Contraception

Contraception 90 (2014) 535–541

Original research article

A comparison of multiphasic oral contraceptives containing norgestimate or desogestrel in acne treatment: a randomized trial ☆,☆☆,★

Unnop Jaisamrarn[a,*], Somsak Chaovisitsaree[b], Surasak Angsuwathana[c], Osot Nerapusee[d]

[a]Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[b]Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand
[c]Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand
[d]Medical Affairs, Janssen-Cilag, Bangkok, Thailand

Received 31 December 2013; revised 28 May 2014; accepted 5 June 2014

Abstract

Objective: This study aimed to compare the effectiveness and safety of triphasic combined oral contraceptives (OCs) containing ethinyl estradiol (EE) and norgestimate (NGM) and biphasic combined OCs containing EE and desogestrel (DSG) in the treatment of mild to moderate acne.
Study design: This was an investigator-blinded, randomized, parallel group trial conducted at 3 centers in Thailand. Female subjects 18–45 years old were assigned to one or the other OCs and evaluated for efficacy and safety parameters at the baseline visit and after 1, 3 and 6 months of treatment.
Results: Among 201 randomized subjects, data from 93 subjects in the EE/NGM group and 95 subjects in the EE/DSG group were analyzed. After 6 months of treatment with EE/NGM and EE/DSG, no differences between formulations were found for the decrease in total acne lesion counts (74.4% vs. 65.1%, respectively, p=.070) or facial improvement score. More women using EE/NGM showed a decrease in severity of facial seborrhea than those using EE/DSG (p=.005). No changes in weight were noted in either group as compared to baseline.
Conclusion: Multiphasic OCs containing EE/NGM and EE/DSG provided comparable efficacy and tolerability in the treatment of acne. However, EE/NGM had a more beneficial effect on facial seborrhea reduction than EE/DSG.
Implications: EE/NGM and EE/DSG are multiphasic OCs, which were shown to be clinically equally effective for mild to moderate facial acne, and the multiphasic combined OC with NGM was more effective for women with facial seborrhea. Clinicians may apply the results of this study when considering treatment options for facial acne and seborrhea.

Keywords: Triphasic oral contraceptive; Biphasic oral contraceptive; Acne lesion; Facial seborrhea

1. Introduction

Acne vulgaris is a skin disorder caused by many factors including increased sebum production (seborrhea), follicular hyperkeratinization, infection with *Propionibacterium acnes* and release of inflammatory mediators, resulting in comedones, papules, pustules and nodules [1]. Various medications targeting different mechanisms are used for acne treatment [2]. Androgen levels may affect the development of acne by causing an increase in sebum production [3]. Therefore, reduction of free serum androgen levels is one of the treatment options.

☆ Source of funding and other support: This study was sponsored by Janssen-Cilag Thailand.
☆☆ Disclosure statement: Osot Nerapusee is an employee of Janssen-Cilag and owns stock options at Johnson & Johnson. Other authors declared no conflicts of interest in conducting this study.
★ ClinicalTrials.gov Identifier: NCT01466673.
* Corresponding author. Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. Tel.: +66-2-256-4288.
E-mail addresses: Unnop.J@Chula.ac.th, dr.unnop@yahoo.com (U. Jaisamrarn).

http://dx.doi.org/10.1016/j.contraception.2014.06.002
0010-7824/

The combined oral contraceptives (OCs) containing estrogen and progestin is one of the options for acne treatment. Ethinyl estradiol (EE) may directly oppose androgens at the local level resulting in reduced sebum production and reduced sebaceous gland growth. It provides negative feedback on the pituitary/hypothalamus that leads to decreased ovarian production of the testosterone, and it increases sex hormone binding globulin (SHBG), thus decreasing free testosterone available to bind with the androgen receptor [4]. In contrast, progestins exert a wide spectrum of effects on acne. First- and second-generation progestins that bind to the androgen receptor with a relatively high affinity may aggravate acne, whereas the newer-generation progestins norgestimate (NGM) and desogestrel (DSG) manifest reduced androgen receptor binding [5] and thus may have beneficial effects on acne by minimizing androgenic effects.

