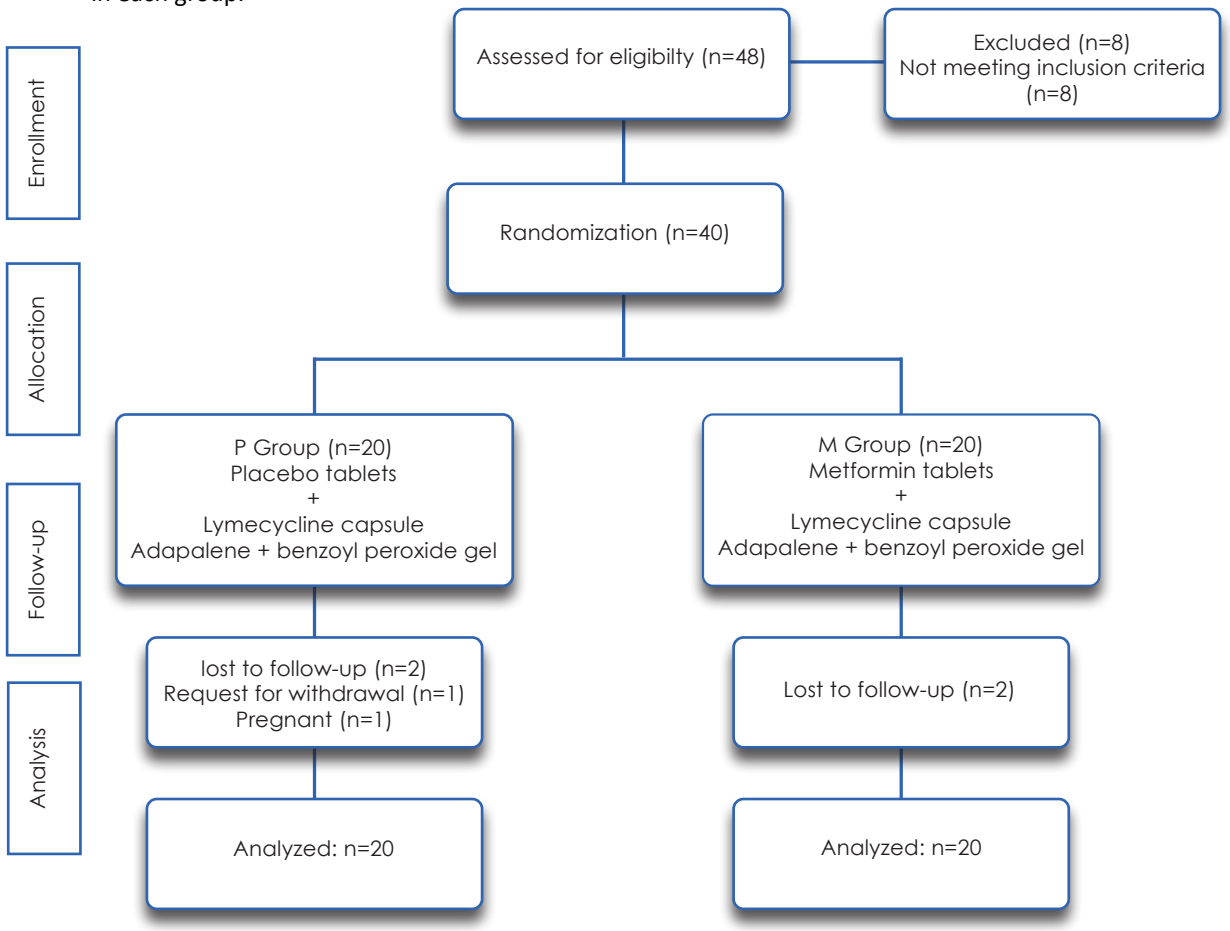
All data were analyzed using Stata version 10.0.

RESULTS

A. Patient Disposition

A total of 48 patients were assessed for eligibility. Eight patients were excluded from the study due to findings of polycystic ovaries on transvaginal/ transrectal ultrasound. Out of the 40 patients, 20 were randomized to the metformin (M) group and received lymecycline capsule, adapalene 0.1%+ benzoyl peroxide 2.5% gel, and metformin tablet. The other 20 were assigned to the placebo (P) group and received lymecycline capsule, adapalene 0.1%+ benzoyl peroxide 2.5% gel, and placebo tablet. Thirty-four out of the 40 patients (85%) completed the study. In the P group, four patients discontinued from the study. Two of these patients could no longer be contacted after their 8th and 10th week of treatment, respectively. One patient requested to be withdrawn from the study on the 4th week of treatment due to conflicts in schedule. One patient in the group had a positive pregnancy test during the 14th week of treatment. In the M group, two patients were lost to follow-up after the 4th and 10th week of treatment, respectively due to conflicts in schedule. The intent-to-treat analysis included all the randomized subjects who were provided the study medications. The disposition of the patients in the study is shown in Figure 2.

Figure 2. Disposition of patients. The number of patients included at each study stage and the reason for drop out in each group.



B. Demographic and Baseline Characteristics

At baseline, the two treatment groups were observed to be homogeneous and statistically comparable (Table 1) in terms of the demographic characteristics of gender distribution (Pearson chi-square test, $p > 0.05$) and mean age

(Student's t test, p >0.05). Likewise, there were no statistically significant differences in the mean number of non-inflammatory, inflammatory, and total lesion count at baseline (Mann-Whitney test, p >0.05).

Table 1. Demographic characteristics of the metformin (M) and placebo (P) groups at baseline

Variable	M Group n= 20	P Group n= 20	p value
Gender			
Male	13 (65%)	12 (60%)	0.744 (NS)[a]
Female	7 (35%)	8 (40%)	
Age in years			
Mean ± SD	22.75 ± 7.04	21.45 ± 4.58	0.4931 (NS) [b]
Baseline noninflammatory	64.85 ± 50.08	82.55 ± 49.79	0.0810 (NS)[c]
lesion count, mean ± SD			
Baseline inflammatory lesion count, mean ± SD	39.65 ± 22.09	41.7 ± 28.98	0.8710(NS)[c]
Baseline total lesion count, mean ± SD	104.5 ± 54.84	124.25 ± 49.13	0.1516 (NS)[c]

[a]Pearson chi- square test [b]Student's t test [c]Mann-Whitney U test

The baseline and final scores of body mass index and fasting blood sugar between the two groups (Table 2) showed no statistical difference as well.

Table 2. Mean baseline and final body mass index and fasting blood sugar of metformin (M) and placebo (P) groups

Variable	M Group Mean ± SD	P Group Mean ± SD	p value
Baseline body mass index (kg/m2)	22.4 ± 3.76	20.8 ± 2.73	0.1318[b]
Final body mass index (kg/m2)	21.95 ± 3.98	20.55 ± 2.87	0.8950[b]
Baseline fasting blood sugar (mmol/L)	90.7 ± 8.70	89.57 ± 8.35	0.6769[b]
Final fasting blood sugar (mmol/L)	90.21 ± 7.67	87.35 ± 7.01	0.2263[b]

C. Efficacy Outcomes

I. Mean reduction rates of lesion counts

The mean reduction rate of the non-inflammatory (comedonal) lesions at each follow-up visit showed consistent improvement compared to baseline in both the M and P groups. Intergroup analysis using the Wilcoxon signed rank test showed that there were significant statistical differences across the different weeks in the mean reduction rates for both groups from baseline until week 18 of the treatment period with a p value <0.05. The Mann-Whitney U test showed that the mean reduction rates of both groups were statistically comparable (p>0.05). (Figure 3)

