Comparison of 2 Clindamycin 1%–Benzoyl Peroxide 5% Topical Gels Used Once Daily in the Management of Acne Vulgaris

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Combination therapy for the topical treatment of acne vulgaris using benzoyl peroxide (BPO) and an antibiotic is more efficacious and better tolerated than treatment with either component alone. Moreover, the addition of BPO to antibiotic therapy is recommended as a means of preventing the development of Propionibacterium acnes *antibiotic resistance. However, BPO is an irritant, and the dryness and irritation experienced by some patients using topical therapy containing BPO can negatively impact compliance. Historically, once-daily treatment application has enhanced compliance versus twice daily.*

The current 12-week study aimed to compare the efficacy of a clindamycin 1%–BPO 5% topical gel with the hydrating excipients dimethicone and glycerin (C/BPO HE) and a clindamycin 1%–BPO 5% topical gel that does not contain hydrating excipients (C/BPO) applied once daily for the treatment of 20 participants with facial acne vulgaris and to determine if there were differences in product preference and participant acceptability between the treatments.

Both C/BPO HE and C/BPO were effective in the treatment of acne, with substantive reductions (−60.8% and −61.3%, respectively) in total inflammatory lesions at week 4 in both treatment groups. Participants receiving C/BPO HE demonstrated a more consistent treatment response than with C/BPO, with incremental reductions in total inflammatory lesions at each time point, whereas the response to C/BPO waned at week 8. As a result, greater percentage reductions in inflammatory and noninflammatory lesions were observed with C/BPO HE treatment than C/BPO treatment at week 8 (papules: −71.9% vs −49.4%, P=*.053; pustules: −64.8% vs −28.0%,* P=*.134; open comedones: −44.5% vs 2.6%,* P=*.480; closed comedones: −35.5% vs −26.3%,* P=*.501). With the exception of papules, greater reductions in all lesion subtypes also were observed at week 12. None of the between-group differences reached statistical significance. Both treatment groups displayed similar disease signs and symptoms throughout the study period. However, scaling, erythema, dryness, and pruritus occurred more frequently in participants using C/BPO.*

Treatment satisfaction was greatest with C/BPO HE; participants reported that this formulation was easy to apply and 100% (9/9) of participants reported that they would continue using C/BPO HE compared with 80% (8/10) of participants using C/BPO. Both treatments were well-tolerated.

In this pilot study, both formulations were effective in the treatment of inflammatory and noninflammatory acne lesions, but C/BPO HE produced a more consistent reduction in total inflammatory lesions over 12 weeks. The addition of hydrating excipients in the C/BPO HE formulation appears to improve patient tolerance and acceptance, which will likely help patients to comply with therapy.

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Acne is a chronic inflammatory disease that occurs in at least 80% of individuals aged 11 to 30 years.[1,2] Four factors are responsible for the development of acne: excessive follicular keratinization, hyperplasia of the sebaceous gland, proliferation of *Propionibacterium acnes* bacteria and other microbes found in the sebum-rich skin, and perifollicular inflammation.[1] Acne vulgaris, the most common form of acne, is characterized by a mixture of inflammatory (papules, pustules, nodules, cysts) and noninflammatory (open and/or closed comedones) lesions.

Combination therapy for acne targets more than one causative factor and current guidelines recommend initiating combination therapy as early as possible.[1] For inflammatory acne, a topical antibiotic combined with an agent such as benzoyl peroxide (BPO) is recommended to increase efficacy and prevent the development of *P acnes* antibiotic resistance.[1-5] Clindamycin and BPO is one combination. Benzoyl peroxide is lipophilic and able to penetrate the stratum corneum where it has broad-spectrum antimicrobial activity and mild comedolytic effects,[2] and it does not appear to induce *P acnes* resistance.[1] The combined antimicrobial activity of clindamycin and BPO against *P acnes* is greater than clindamycin alone,[6,7] and the reduction in the *P acnes* bacterial colonies correlates with the clinical impact of treatment on lesion and comedone counts.[7] Moreover, the combination of clindamycin and BPO is more efficacious than either agent administered as monotherapy for reducing lesion counts.[6-8]

Benzoyl peroxide initially may irritate the skin, and although clindamycin may help to alleviate BPO-induced irritation, there is the potential for topical preparations containing clindamycin and BPO to cause dryness and irritation. Excipients can be added to the topical preparations to ameliorate or soothe these effects. Among the clindamycin-BPO formulations available in the United States is a clindamycin 1%–BPO 5% topical gel with the hydrating excipients dimethicone and glycerin (C/BPO HE),[9] and a clindamycin 1%–BPO 5% topical gel that does not contain hydrating excipients (C/BPO).[10] The C/BPO HE formulation is indicated for once-daily treatment,[9] while C/BPO is indicated for twice-daily application[10] but is frequently applied once daily by patients.