Triphasic OCs attempt to mimic the hormonal fluctuations of the menstrual cycle more accurately than older regimens [6] and with a lower total monthly steroid dosage. NGM is the progestin component of EE/NGM, a triphasic OC formulation. Apart from the antiandrogenic effect of EE, NGM, a gonane progestin with low androgenicity and minimal antiestrogenic potential, binds to progestin receptors selectively and has negligible affinity for androgen receptors. Its ratio of androgen to progestin activity and that of its major metabolite, 17-deacetylated norgestimate (norelgestromin), is lower than other currently available progestins [7]. In addition, there are two randomized, double-blind, placebo-controlled trials showing the efficacy of triphasic EE/NGM on moderate acne [8,9].

DSG is the progestin component of EE/DSG, a biphasic OC formulation. DSG is reported to be a highly selective progestin with minimal androgenic activity [10]. Combined with EE, the improvement of mild to moderate acne is related to a significant increase of SHBG and a reduction of free testosterone levels [11,12].

Relatively few combined OC products are licensed for use in acne vulgaris. It would therefore be useful for clinicians to have empirical evidence concerning available medicines when selecting the appropriate treatment for their patients. Since there is no study comparing the clinical effects of EE/NGM and EE/DSG, this head-to-head study aimed to show the effectiveness and safety of triphasic EE/NGM in comparison to biphasic EE/DSG on facial acne in women who require contraception.

2. Materials and methods

2.1. Study design

This study was an investigator-blinded, randomized, parallel group study conducted from December 2008 to March 2010 at the Family Planning Clinics of three university hospitals in Thailand (Chulalongkorn University, Siriraj Hospital of Mahidol University and Chiang Mai University). The investigator was unaware of the type of medication being provided to the subjects and assessed facial acne and seborrhea while blinded in this way. The study medications were dispensed by the study nurse. The investigator remained blinded during data analysis. The study was approved by the ethics committees in all study centers and was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

2.2. Treatment

Subjects were randomly assigned in a 1:1 ratio to each group according to a pregenerated permuted block randomization scheme. Subjects in the EE/NGM group received triphasic EE/NGM treatment at the dosage of 0.035/0.18, 0.035/0.215 and 0.035/0.25mg on days 1–7, 8–14 and 15–21, respectively, and took inactive tablets for 7 days before starting the next treatment cycle. Subjects in the EE/DSG group received biphasic EE/DSG treatment at the dosage of 0.04/0.025 and 0.03/0.125mg on days 1–7 and 8–22 of each cycle, respectively, and discontinued treatment for 6 days before starting the next treatment cycle. Subjects received their allocated treatment for 6 cycles.

2.3. Subjects

Eligible subjects for inclusion were healthy females aged between 18 and 45 years with mild to moderate acne vulgaris [13]. Mild acne vulgaris was defined as having no more than 5 comedones or papules and no pustule while moderate acne vulgaris was defined as 6–15 comedones or papules and/or a maximum of three pustules. Subjects signed and dated an informed consent to participate in the study and agreed to take the supplied study drug as their only treatment for acne during the 6 months of this study. Excluded were subjects who were pregnant or breastfeeding or who had experienced hypersensitivity to EE, NGM, DSG or any of the study medication ingredients. Other exclusion criteria were the use of a concomitant medication that was likely to interfere with the safety of EE/NGM and or EE/DSG, the use of topical acne treatments, systemic antimicrobials or a systemic retinoid within 2 weeks, 1 month and 6 months prior to enrollment, respectively, and having a contraindication to OCs.

2.4. Clinical assessments

Subjects were evaluated for efficacy and safety parameters at the baseline visit and during the three treatment visits after 1, 3 and 6 months of treatment. The efficacy and safety parameters including body weight, body mass index (BMI), vital signs (body temperature, blood pressure, pulse rate and respiratory rate), acne lesion counts, facial sebum output, adverse events and concomitant medications were recorded at each treatment visit. Each type of lesion including comedones, papules, pustules and nodules was counted separately. The summation of all lesion counts was the total lesion count. Sebum output was assessed by using sebum