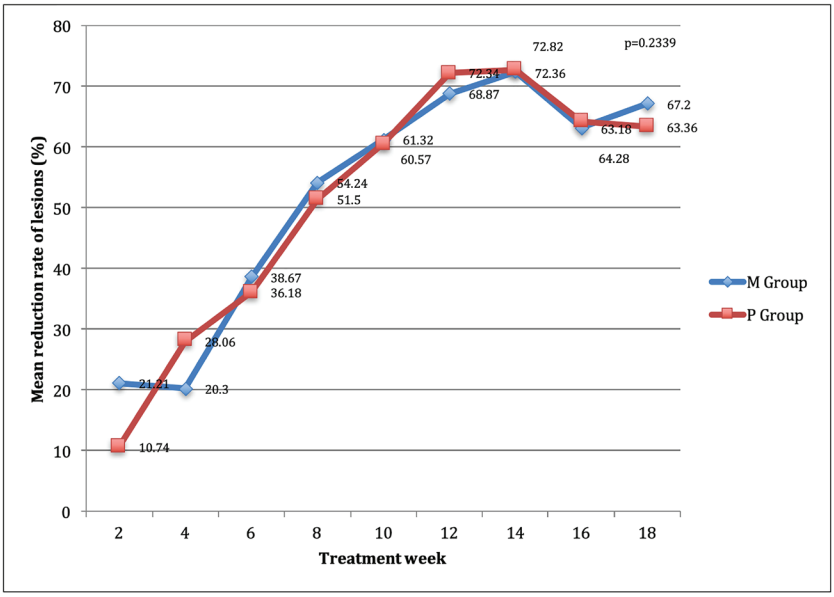


Figure 3. Mean reduction rate of non-inflammatory (comedonal) lesions in patients in the M and P groups at baseline and treatment weeks 2, 4, 6, 8, 10, 12, 14, 16, and 18

Both the M and P groups also showed improvement in the mean reduction rates of inflammatory lesion counts at each follow-up visit when compared to baseline. Intergroup analysis using the Wilcoxon signed rank test showed that there were significant statistical differences across the different weeks in the mean reduction rates for both groups from baseline until week 18 of the treatment period with a p value <0.05. The Mann-Whitney U test showed that there was a significant mean reduction rate in the M group at week 16, which was statistically higher compared to the P group (p=0.0047). At week 18, although the mean reduction rate in the M group was still higher compared to the P group, both groups were statistically comparable. (Figure 4)

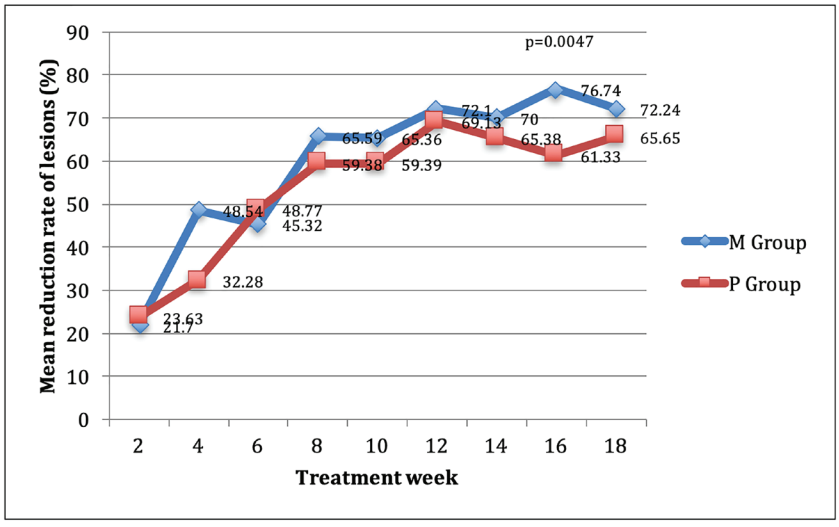


Figure 4. Mean reduction rate of inflammatory lesions in patients in the M and P groups at baseline and treatment weeks 2, 4, 6, 8, 10, 12, 14, 16, and 18

For the total lesion count, both groups showed improvement in the mean reduction rates at each follow-up visit when compared to the baseline. Intergroup analysis using the Wilcoxon signed rank test showed that there were significant statistical differences across the different weeks in the mean reduction rates for both groups from baseline until week 18 of the treatment period with a p value <0.05. The Mann-Whitney U test showed that there was a significant mean reduction rate at week 16 in the M group, which was statistically higher compared to the P group (p=0.0453). This observation also persisted at week 18, where the M group still had a statistically higher mean reduction rate compared to the P group with a p value of 0.0453. (Figure 5)

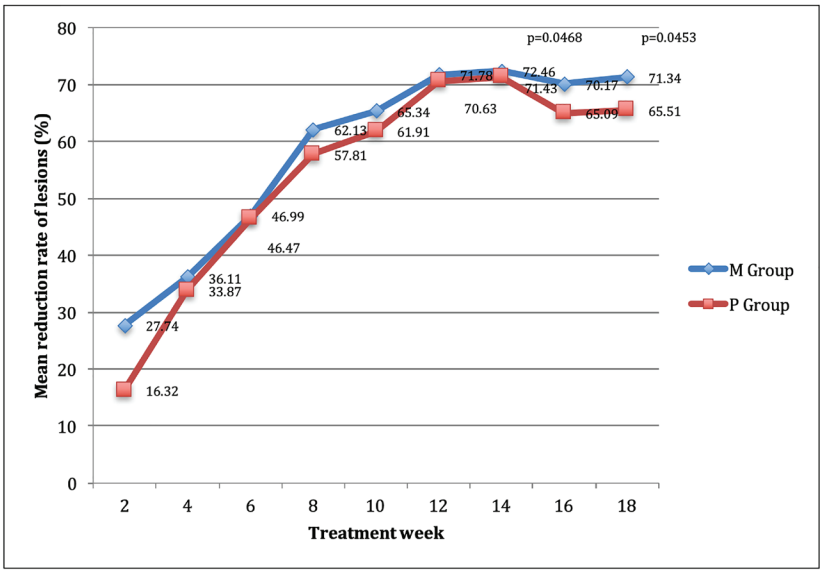


Figure 5. Mean reduction rate of total acne lesions in patients in the M and P groups at baseline and treatment weeks 2, 4, 6, 8, 10, 12, 14, 16, and 18

II. Modified Global Severity Score

Both M and P groups showed a decline in the mean modified global severity score. Results of the Mann-Whitney U test showed that there was a significant decrease in the mean modified global severity score at week 16 where the M group had a statistically lower mean score compared to the P group (p=0.034). At week 18, the mean modified global severity score of the M group was still lower compared to that of the P group, however, both groups were statistically comparable (p=0.1215). (Figure 6)

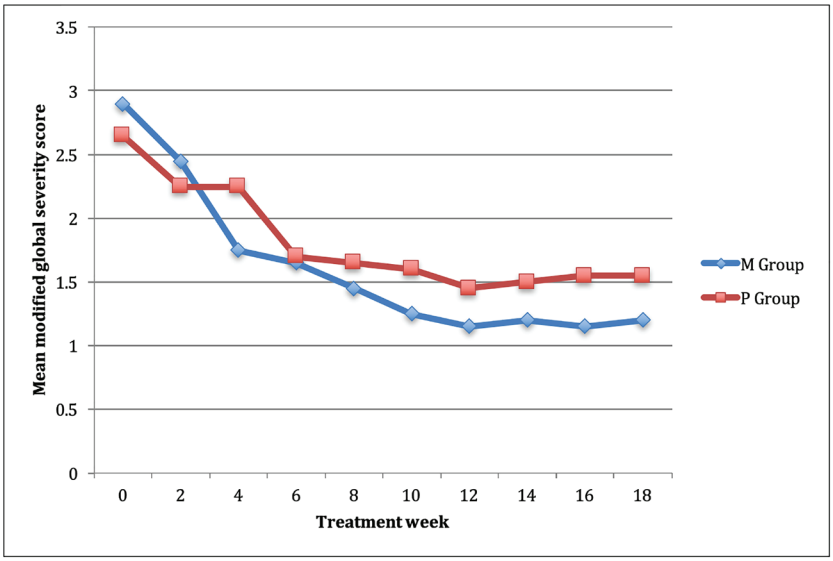


Figure 6. Mean modified global severity score of patients in the M and P groups at baseline and treatment weeks 2, 4, 6, 8, 10, 12, 14, 16, and 18