A recent split-face comparative study suggested that C/BPO HE was better tolerated than C/BPO, but the active treatment phase was short (2 weeks) and all participants also used topical tretinoin.[11] The aim of the current study was to compare the efficacy of C/BPO HE and C/BPO applied once daily for the treatment of participants with facial acne vulgaris and to determine if there were differences in product preference and participant acceptability between the 2 treatments.

MATERIALS AND METHODS

Participants

For inclusion, participants were required to have 25 or more inflammatory facial lesions (papules and/or pustules); 10 or more noninflammatory facial lesions (open and/or closed comedones); 2 or fewer facial nodulocystic lesions (≤5 mm in diameter); and stable, nonrapidly regressing facial acne vulgaris. Female participants were not eligible if they were pregnant, breastfeeding, or of childbearing potential and not practicing a reliable method of birth control. Other exclusion criteria included allergy or sensitivity to any medication component; known hypersensitivity to lincomycin; history of enteritis; any uncontrolled systemic disease; recent alcohol or drug abuse; history of poor cooperation, noncompliance, or unreliability; participation in an investigational drug study within 30 days of the baseline visit; or cosmetic or surgical procedures complementary to acne treatment within 15 days of the baseline visit.

This study was performed in accordance with Good Clinical Practice guidelines. Participants or guardians (if the participant was younger than 18 years) provided written informed consent before inclusion in the study, and the protocol was reviewed and approved by Veritas Institutional Review Board.

Study Medications

Participants received study medication kits that included either C/BPO HE dispensed in 45-g tubes (each gram contained 10 mg [1%] clindamycin as phosphate and 50 mg [5%] BPO in a base consisting of carbomer 940, dimethicone, disodium lauryl sulfosuccinate, edetate disodium, glycerin, methylparaben, poloxamer, purified water, silicon dioxide, and sodium hydroxide)[9] or C/BPO dispensed in 25-g jars (each gram contained 10 mg [1%] clindamycin as phosphate and 50 mg [5%] BPO in a base of carbomer, sodium hydroxide, dioctyl sodium sulfosuccinate, and purified water).[10] The jar gel was compounded with 5 mL of purified water prior to dispensing.[10]

Participants were instructed to apply the study medication once daily in the morning after washing the face with a soap-free facial cleanser. The use of other therapies for facial acne was prohibited during the study.

Study Design

In this single-center, investigator-blinded, prospective, 12-week pilot study, participants were randomized in a 1:1 ratio to either C/BPO HE tube gel (n=10) or C/BPO jar gel (n=10). Because of the

difference in formulation packaging, participants were not blinded to their treatment allocation.

Efficacy and safety were evaluated at each visit (weeks 4, 8, and 12). The primary efficacy end point was the percentage reduction in total inflammatory lesions (papules and/or pustules) at week 12 on the whole face (from the hairline edge down to the mandibular line). Noninflammatory lesions (open and/or closed comedones) also were counted using the same procedure.

Secondary efficacy end points included papule and pustule counts and noninflammatory lesion counts (open and closed comedones) as well as investigator assessment of severity of scaling, erythema, dryness, burning, or pruritus using a 6-point grading scale (0=none; 5=severe) at each visit. Product acceptability and preference questionnaires were completed by participants at weeks 4 and 12. Product acceptability was based on the presence and severity of adverse events (AEs) at the application site. Preference questions related to ease of application, comfort, satisfaction with treatment, comparison with prior therapies, and willingness to continue using the product. At each visit, participants were assessed for the presence of AEs.

Statistical Analysis

Formal justification of the sample size was not undertaken for this pilot study. The efficacy analysis was conducted on all randomized participants with data at each time point. All statistical tests were 2 sided and interpreted at a 5% significance level, with no adjustment for multiple comparisons. Baseline comparisons were made using a Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables. The *t* test was used for between-group comparisons of lesion counts and the Wilcoxon rank sum test for the between-group comparison of change in lesion counts. Questionnaire data and the frequency of AEs were compared using the Fisher exact test.