collecting devices (SEBUTAPE® skin indicators: CuDerm Corp., Dallas, TX, USA) on the forehead. The samples were evaluated by comparing them with reference patterns and were classified into 5 levels ranging from 1 (lowest) to 5 (highest). Data on bleeding and spotting were recorded throughout the study period. Compliance with treatment was assessed using the patients' diary cards. In addition, unused study medications were collected with drug accountability documented. At the final visit, after 6 months of treatment, a physical examination was performed and the self-assessment questionnaire was completed. The therapeutic effect of treatment of acne and seborrhea was categorized by investigators as "excellent", "good", "fair", "no change" or "worse" and categorized retrospectively by subjects using a self-assessment questionnaire as "much improved", "somewhat improved", "not improved", "worse" or "much worse".

2.5. Statistical analysis

The percentage change in total lesion count from baseline to cycle 6 was assessed by a two-sided *t* test and change in facial seborrhea levels was assessed by the Wilcoxon rank sum test at a significance level of 5%. To assess any significant difference in the numbers of adverse events and breakthrough bleeding and spotting while taking the medication, Fisher's exact test was used. The SAS® version 9.1.3 software suite was used for statistical analyses.

All randomized subjects who received at least one dose of study medication and fulfilled all inclusion and exclusion criteria were included in the intention-to-treat (ITT) population. All subjects in the ITT population who completed the study without major protocol deviations were included in the per protocol (PP) population. Data collected for the PP population were analyzed for efficacy endpoint assessments while the data from the ITT population were used for safety and tolerability assessments.

2.6. Sample size calculation

The sample size was determined by a decrease in comedone counts based on a study of EE/DSG in the treatment of acne [14], which showed that the number of comedones was decreased by 37% at the last visit (after 6 cycles) from baseline with 80% power and detected a type I error of 0.05 (two-sided). To prevent uncertainty from treatment failure and loss to follow-up, the sample size was increased by 20% and thus it was determined that a total of 200 subjects were needed to be randomized to treatment.

3. Results

3.1. Subjects

In total, 203 Thai women were screened, of whom 201 were randomized to receive either EE/NGM (*n*=100) or EE/DSG (*n*=101). One screened patient entered another trial and therefore did not participate in this trial. Another patient declined to participate without giving a reason. For subjects' baseline characteristics, there were no significant differences in age, body weight or BMI between the two treatment groups (Table 1). Premature discontinuation of study medication was reported in 7 subjects (7.0%) in the EE/NGM group and 6 subjects (5.9%) in the EE/DSG group. The reasons for premature discontinuation of study medication in the EE/NGM and EE/DSG, respectively, were poor compliance (2 and 0 subjects), discomfort from adverse events (2 and 1 subjects) and lost to follow-up with reason unknown (3 and 5 subjects). In total, 93 subjects from the EE/NGM group and 95 subjects from the EE/DSG group completed the study (Fig. 1). Regarding the treatment compliance, there was no significant difference between the two groups. The percentages of patients who missed one or more doses in months 1, 3 and 6 ranged from 7.0% to 13.9% for the EE/NGM group and from 4.9% to 10.4% for the EE/DSG group. Average numbers of days per month of missed drugs (in months 1, 3 and 6) ranged from 1.5 to 3.0 days for the EE/NGM group and from 1.6 to 3.0 days for the EE/DSG group.

3.2. Efficacy

Numbers of each type of acne lesion and the total lesion count at each visit and after 6 months of treatment are shown in Table 2. The total lesion count continuously decreased throughout the 6 months of treatment in both treatment groups compared to baseline. The relative decrease from baseline to cycle 6 in the mean percentage of total lesion count in EE/NGM and EE/DSG was 74.4% and 65.1%, respectively, with mean difference of 9.28 (95% confidence interval, −0.78 to 19.34; p=.070) (Fig. 2).

Facial seborrhea grading is shown in Fig. 3. The proportion of grade 5 facial seborrhea episodes decreased in both treatment groups after 6 months of treatment compared to baseline for EE/NGM vs. EE/DSG (13.0% to 1.1% vs. 4.0% to 0.0%, respectively). Decreases were also noted for grade 4 episodes (31.0% to 6.5 vs. 34.7% to 5.3%) and grade 3 episodes (43.0% to 20.4% vs. 44.6% to 29.5%). Meanwhile, there was a substantial increase in the proportion of grade 2 episodes (10.0% to 28.0% vs. 12.9% to 43.2%) and grade 1 episodes (3.0% to 44.1% vs 4.0% to 22.1%). An analysis of facial seborrhea grades using the Wilcoxon rank sum test showed that treatment with EE/NGM improved the facial seborrhea grade compared to baseline more than EE/DSG after 6 months of treatment (p=.005).