III. Subjective Self-Assessment Score of Change in Acne Severity

The mean subjective self-assessment score of patients in both groups showed improvement during each treatment visit. Statistical analysis using the Mann-Whitney U test of mean scores at each treatment visit up to week 18 showed comparable results between the two groups (p >0.05). (Figure 7)

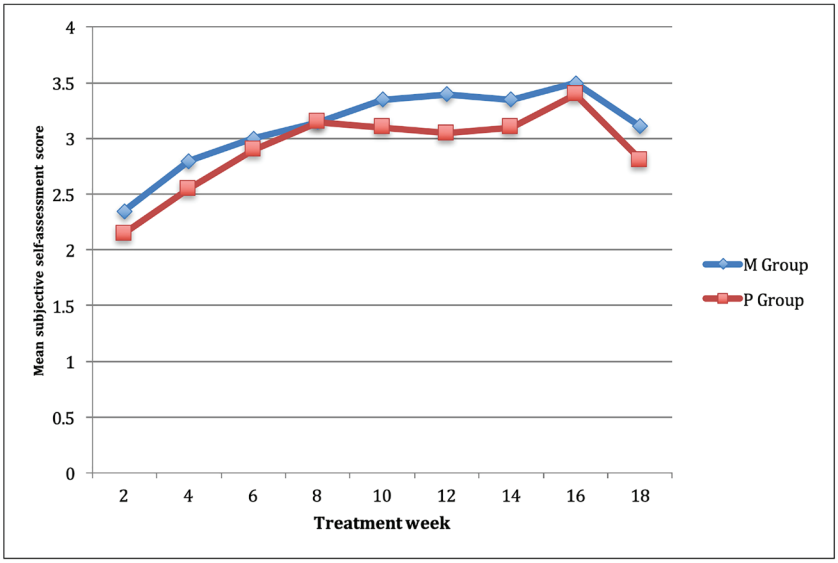


Figure 7. Mean subjective self-assessment score of patients treated in the M and P groups at baseline and treatment weeks 2, 4, 6, 8, 10, 12, 14, 16, and 18

IV. Dermatology Life Quality Index (DLQI)

At baseline, the mean DLQI scores of M group was 10.40 while that of the the P group was 9.75. The Mann-Whitney U test showed that both groups were statistically comparable. The mean post-treatment DLQI scores were 1.75 and 3.6 for the M and the P groups, respectively. Wilcoxon signed rank test showed that there was a significant decrease in the mean DLQI scores before and after treatment in both groups (p <0.0001). Using the Mann-Whitney U test, the DLQI scores of both groups were shown to be statistically comparable (p=0.08). (Figure 8)

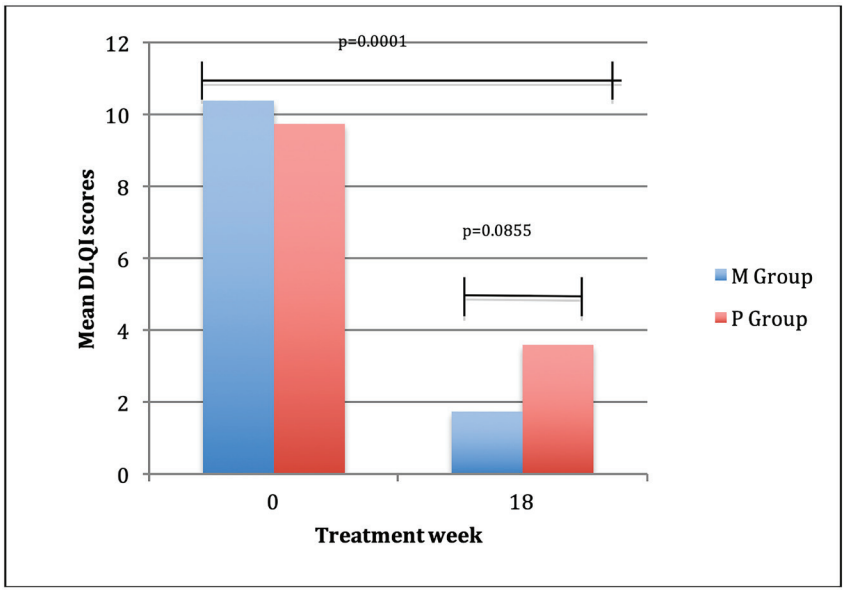


Figure 8. Mean DLQI scores of patients treated in the M and P groups at baseline and after treatment

IV. Safety Outcomes

Erythema was only observed in both groups during the first two weeks of treatment. The subjects in both groups did not experience any erythema thereafter until the end of the treatment period. The mean erythema scores of the M group (0.15) and P group (0.15) were statistically comparable based on the Mann-Whitney U test (p=0.6886). (Table 3)

Pain was reported as an adverse effect in both groups. It was observed only at week 2 in the M group while the P group reported pain at all weeks except week 8. The mean pain scores between the two groups were comparable for all visits (Mann-Whitney U test, p > 0.05). (Table 3)

	Mean erythema score			Mean pain score		
	M Group (mean ± SD)	P Group (mean ± SD)	p value[a]	M Group (mean ± SD)	P Group (mean ± SD	p value[a]
Week 2	0.15 ± 0.37	0.15 ± 0.49	0.6886	0.40 ± 0.60	0.40 ± 0.50	0.8476
Week 4	0	0	-	0	0.15 ± 0.37	0.0754
Week 6	0	0	-	0	0.05 ± 0.16	0.3173
Week 8	0	0	-	0	0	-
Week 10	0	0	-	0	0.05 ± 0.22	0.3173[a]
Week 12	0	0	-	0	0.05 ± 0.22	0.3173[a]
Week 14	0	0	-	0	0.05 ± 0.22	0.3173[a]
Week 16	0	0	-	0	0.05 ± 0.22	0.3173[a]
Week 18	0	0	-	0	0.05 ± 0.22	0.3173[a]

[a]Mann-Whitney U test

Table 3. Mean erythema and pain count of patients treated in the M and P groups at baseline and treatment weeks 2, 4, 6, 8, 10, 12, 14, 16, and 18

Scaling was noted by the M group at weeks 2 and 6 while the P group reported it at week 2. (Table 4) Neither group reported scaling as an adverse effect at weeks 4, 8, 10, 12,14, 16, and 18. At week 6, the mean scaling score of the M group was 0.05 while the P group had no adverse effect of scaling. The mean scaling scores of both groups at week 2 and week 6 were comparable with p values of 0.2177 and 0.3173, respectively, using the Mann-Whitney U test.

Dryness was noted by the M group at weeks 2, 4, 6, and 14 while the P group reported it at weeks 2, 4, and 10. Neither group reported dryness as an adverse effect at weeks 8,12, 16, 18. (Table 4) The mean dryness scores of both groups were statistically comparable, (Mann-Whitney U test, p>0.05).

Table 4. Mean scaling and dryness count of patients treated in the M and P groups at baseline and treatment weeks 2, 4, 6, 8, 10, 12, 14, 16, and 18

	Mean scaling score			Mean dryness score		
	M Group (mean ± SD)	P Group (mean ± SD)	p value[a]	M Group (mean ± SD)	P Group (mean ± SD	p value[a]
Week 2	0.25 ± 0.44	0.10 ± 0.31	0.2177	0.20 ± 0.41	0.25 ± 0.55	0.9379
Week 4	0	0	-	0.05 ± 0.22	0.25 ± 0.52	0.2865
Week 6	0.05 ± 0.22	0	0.3173	0.11 ± 0.32	0	0.1757
Week 8	0	0	-	0	0	-
Week 10	0	0	-	0	0.10 ± 0.45	0.3173
Week 12	0	0	-	0	0	-
Week 14	0	0	-	0.05 ± 0.22	0	0.3173
Week 16	0	0	-	0	0	-
Week 18	0	0	-	0	0	-

[a]Mann-Whitney U test

The most frequent systemic adverse events (Table 5) reported by the patients in the M group were diarrhea (15%) and flatulence (15%) while in the P group, diarrhea was reported by 20% of patients. Headache and epigastric pain were the other systemic adverse events reported only by the patients in the M group while only patients in the P group reported weakness and nausea.