Table 1
Baseline characteristics of subjects who were randomized to receive treatment with either EE/NGM or EE/DSG

	EE/NGM[a] (*n*=100)	EE/DSG[a] (*n*=101)
Mean age (years)	30.6±6.4	29.9±5.9
Mean weight (kg)	55.6±8.9	54.2±9.4
Mean BMI (kg/m^2)	22.6±3.9	22.0±3.4

[a] Continuous variables are presented as mean±S.D.

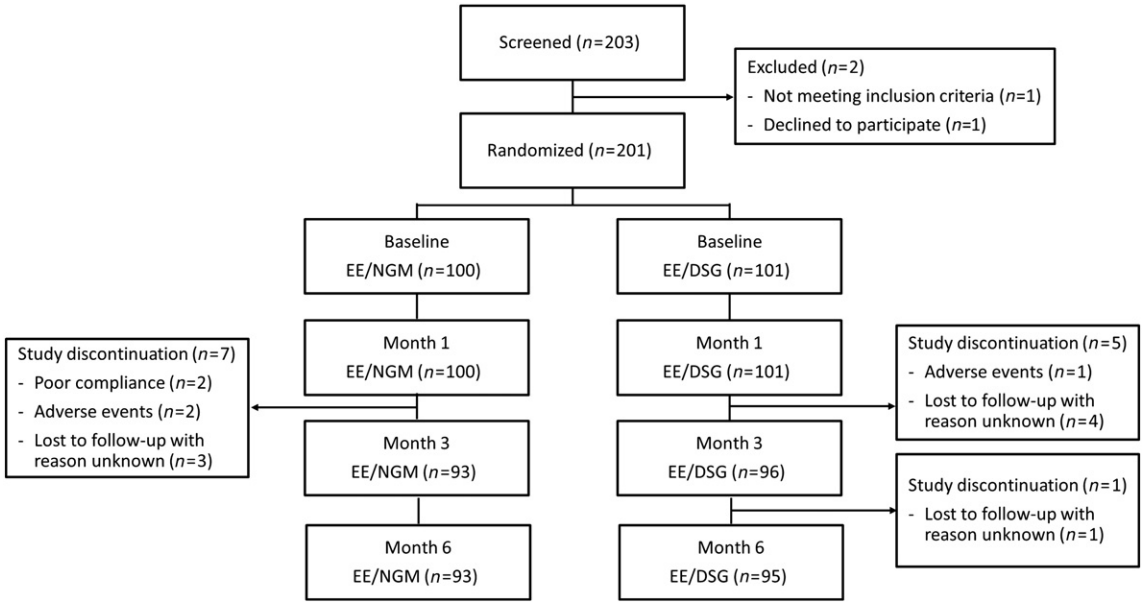

Fig. 1. Flow of subjects through the study.

At the final evaluation visit, the investigator's global assessment of the effect of treatment was recorded (Fig. 4A). In the EE/NGM group, 86.8% of subjects were graded as having an "excellent" or "good" response to treatment. In contrast, 74.3% of subjects in the EE/DSG group were graded as having "excellent" or "good" response to treatment. In addition to the investigator's global assessment, subjects self-evaluated changes in their facial acne at the end of therapy compared to baseline (Fig. 4B). In the EE/NGM group, 92.9% of subjects rated their acne as "much improved" or "somewhat improved". In the EE/DSG group, 95.9% of subjects rated their acne as "much improved" or "somewhat improved".

3.3. Safety and tolerability

Both treatments were generally well-tolerated. Nausea was the most frequent adverse event related to medication that occurred in both treatment groups. The number of episodes of nausea after treatment with EE/DSG (26.7%) was higher than treatment with EE/NGM (13.0%) (p=.021). Other adverse events that frequently occurred in EE/NGM and EE/DSG treatments were headache (5.0% vs. 9.9%) and breast pain (5.0% vs. 8.9%) (Table 3). Serious adverse events (SAEs) were reported in two patients during this study, both of whom were in the EE/NGM group. Neither SAE was related to the study medication.

The number of episodes of breakthrough bleeding and spotting was also evaluated. After 1 month of treatment, the rate of breakthrough bleeding and spotting after treatment with EE/NGM (18.0%) was higher than EE/DSG (5.9%) (p=.024). However, there was no significant difference in the number of episodes of breakthrough bleeding and spotting after 3 and 6 months of treatment (Table 4). There were no significant changes in body weight, BMI or vital signs between baseline and each study visit for either treatment group. In addition, no pregnancies occurred in any study subjects during the treatment period.

Table 2
Acne lesion counts in subjects evaluable for efficacy after treatment with EE/NGM or EE/DSG

Testing for Efficacy	EE/NGM[a]				EE/DSG[a]			
	Baseline (*n*=100)	Month 1 (*n*=100)	Month 3 (*n*=93)	Month 6 (*n*=93)	Baseline (*n*=101)	Month 1 (*n*=101)	Month 3 (*n*=96)	Month 6 (*n*=95)
	Mean±S.D.	Mean change from baseline±S.D.			Mean±	Mean change from baseline±S.D.		
Acne								
Comedones	11.0±6.5	−3.4±4.8	−5.7±6.9	−9.0±6.3	11.4±7.6	−3.4±5.3	−5.6±6.7	−8.2±7.4
Papules	4.3±4.9	−0.2±3.7	−2.8±3.8	−3.5±5.1	4.5±5.1	−0.6±2.2	−1.9±2.9	−2.8±4.6
Pustules/Nodules	1.0±2.1	−0.5±.3	−0.8±1.8	−0.9±2.3	1.1±2.3	−0.2±0.9	−0.7±1.5	−1.0±2.1
Total lesions	16.3±9.6	−4.1±4.9	−8.8±8.1	−13.4±9.7	17.0±10.4	−4.2±5.9	−8.2±7.8	−11.9±10.1

[a] Continuous variables are presented as mean±S.D. Counts show changes month by month within treatment groups.

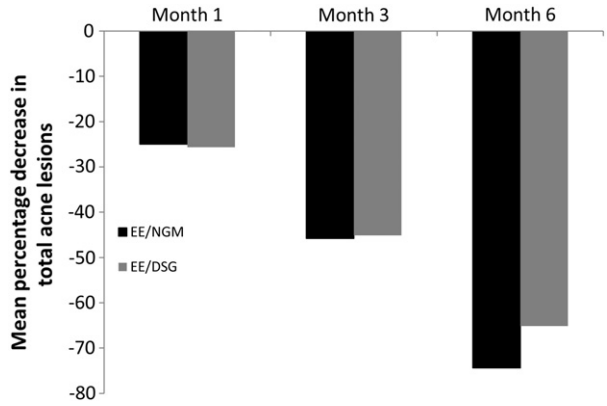

Fig. 2. Mean percentage decrease in total acne lesion counts after 1, 3 and 6 months of treatment with EE/NGM or EE/DSG.

4. Discussion

The effects of the combined triphasic EE/NGM on mild to moderate acne vulgaris observed in this study are comparable to the biphasic EE/DSG. Compared with previous studies, these results show a greater improvement in facial acne. As shown in the present study, treatment with EE/NGM for 6 treatment cycles decreased the total lesion count by 74.4%, while in two randomized double-blinded placebo-controlled studies, the lesion count was reduced compared with baseline after 6 treatment cycles of EE/NGM by approximately 50% [8,9]. This discrepancy may have resulted from different inclusion criteria. The present study included women who had fewer than 15 comedones, whereas the other two studies included subjects with more severe acne, having up to 100 comedones. Consequently, a high initial severity of acne vulgaris may have led to less efficient treatment.