Adverse events	M Group [n(%)]	P Group [n(%)]
Weakness	0 (0)	1 (5)
Diarrhea	3 (15)	4 (20)
Flatulence	3 (15)	3 (15)
Headache	1 (5)	0 (0)
Epigastric pain	2 (10)	0 (0)
Nausea	0 (0)	1 (5)

Table 5. Incidence of systemic adverse events reported per treatment group

The frequency of systemic adverse events of the M and P groups showed no statistical difference between the two groups at weeks 2, 4, 6, 8, 10, 12, 14, and 18 (Fisher's exact test, $p>0.05$). No adverse events were noted at week 16 for both groups. (Table 6)

Week	M group [n(%)]	P group [n(%)]	p value [a]
2	11 (55)	6 (30)	0.200
4	5 (25)	5 (25)	1.000
6	3 (15)	1 (5)	0.605
8	2 (10)	1 (5)	1.000
10	4 (20)	1 (5)	0.342
12	1 (5)	1 (5)	1.000
14	1(5)	0(0)	1.000
16	0(0)	0(0)	-
18	0(0)	1 (5)	1.000

Table 6. Frequency of systemic adverse events per follow-up visit

DISCUSSION

Based on this randomized controlled trial, metformin was found to be safe and effective as an adjunct treatment to lymecycline and topical adapalene+ benzoyl peroxide gel in the treatment of moderate to severe acne vulgaris. In this study, the antibiotic, lymecycline, which is part of the standard of care for moderate to severe acne, was discontinued after six weeks.[14] Six weeks is considered the shortest and appropriate time point to evaluate the effect of the drug. For the subsequent 12-week observation period from weeks 7 to 18, only metformin and placebo were given as systemic treatment together with the topical fixed-dose combination of adapalene and benzoyl peroxide. The efficacy of metformin as an adjunct was supported by the continuous decline of the total lesion counts and modified global severity scores. The statistically significant reduction rates in the metformin-treated group in terms of the number of their inflammatory lesions and modified global severity scores at week 16, and in the total lesion count scores at weeks 16 and 18 imply that even with the discontinuation of the oral antibiotics after six weeks, metformin was still able to sustain the effectiveness of maintaining clearance of acne lesions. Although the reduction rates in the number of non-inflammatory lesions in the metformin group was not statistically different from the placebo group, there was still a clinically higher mean reduction rate by week 18 with the use of metformin. These results are valuable because they imply that the intake of oral antibiotics may be confined to a minimum duration and patient may be maintained on adjunct therapies to lessen relapse of lesions. This idea concurs with the guidelines of the Global Alliance to Improve Outcomes in Acne Group regarding the strategies for limiting antibiotic resistance in *P. acnes* and other bacteria,[14] by limiting the use of antibiotics to short periods.

The pathogenesis of acne is complex and multifactorial. Lymecycline and benzoyl peroxide act through the inhibition of the *P. acnes* and its subsequent inflammatory effects while adapalene acts mainly as keratolytic with mild anti-inflammatory effect. Metformin, on the other hand, acts through the inhibition of androgens.

Sebum production is mainly determined by androgens,[33] and a drug that will inhibit androgen effects will be beneficial in ameliorating acne lesions. Metformin is a drug known to decrease insulin levels. This will decrease the hepatic secretion of IGF-1 and the biosynthesis of androgen. This will ultimately lead to a decrease in sebum production and lipogenesis and follicular hyperkeratinization.[34]

According to Lakshmi,[35] metformin can also decrease the insulin levels through the interaction between peroxisome proliferator-activated receptor (PPAR-PPARγ). PPAR is a part of the cascade of

eicosanoid synthesis in the skin, as an inflammatory signaling pathway, possibly involved in the development of acne. PPAR is derived from leukotriene B4 (LTB4), which is a pro-inflammatory mediator, synthesized from arachidonic acid. It promotes synthesis of free fatty acids, at the same time stimulates the production of pro-inflammatory cytokines.[36] Thus, the reduction of PPAR by metformin reduces the production of free fatty acids by *P. acnes* and indirectly, reduces the production of inflammatory cytokines, subsequently reducing inflammatory lesions in acne. This could be another possible mechanism of action of metformin in reducing the inflammatory lesion counts, leading to marked clinical improvement.

Several other factors have been suggested to aggravate signs of acne vulgaris through the level of genomic regulation. One factor includes the consumption of milk, which can induce high serum levels of IGF-1, leading to the reduction of nuclear levels of Fox01, subsequently activating comedogenesis. Another factor is the intake of a high index glycemic diet that can induce hyperglycemia, hyperinsulinemia, and increased IGF-1 levels.[37] Smoking is also associated with an increased insulin/P13K/Akt signaling of the pilosebaceous unit, leading to hyperinsulinemia and dyslipidemia.[38] These external factors could theoretically have affected the maximum potential of metformin in reducing the non-inflammatory lesion counts at the end of the treatment period. However, the determination of these factors among the treated patients was not part of the present study.

The subjective self-assessment score of change in acne severity was also measured throughout the study and both groups demonstrated a higher score at the end of 18 weeks compared to baseline. At the end of the treatment period, the mean subjective self-assessment scores between the two groups were statistically comparable. Since the patients subjectively gave the scores, the interpretation of clinical improvement varied from one person to another, which may have led to a lack of statistical difference between the two groups.

At the end of the study, the clinical improvement in both groups was evident based on the significant decrease in their daily life quality index (DLQI) scores. The mean DLQI score of 1.75 in the metformin group at week 18 connotes that the condition had no effect or only small effect to the patient's quality of life. The DLQI score of 3.5 in the P group at week 18 connotes only a small effect of the disease in the patient's quality of life. Thus, both groups were statistically comparable. In this study, metformin was added as an adjunct to the standard acne treatment of lymecycline and adapalene+ benzoyl peroxide gel. The P group also received these standard treatments. This can explain why both groups had improvement and statistically comparable DLQI scores at the end of treatment.

The cutaneous adverse effects, such as erythema, pain, scaling, and dryness were reported by the patients in both groups and were generally observed during the few initial weeks of treatment. These cutaneous adverse effects eventually lessened throughout the treatment period. These findings are consistent with general observations that these predictable side effects of topical retinoids, which were given at the beginning of treatment, are temporary, peaking within the first month of use and diminishing thereafter.[39]

The systemic adverse events noted by the patients in both groups were diarrhea and flatulence. Most of these adverse events were observed during the first six weeks of treatment. Although gastrointestinal disturbances have been reported as adverse effects of lymecycline,[12] abdominal discomfort, indigestion, diarrhea, and flatulence are also known adverse effects of metformin. These side effects, however, were tolerable with continued use.[40] Since both metformin and lymecycline were given simultaneously during the first six weeks of treatment, the drug most probably responsible for these adverse events could not be pinpointed.

Other adverse events exclusively observed in the M group were headache and epigastric pain. These were not observed in the P group. Since these are known side effects of metformin, it can be deduced that metformin has probably caused these adverse events. Gastrointestinal side effects of metformin may be addressed by the intake of the drug after meals and by slower titration of its dose. The patients who reported these symptoms claimed that these were not consistent or persistent, resolving spontaneously within the first month without any need for further management. The levels of fasting blood sugar of all subjects who received metformin remained normal by the end of treatment.

The results of this study support the idea that the additon of metformin as adjunct treatment was beneficial in maintaining clearance of acne lesion even after the discontinuation of oral antibiotics. Furthermore, this drug can be used for a long period of time with minimal side effects and without the fear of inducing antibiotic resistance.