Treatment of facial seborrhea with combined OCs currently has limited investigational evidence. Previously, triphasic EE/DSG [15], EE/drospirenone [16] and EE/chlormadinone acetate [17,18] demonstrated improvements in facial seborrhea, though there is no study on the effects of EE/NGM. Therefore, this is the first study to investigate the effect of triphasic EE/NGM on reducing facial seborrhea and it shows that EE/NGM had a beneficial effect on facial seborrhea with superiority over EE/DSG.

Treatment with EE/NGM and EE/DSG both brought about improvements from investigators' as well as subjects' point of view after 6 months of treatment but there were some discrepancies between investigators' and subjects' assessments. For the investigators' global assessments, marked improvement on facial acne was observed in more subjects treated with EE/NGM (86.8%) than EE/DSG (74.3%). In the subjects' self-assessment, those treated with EE/DSG (95.9%) showed a similar improvement to EE/NGM (92.9%). The slight differences between the investigators' assessments and subjects' self-assessments may be influenced, in part, by the fact that the subjects were not blinded.

Most adverse events (occurring with ≥2% frequency) in 6 months of treatment occurred more frequently in the EE/DSG group, especially nausea that occurred significantly more often than in the EE/NGM group. This may have been caused by the higher level of EE (0.040mg) in EE/DSG on days 1–7 of the treatment cycle and longer exposure to OCs (22 days) in each cycle. The other adverse events including headache and breast pain were found to be more frequent in the EE/DSG group but these differences were not statistically significant.

Cycle control is associated with compliance to contraceptive treatment [19]. Previously, triphasic EE/NGM has been shown to provide good cycle control [20] and similar

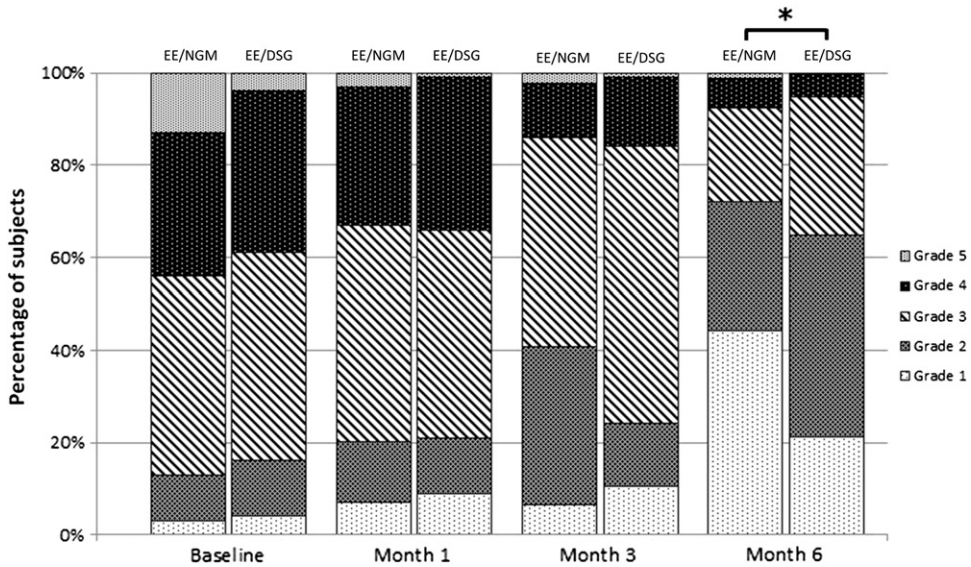

Fig. 3. Facial seborrhea graded with increasing severity from grade 1 to grade 5 at baseline and after 1, 3 and 6 months of treatment with EE/NGM or EE/DSG. *p=.005: significant difference of proportion's change from baseline between EE/NGM and EE/DSG groups.