CONCLUSION

Metformin is an effective and safe adjunct to oral lymecycline and topical adapalene+benzoyl peroxide gel in the treatment of moderate to severe acne vulgaris.

There was significant reduction of the inflammatory and the total lesion counts, with improvement of the modified global severity scores of acne.

The non-inflammatory lesion count, and subjective self-assessment scores improved in both groups, but they were statiscally comparable at the end of the 18-week period.

There was a significant improvement of the daily life quality in both groups at the end of the 18-week period.

Several cutaneous adverse events, such as erythema, pain, scaling, and dryness of the skin, attributed to topical adapalene and benzoyl peroxide gel were observed in both groups but were self-limited. Systemic adverse events, such as diarrhea and flatulence, were observed in both groups while headache and epigastric pain were only observed with the metformin group. These adverse events were self-limited and did not warrant the discontinuation of the treatment.

LIMITATIONS AND RECOMMENDATIONS

One limiting factor of this study is the long duration of treatment, which could have affected patient compliance to medications and follow-up visits. Other external factors, which are known to have an association with acne, such as diet, stress and smoking can also be included as part of the baseline characteristics.

For future studies, a multicenter randomized controlled trial is highly recommended.

DISCLOSURE

This is an investigator- initiated research trial. The protocol of this study was submitted during the 2013 Asian Acne Board Research Grant competition and the authors were chosen to be the awardees. There is no potential conflict of interest.

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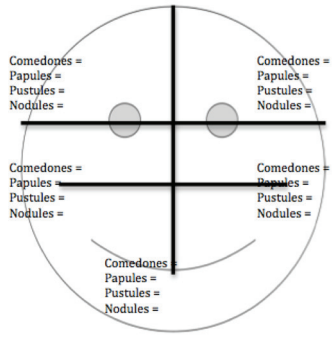
APPENDIX A

Needs Acne Lesion Counting System



Initial	Comedones	Papules	Pustules	Nodules
Left forehead				
Right forehead				
Left cheek				
Right cheek				
Chin				
Total				

APPENDIX B

Modified Global Severity Score

Global Severity Score	Description	Simplified Classification
1	Comedones are the main lesions. < 10 papules and pustules + < 6 nodules	**Mild**
2	<10 papules & pustules + > 6 nodules or 10-40 papules & pustules + < 6 nodules	**Moderate**
3	10-40 papules & pustules + > 6 nodules or 40-100 papules & pustules + < 6 nodules	**Moderately severe**
4	40-100 papules & pustules + > 6 nodules or >100 papules & pustules or Nodulocystic	**Severe**

APPENDIX C

Subjective Self-Assessment Score of Change in Acne Severity

0	Worsened/ *Lumala*
1	No change/ *Walang pagbabago*
2	Mild improvement/ *May konting pagbabago*
3	Moderate improvement/ *May katamtamang pagbabago*
4	Marked improvement/ *May malaking pagbabago*

APPENDIX D

Indeks sa kalidad ng Pamumuhay sa may Sakit sa Balat (IKPAS)41
Dermatology Life Quality Index (DLQI)

Layunin ng pagtatanong ito na masukat ang epekto ng sakit sa balat sa iyong pamumuhay sa **NAKARAANG LINGGO**. Pakimarkahan ng tsek (✔) ang isang sagot sa bawat tanong. Anumang impormasyong nakalathala rito ay mananatiling lihim at ang iyong duktor lamang ang nakaaalam.

The aim of this questionnaire is to measure how much your skin problems has affected your life **OVER THE LAST WEEK**. Please tick £box for each question.

1. *Sa nakaraang linggo, gaano **kakati, kahapdi o kasakit** ang iyong balat?*
   Over the last week, how **itchy, sore, painful or stinging** has your skin been?
   ☐Sobra-sobra ☐Sobra ☐Medyo ☐Wala
   ☐Very much ☐A lot ☐A little ☐Not at all

2. *Sa nakaraang linggo, **nahihiya** ka ba dahil sa iyong balat?*
   Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?
   ☐Sobra-sobra ☐Sobra ☐Medyo ☐Wala
   ☐Very much ☐A lot ☐A little ☐Not at all

3. *Sa nakaraang linggo, gaanong abala ito sa iyong pag-**shopping** o **pamamalengke** o **gawaing bahay**?*
Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?

☐Sobra-sobra ☐Sobra ☐Medyo ☐Wala
☐Very much ☐A lot ☐A little ☐Not at all

4. *Sa nakaraang linggo, naaperktuhan ba ang iyong **pananamit** nito?*
Over the last week, how much has your skin influenced the **clothes** you wear?

☐Sobra-sobra ☐Sobra ☐Medyo ☐Wala
☐Very much ☐A lot ☐A little ☐Not at all

5. *Sa nakaraang linggo, paano naapektuhan ang iyong gawaing **pansosyal** o pan**libangan** (halimbawa, panunood ng sine) ng dahil sa iyong sakit sa balat?*
Over the last week, how much has your skin affected any **social** or **leisure** activities?

☐Sobra-sobra ☐Sobra ☐Medyo ☐Wala
☐Very much ☐A lot ☐A little ☐Not at all

6. *Sa nakaraang linggo, gaano kang nahirapan sa paglaro ng anumang **isport** o paggawa ng anumang **ehersisyo** ng dahil sa iyong sakit sa balat?*
Over the last week, how much has your skin made it difficult for you to do any sport?

☐Sobra-sobra ☐Sobra ☐Medyo ☐Wala
☐Very much ☐A lot ☐A little ☐Not at all

7. *Sa nakaraang linggo, napigilan ka bang makapag**trabaho** o makapag **aral** ng dahil sa iyong sakit sa balat?*
Over the last week, has your skin prevented you from **working** or **studying**?

☐Oo ☐Hinde ☐Walang kinalaman
☐Yes ☐No ☐Not relevant

*Kung "Hindi" ang sagot, gaanong nakaapekto sa iyong **trabaho** o pag- a**aral** ang iyong sakit sa balat sa nakaraang linggo?*
If no, over the last week how much has your skin been a problem at **work** or **studying**?

☐Sobra-sobra ☐Sobra ☐Medyo ☐Wala ☐Walang kinalaman
☐Very much ☐A lot ☐A little ☐Not at all ☐Not relevant

8. *Sa nakaraang linggo, paano naging problema sa iyong **partner** o matalik na **kaibigan** o **kamag-anak** ang iyong sakit sa balat?*
Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?

☐Sobra-sobra ☐Sobra ☐Medyo ☐Wala ☐Walang kinalaman
☐Very much ☐A lot ☐A little ☐Not at all ☐Not relevant

9. *Sa nakaraang linggo, gaanong nakaapekto sa pakikipagtalik (**sex**) ang iyong sakit sa balat?*
Over the last week, how much has your skin caused any ***sexual difficulties***?

☐Sobra-sobra ☐Sobra ☐Medyo ☐Wala ☐Walang kinalaman
☐Very much ☐A lot ☐A little ☐Not at all ☐Not relevant

10. *Sa nakaraang linggo, paano naging problema ang **paggamot** ng iyong sakit sa balat, halimbawa, dahil sa idinulot nitong kalat sa bahay o sa pagkaubos ng iyong oras na iyong inuukol dito?*
Over the last week, how much of a problem has the **treatment** for your skin been, for example, by making your home **messy**, or by taking up your time?

☐Sobra-sobra ☐Sobra ☐Medyo ☐Wala
☐Very much ☐A lot ☐A little ☐Not at all

Paki-tsek kung nasagot mo ang lahat ng tanong. Maraming salamat!
Please check that you have answered EVERY question. Thank you.

APPENDIX E

Dermatology Life Quality Index Scoring System

The scoring of each question is as follows:

Very much / *Sobra-sobra*	Scored 3
A lot / *Sobra*	Scored 2
A little / *Medyo*	Scored 1
Not at all / *Wala*	Scored 0
Question unanswered / *Walang kinalaman*	Scored 0
Question 7: "prevented work or studying" / "*nakaapekto sa iyong trabaho o pag-aaral"*	Scored 3

The sum of the score of each question results to a DLQI maximum score of 30 and a minimum of 0. A higher score means there is more impairment of the quality of life.

Interpretation of DLQI Scores
0-1 = no effect at all on patient's life
2-5 = small effect on patient's life
6-10 = moderate effect on patient's life
11-20 = very large effect on patient's life
21-31 = extremely large effect on patient's life

APPENDIX F

Participant Information Sheet/ Talaan ng Impormasyon Para sa Pasyente

Title of the Study/ Pamagagat ng Pananaliksik:

Double-blind randomized controlled trial on the efficacy and safety of metformin as adjunct to lymecycline and adapalene 0.1% + benzoyl peroxide 2.5% gel in the treatment of moderate to severe acne

If you have questions about this study after reading this information sheet, you may contact the primary investigator at cellphone number ____or office number _____.

The IRB of the tertiary hospital has approved this study. For any inquiries regarding your rights as a study participant, including grievances and complaints, you may contact the IRB chair at the IREC office, _____at _____or you can send an email at _____.

All serious adverse events encountered within the study period should be reported within 24 hours to the primary investigator, as well as to the Ethics Review Board of the tertiary hospital.

Kung mayroon kayong pag-aalinlangan tungkol sa pag-aaral pagkatapos basahin ang talaang ito, makipag- ugnayan sa pangunahing tagapagsaliksiki na si Dr._____ sa numerong _____ (cellphone) o _____.

Ang pananaliksik na ito ay aprubado ng IRB ng ospital. Para sa anumang katanungan tungkol sa iyong karapatan bilang kalahok sa pananaliksik na ito, maari mong tawagan si _____ sa IREC office_____ sa numerong _____or maaari kang magpadala ng liham sa_____.

Lahat ng mga hindi kanais-nais na epektong maaring maranasan sa pananaliksik na ito na maaring magdulot ng pagkamatay o nangangaliangan ng ospitalisasyon ay karapat-dapat na ipagbigay-alam sa pangunahing tagapagsaliksik at sa Institutional Review Board (IRB) ng ospital sa loob ng 24 oras.

Introduction/ *Panimula*:

You are invited to join a research. It is important for you to know the details of this study so that you may fully understand the role you will assume and the risks you will undertake, should you decide to participate. You may ask questions if there is anything unclear to you. Once you have read and understood all the information presented to you, and you decide to join this study,

you may then provide your informed and written consent after showing a government-issued ID for identification purposes.

Ikaw ay inaanyayahang makilahok sa isang pananaliksik. Mahalagang malaman mo ang kabuuang detalye ng pananaliksik na ito upang lubusan mong maunawaan ang iyong gagampanang papel at ang mga posibleng panganib na dulot ng iyong pagsali. Maaari kang magtanong kung mayroong hindi naiintindihan. Pagkatapos basahin at unawain ang lahat ng impormasyon na inihayag sa iyo at napagpasyahan mong sumali sa pananaliksik na ito, maaari ka nang magbigay ng pahintulot ng inyong pagpayag sa pagsalipagkatapos magpakita ng isang "ID" bilang tanda ng inyong pagkatao.

Purpose of the Study/ *Layunin ng Pananaliksik*:

Acne vulgaris is a common ailment that afflicts all ages, particularly adolescents and young adults. Aside from being a cosmetic problem, the burden of this disease arises especially when it leads to depression, low self-esteem, and isolation from society.

There are many forms of treatment that have been prescribed for acne. These include topical treatments such as adapalene and benzoyl peroxide, oral medications such as antibiotics (lymecycline), and combinations of these. However, there is still dissatisfaction in treatment among both clinicians and patients. There is thus a need for treatment alternatives.

Metformin is an FDA-approved drug used in the treatment of diabetes. At present, it is not yet approved for use in acne. However, recent studies show that metformin may also have an effect on Fox01, the same transcription factor that is important in the pathogenesis of acne.

The purpose of this study is to determine if metformin is safe and effective as an adjunct to lymecycline and topical adapalene+ benzoyl peroxide in the treatment of acne vulgaris. At least 34 patients diagnosed with acne vulgaris will be recruited to participate in this study. This study will last for 1 year.

Ang tigyawat ay isang pangkaraniwang kondisyon na nakikita sa kahit anong edad, lalung-lalo na sa mga nagbibinata/nagdadalaga. Bukod sa pagiging sakit sa balat, ang higit na pasanin ng kondisyong na ito ay ang pagdulot ng depresyon, pagkababa ng tingin sa sarili, at pagbukod mula sa komunidad.

Maraming mga gamut na ibinibigay para sa tigyawat. May mga pinapahid na gamut tulad ng "adapalene" at "benzoyl peroxide", at iniinom tulad ng mga "antibiotic" ("lymecycline"), at mga kombinasyon ng mga gamot na ito. Subalit mayroon paring hindi pagkakuntento ng mga manggagamot at pasyente sa lunas na ibinibigay ng mga ito. Dahil dito, kinakailangan pa rin ng mga alternatibong gamot.

Ang "metformin" ay gamot na naaprubahan ng FDA sa paggamot ng sakit na "diabetes". Sa kasalukuyan, hindi pa ito naaprubahang gamitin para sa tigyawat. Ngunit mayroong mga bagong pagsisiyasat na nagsasaad na may epekto din ito sa Fox01, isang "transcription factor" na may kabuluhang bahagi sa pagkakaroon ng tigyawat.

Ang layunin ng pagsisiyasat na ito ay alamin kung ang pag-inom ng "metformin", kasama ng "lymecycline" at pagpahid ng "adapalene+ benzoyl peroxide", ay ligtas sa masamang epekto at epektibo sa paggamot ng tigyawat. Tatlumpu't- apat na pasyenteng may tigyawat ang isasali sa pananaliksik na ito. Ang pananaliksik na ito ay magtatagal ng isang taon.

Study Procedure/ *Pamamaraan ng Pananaliksik*:

Before joining this study, your serum fasting blood sugar, and creatinine will be taken. This

will involve fasting for 6-8 hours, as well as pain and discomfort during the drawing of blood. If female, a pelvic ultrasound and a pregnancy test will be done to rule out ovarian pathology and pregnancy, respectively. The pelvic ultrasound may involve pain and discomfort due to insertion of an ultrasound head by the transvaginal or transrectal route. If results are normal for all these tests, you will be included in the study. Otherwise, you will be referred to a medical internist or obstetrician-gynecologist, respectively. You will receive treatment that comprises of topical adapalene + benzoyl peroxide gel to be applied nightly, lymecycline 300mg/capsule 1capsule once daily, and either metformin (Glumet) 500mg/tablet or placebo tablet (a medication that does not contain an active drug), 1 tablet thrice a day. You will not be informed if you will be receiving metformin or placebo, until the study is completed. You will be asked to follow-up every 2 weeks for a total duration of 18 weeks. Your photographs will be taken at each follow-up visit, so that your response to treatment can be monitored. Your eyes will be covered in order to protect their identity. All information, including your identity, will be kept confidential.

Bago sumali, kukunan ka ng dugo para malaman ang iyong "fasting blood sugar" at "creatinine". Hindi maaaring kumain o uminom ng 6-8 na oras bago ka kunan ng dugo, at maaaring makaramdam ng sakit dahil sa pagturok. Para sa mga babae, sasailalim sa "pelvic ultrasound" upang siguraduhin na walang sakit sa mga obaryo, at "pregnancy test" upang siguraduhin na walang pagbubuntis. Ang "transvaginal o transrectal ultrasound" ay maaaring magdulot ng sakit o pagkabalisa dahil kinakailangang padaanin ang "ultrasound head" sa puwerta o sa puwit. Kung normal ang mga resulta nito, maaari nang sumali sa pag-aaral.