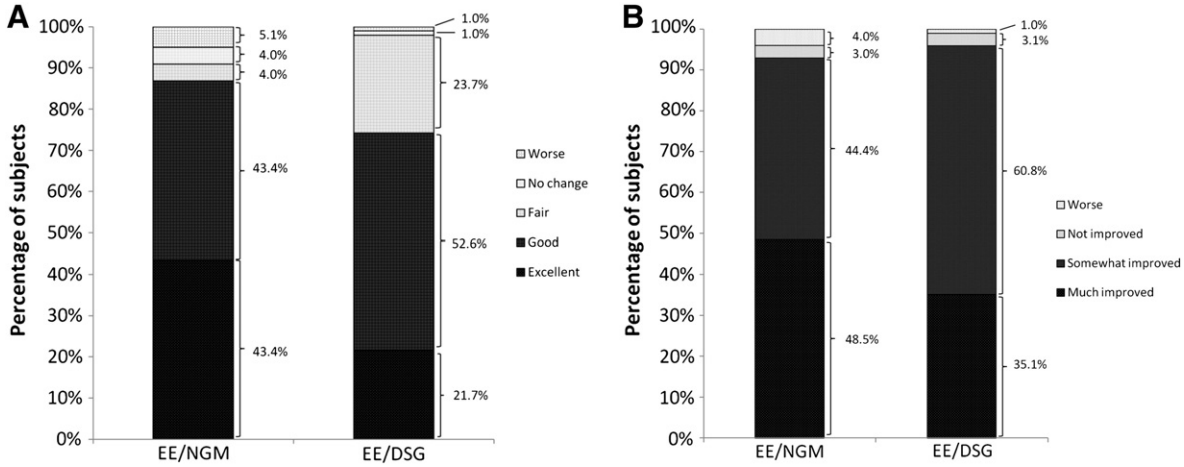

Fig. 4. (A) Investigator's global assessment and (B) subject's self-assessment of efficacy after 6 months of treatment with EE/NGM or EE/DSG.

results were found in this study. After 6 months of treatment, both treatments provided good cycle control. Although treatment with EE/NGM showed a higher rate of breakthrough bleeding and spotting during the first month of treatment, reevaluation at 3 and 6 months of treatment showed a smaller proportion of subjects experiencing this problem, which is similar to previous studies [21]. This indicates that the rate of breakthrough bleeding/spotting reduces over time.

This study demonstrates that both EE/NGM and EE/DSG provide effective and well-tolerated treatment options for female subjects with mild to moderate facial acne who need contraception. Their effects on total acne lesion count are similar, but EE/NGM shows a more beneficial effect on facial seborrhea reduction than EE/DSG.

The strengths of the present study include randomization to prevent selection bias, adequate sample size to determine the statistical significance of the primary endpoint and conducting the study in multiple centers to increase generalizability of the study to the general population. However, the lack of double-blind methodology was this study's important limitation because single-blinded (here, investigator-blinded) studies may be affected by bias.

5. Conclusion

The combined triphasic OC EE/NGM provides an effective and well-tolerated treatment option for women with mild to moderate facial acne. The effect of combined triphasic EE/NGM on total acne lesion count is comparable to the combined biphasic OC EE/DSG, with EE/NGM having a more beneficial effect on facial seborrhea reduction.

Acknowledgment

The authors would like to thank Mr. Puttavee Charoenwanthanang for his editorial assistance.

Table 3
Adverse events related to medication (occurring with ≥2% frequency) after treatment with EE/NGM or EE/DSG

Adverse events	EE/NGM *n* (%)	EE/DSG *n* (%)
Nausea	13 (13.0)	27 (26.7)*
Headache	5 (5.0)	10 (9.9)
Breast pain	5 (5.0)	9 (8.9)
Drowsiness	3 (3.0)	2 (2.0)
Blemish/acne	2 (2.0)	2 (2.0)
Swollen hands and feet	4 (4.0)	0 (0.0)
Dizziness	0 (0.0)	3 (3.0)

* p=.021 significant difference compared to EE/NGM treatment group.

Table 4
Incidence of breakthrough bleeding and spotting after treatment with EE/NGM or EE/DSG

	EE/NGM (*n*=100)		EE/DSG (*n*=101)	
	No. of subjects (%)	Days of bleeding (mean±S.D.)	No. of subjects (%)	Days of bleeding (mean±S.D.)
Month 1	18 (18.0)*	4.9±3.6	6 (5.9)	8.5±6.1
Month 3	10 (10.8)	4.9±4.4	11 (11.5)	5.6±3.3
Month 6	10 (10.8)	5.2±2.4	7 (7.4)	7.0±2.7

* p=.024 significant difference compared to EE/DSG treatment group.

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