Kung hindi, ikaw ay bibigyan ng sangguni sa "medical internist" o "obstetrician-gynecologist". Ikaw ay bibigyan ng "adapalene+ benzoyl peroxide" na ipapahid sa mukha kada gabi, lymecycline 300mg/capsule, 1 kapsula isang beses sa isang araw, at metformin (Glumet) 500mg/tableta o kaya "placebo tablet" (isang medikasyon na hindi naglalaman ng aktibong gamot) 1 tableta tatlong beses sa isang araw. Hindi mo malalaman kung ikaw ay makakatanggap ng "metformin" o "placebo", hangga't matapos ang pag-aaral. Ikaw ay kokonsulta sa amin kada dalawang linggo sa loob ng labingwalong linggo. Kukuhanan ka ng mga litrato sa bawat konsulta, para masubaybayan ang mga pagbabago habang ikaw ay nagpapagamot. Ang mga mata ng mga kalahok ay tatakpan upang maprotektahan ang kanilang pagkakakilanlan. Lahat ng impormasyon, pati ang iyong pagkakakilanlan, ay ililihim sa iba.

Risks of Participation/ *Panganib ng Pagsali*:

Metformin should be used with caution in patients with heart disease, renal impairment, and stress-related states like fever, trauma, infection or surgery. Side effects may include anorexia, headache, lightheadedness, nausea, vomiting, abdominal discomfort, indigestion, diarrhea, weight loss, flatulence, occasional metallic taste, weakness, hypoglycemia, rash, vitamin malabsorption, chest discomfort, flushing, palpitations, chills, and lactic acidosis in the presence of renal failure and alcoholism.

Lymecycline should be avoided in pregnancy, lactation, porphyria, tetracycline hypersensitivity, severe hepatic dysfunction, and those with prolonged exposure to sunlight. It should be used with caution in those with impaired hepatic function and in those with history or predisposition to oral candidiasis. Side effects include permanent staining of teeth, glossitis, rash, superinfection, nausea, dysphagia, gastrointestinal disturbances, photosensitivity, blood dyscrasias and anaphylaxis.

Adapalene cannot be given to pregnant women because it may cause fetal harm. It should not be used on those with retinoid hypersensitivity, nor should it be applied on eczematous, sunburned or abraded skin. Sunlight exposure during use should be avoided. Side effects include pain, redness, dryness and scaling of skin, which will be monitored at every follow-up visit. Benzoyl peroxide

can cause local irritation and contact allergy.

Due to the risks and harms aforementioned, pregnancy should be avoided during the entire 18-week duration of the study. Natural methods of birth regulation such as abstinence and the rhythm method may be practiced. A pregnancy test will be done once every month for sexually active women of reproductive age. If pregnancy is detected, all medications will be immediately discontinued, and you will be referred to an obstetrician-gynecologist. If the above measures are followed and the subject still gets pregnant, the investigator, sponsor and the institution will not be held liable.

The study may be discontinued once periodic assessment reveals definite harm or lack of benefit of the experimental drug (metformin).

Any other clinically important findings should be reported to the investigator, so that the appropriate and necessary management may be performed. In the event that you experience any adverse reactions during the course of this research, immediately get in touch with the investigator.

Kinakailangang maingat ang paggamit ng "metformin" sa mga may sakit sa puso o bato, sa panahon ng paglalagnat, "trauma", impeksyon at siruhiya. Ang mga hindi kanais-nais na epektong maaaring maidulot ng pag-inom nito ay ang pagkawalang ganang kumain, sakit ng ulo, pagkahilo, pagsusuka, pananakit ng tiyan, hindi pagkatunaw ng pagkain, pagtatae, pangangayayat, kabag, pagbabago sa panlasa, panghihina, pagbaba ng "blood sugar", pagpapantal o pagbubutlig ng balat, "malabsorption" ng bitamina, paninikip ng dibdib, pamumula, pagkabog ng dibdib o kaba, pangingiki, at "lactic acidosis" sa mga may sakit sa bato at sa mga manginginum ng alak.

Ang "lymecycline" ay hindi dapat ginagamit ng buntis, sa mga nagpapasuso, sa may mga sakit na "porphyria", sa mga nagkakaroon ng masamang reaksyon sa pag-inom ng mga "tetracycline", malubhang sakit sa atay, at sa mga laging nagbibilad sa araw. Maingat ang paggamit ng "lymecycline" sa mga may sakit sa atay, at mga taong nagkakaroon o madaling magkaroon ng "oral candidiasis". Ang mga hindi kanais-nais na epektong maaaring maidulot ng pag- inum nito ay ang pagbabago ng kulay ng ngipin, pamamaga ng dila, pamamantal o pagbubutlig ng balat, impeksyon, pagkahilo, hirap sa paglunok, pananakit ng tiyan, reaksyon sa pagbilad sa araw, mga pagbabago sa dugo o "blood dyscrasias", at "anaphylaxis" o matinding reaksyon sa gamot na maaaring humantong sa pagkamatay kung hindi maaagapan.

Ang "adapalene" ay hindi maaaring ibigay sa mga buntis dahil maaari itong magbigay ng masamang epekto sa sanggol na nasa sinapupunan. Hindi ito dapat gamitin sa mga taong may dating reaksyon sa "retinoid"at hindi dapat ipahid sa balat na may eksema, balat na nasunog sa pagkabilad sa araw, o sa balat na nasugatan. Dapat iwasan ang pagpapaaraw habang gamit ito. Ang mga hindi kanais-nais naepekto ng pagpahid nito ay pagkahapdi, pamumula, pagkatuyo, at pangangaliskis ng balat na babantayan sa kada bisita sa doktor. Ang "benzoyl peroxide" ay pwedeng magdulot ng iritasyon sa balat na pinagpahiran at "contact allergy".

Dahil sa mga panganib na naisaad, hindi maaaring magbuntis habang hindi pa natatapos ang 18 na linggong pananaliksik na ito. Maaaring gumamit ng mga natural na pamamaraan ng pag-iwas sa pagbubuntis, gaya ng pagpipigil ("abstinence") at "rhythm method". Para sa may posibilided na mabuntis, uulitin ang pregnancy test, isang beses sa kada buwan ng pagsali. Kung sakaling mabuntis habang nakikilahok sa pananaliksik na ito, lahat ng gamot ay ititigil at isasangguni ka sa isang "obstetrician-gynecologist". Kung sakaling mabuntis sa kabila ng pagsunod sa mga nabanggit na pamamaraan, ang pangunahing tagapagsaliksiki, sponsor at ang institusyon ay walang pananagutan.

Ang iba pang importanteng mga resulta o reaksyon na iyong makikita sa pagsisiyasat na ito ay dapat na ipaalam sa amin upang ito ay agad na matugunan at mabigyang lunas. Kung sakaling makaramdam ka ng kahit anong hindi magandang reaksyon sa gamot, ipagbigay alam agad sa may akda.

Benefits of Participation/ *Benepisyo ng Pagsali*:

The information obtained from your participation will be invaluable in the research for treatment alternatives for acne vulgaris. Laboratory examinations (fasting blood glucose, serum creatinine, transvaginal/transrectal ultrasound, pregnancy test), consultations and medications will be provided free of charge. Any study-related injury or illness that will be incurred as a result of your participation in the study will be given appropriate treatment, free of charge.

Ang impormasyong nakukuha sa inyong pagsali ay napakahalaga sa paghahanap ng alternatibong gamot para sa tigyawat. Ang mga pagsusuring laboratoryo (fasting blood glucose, serum creatinine, transvaginal/transrectal ultrasound, at pregnancy test), konsultasyon at mga gamot ay walang bayad. Anumang hindi kainais-nais na epektong mararanasan ng pasyente sa pakikilahok sa pananaliksik na ito ay bibigyang kaukulang gamot / proseso nang walang bayad.

Compensation/ *Kompensasyon*:

All of the laboratory examinations (fasting blood glucose, serum creatinine, transvaginal/ transrectal ultrasound, pregnancy test), consultations, and medications that you will receive will be free of charge. No compensation will be provided for your participation. You will be given Php 20 for transportation expenses for every visit. You will be informed of the results of the research once it has been completed.

Ang lahat ng pagsusuring pang-laboratoryo ("fasting blood glucose", "serum creatinine", "transvaginal/ transrectal ultrasound "," pregnancy test"), konsultasyon, at mga gamot na inyong matatanggap ay walang kapalit na halaga. Ang inyong pakikilahok sa pananaliksik naito ay wala ring kabayaran. Ikaw ay bibigyan ng halagang Php 20 para sa iyong pamasahe kada pagbisita sa klinika Ipapaalam sa iyo ang mga resulta ng pananaliksik na ito sa katapusan ng pagsisiyasat.

Right to Refuse Participation and to Withdraw/ *Karapatang Tumanggi o Bawiin ang Pagsali*:

Participation in this study is completely voluntary. You are free to decline if you wish, and you may withdraw anytime during the study. Refusal to participate will not affect the attitude, care and treatment that you will receive from your physician. Should you decide to take part in this study, you will have to sign this form, which states that you have given your free and informed consent to participate. You shall receive a copy of the signed and dated written consent form.

Sadyang kusang-loob ang iyong pakikilahok sa pananaliksik na ito. Malaya kang tumanggi sa pagsali at magbago ng isip sa anumang sandali ng iyong pagsali. Ang hindi pagsali ay hindi makakaapekto sa pakikitungo, pangangalaga at paggamot sa iyo ng iyong doktor. Kung magdedesisyong sumali, kinakailangang pumirma sa kaukulang dokumento bilang tanda ng iyong pag-intindi at malayang pahintulot sa pagsali. Ikaw ay makakatanggap ng kopya ng nalagdaan na katibayan ng pagpayag ng pasyente.

Confidentiality/ *Kompidensiyalidad*:

Information collected in this study will be kept confidential. Your records, to the extent of the applicable laws and regulations, will not be made publicly available. However, the Institutional Ethics Review Board will be granted direct access to your original medical records to check study

procedures and data, without making any of your information public. By signing the Informed Consent Form attached, you are authorizing such access to your study and medical records. Data collected and entered are the property of our institution. In the event of any publication regarding this study, your identity will remain confidential.

Ang lahat ng impormasyong makukuha sa pananaliksik na ito ay pananatilihing lihim. Idodokumento ito nang walang pagkakakilanlan at hindi malalaman ninuman ang anumang impormasyon hinggil sa katauhan mo. Tanging ang manggagamot lamang ang maaaring makaalam ng iyong pansariling impormasyon. Pananatilihing lihim ang lahat ng makukuhang impormasyon sa ilalim ng pamantayang makaagham ng etika. Ang paglilipat ng iyong datos sa loob o maging sa labas ng bansa ay para lamang sa layuning makaagham at mananatiling lihim ang iyong pagkakakilanlan.

APPENDIX G

PATIENT CONSENT FORM
Katibayan ng Pagpayag ng Pasyente

Protocol Title/ *Titulo ng Pag-aaral*:

Double-blind randomized controlled trial on the efficacy and safety of metformin with lymecycline and topical adapalene+benzoyl peroxide gel vs. lymecycline and topical adapalene + benzoyl peroxide gel in the treatment of moderate to severe acne

I voluntarily consent to take part in this study. This study has been explained to me in a language that I understand. The purpose and procedures of this study have been fully discussed and understood by me. I have been given enough time to ask any questions that I have about the study, and all my questions have been answered. I am aware that I may harm myself if I do not fully cooperate with the investigator's instructions.

I, hereby, give my consent that photographs of me be taken at each follow-up visit so that response to treatment can be monitored, provided that my identity be kept confidential.

Ang impormasyon sa talaan na ito ay aking nabasa at ipinaliwanag nang mabuti sa akin. Naintindihan ko ang lahat ng gagawin sa pag-aaral na ito. Nakapagtanong ako tungkol sa mga proseso at nasagot naman nang lubusan ang aking mga katanungan. Kusa akong sumasang-ayon na lumahok sa pag-aaral na ito. Sumasang-ayon din ako na gawin ang mga nakasulat sa talaan na ito. Naiintindihan kong ang hindi pagsunod sa mga alituntunin ng tagapagsuri ay maaaring magdulot ng sariling kapahamakan.

Ako ay sumasang-ayon sa pagkuha ng aking mga litrato sa bawat konsultasyon ko upang masubaybayan ang mga pagbabago sa aking paggamot sa kasunduang mapapanatiling lihim ang aking pagkakakilanlan.

_____	_____	_____
Patient / Pasyente	Signature / Lagda	Date/ Petsa

For patients of minor age (15-17 years old)
Para sa mga minor de edad (edad na 15 taon-17 taon)

_____	_____	_____
Patient / Pasyente	Signature / Lagda	Date/ Petsa
_____	_____	_____
Father/ Legal representative/ Ama/ Legal na Tagapangalaga	Signature / Lagda	Date/ Petsa
_____	_____	_____
Mother/ Legal representative Ina/ Legal na Tagapangalaga	Signature / Lagda	Date/ Petsa

For female patients of reproductive age with married status
Para sa mga pasyenteng may asawa at maaaring mabuntis

I am aware that my spouse has agreed to participate in this study where pregnancy is a contraindication. I understand and will participate in the use of natural methods of birth regulation for the entire duration of the study.

Napagbigay-alam sa akin ang pakikilahok ng aking asawa sa pagsisiyasat na kung saan bawal ang pagbubuntis. Sumasang- ayon ako at makikilahok sa pamamagitan ng mga natural na paraan ng pag-iwas sa pagbubuntis hangga't hindi pa natatapos ang pagsisiyasat na ito.

_____	_____	_____
Spouse/ Asawa	Signature / Lagda	Date/ Petsa

Witness Statement/ *Saksi*

I, the undersigned, certify to the best of my knowledge that the participant signing this informed consent form had the study fully explained in a language understood by him / her and clearly understands the nature, risks and benefits of his / her participation in the study.

Pinapatunayan ko na naipaliwanag ng mabuti at naintindihan ng pasyente ang proseso, benepisyo at panganib ng pagsusuring ito.

_____	_____	_____
Witness/ Saksi	Signature / Lagda	Date/ Petsa

Investigator Statement/ *Tagapagsuri*

I, the undersigned, certify that I explained the study to the participant. To the best of my knowledge

the participant signing this informed consent form clearly understands the nature, risks and benefits of his/her participation in the study.

Pinapatunayan ko na naipaliwanag ko at naintindihan ng pasyente ang proseso, benepisyo at panganib na maaaring idulot ng pagsusuring ito.

_____	_____	_____
Investigator/ Tagapagsuri	Signature / Lagda	Date/ Petsa

APPENDIX H

DATA COLLECTION SHEET

Initial Consultation

Name		Study No.
Address		Contact No.
Age	Sex	Date Enrolled __/___/20
Weight(kg)	Height (cm)	BMI (kg/m2)
Pregnancy +/-/NA		Polycystic ovaries +/-/NA
Initial FBS mg/dl Normal/High/Low		Initial creatinine Normal/High/Low
Final FBS mg/dl Normal/High/Low		Final creatinine Normal/High/Low

Follow-up visits

Week	Date	Wt	BMI	Total Comedones	Total Papules	Total Pustules	Total Nodules	Total Lesions	Global Score	Subjective Grade	DLQI
Initial											
2											-
4											-
6											
8											-
10											-
12											
14											-
16											-
18											

Adverse Effects Monitoring

Week	Date	Erythema	Pain	Scaling	Dryness	Others
2						
4						
6						
8						
10						
12						
14						
16						
18						

None (0), Mild (1), Moderate (2), Severe (3)