RESULTS

Participant Characteristics

Twenty participants with facial acne were enrolled in this study; 18 participants completed 12 weeks of treatment. Two participants in the C/BPO HE group withdrew between weeks 8 and 12. One participant was lost to follow-up and the other declined further participation for reasons not associated with the study. One of these participants had a final visit at week 10 and the data were carried forward to the analysis at week 12; as a result, 19 participants comprised the analysis cohort at week 12. There were no significant differences in baseline demographics. Participants were aged 13 to 42 years (mean age [SD], 21.5 [9.5] years) and 60% (12/20) were female (Table 1). Racial composition varied, with 60% (12/20) of participants classified as other (not white, black, Hispanic, or Asian). Baseline lesion counts were similar in both groups.

Clinical Efficacy

Inflammatory Lesion Counts—Both formulations were effective in reducing the number of total inflammatory lesions, with reductions apparent from week 4 ($P<.0001$ vs baseline in both groups at week 4) (Figure 1). At week 8, C/BPO HE had produced a 20% greater reduction in total inflammatory lesions compared with C/BPO (−68.8% vs −48.4%; $P=.077$), and at week 12, the percentage reduction was −72.6% versus −60.8% for C/BPO HE and

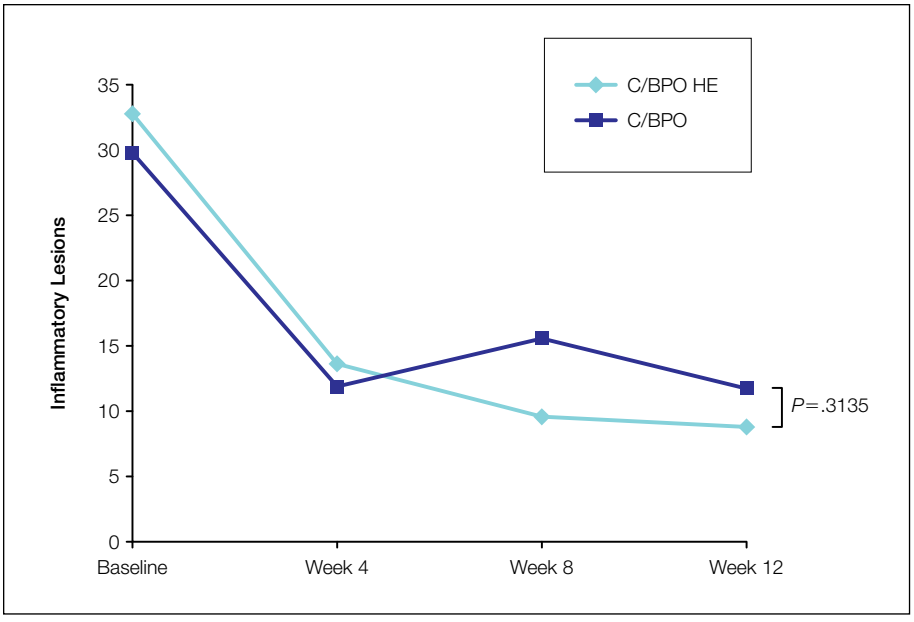

Figure 1. Mean number of total inflammatory lesions over the 12-week study. C/BPO HE indicates clindamycin 1%–benzoyl peroxide 5% topical gel with the hydrating excipients dimethicone and glycerin (tube gel); C/BPO, clindamycin 1%–benzoyl peroxide 5% topical gel that does not contain hydrating excipients (jar gel).

Table 1.

Participant Demographics and Characteristics at Baseline (Intention-to-Treat Population)

	C/BPO HE (n=10)	C/BPO (n=10)	Total (N=20)	*P* Value
Male to female ratio, n	3:7	5:5	8:12	.6499
Mean age (SD), y	22.4 (11.5)	20.5 (7.4)	21.5 (9.5)	.7337
Race, n (%)				
White	1 (10)	1 (10)	2 (10)	.6571[a]
Black	0 (0)	2 (20)	2 (10)	
Hispanic	0 (0)	1 (10)	1 (5)	
Asian	2 (20)	1 (10)	3 (15)	
Other[b]	7 (70)	5 (50)	12 (60)	
Mean (SD) baseline inflammatory lesion count				
Papules	20.90 (9.99)	20.50 (2.51)	20.70 (7.09)	.1943
Pustules	11.90 (4.33)	9.30 (5.74)	10.60 (5.12)	.2677
Total (papules + pustules)	32.80 (12.79)	29.80 (4.54)	31.30 (9.47)	.4163
Mean (SD) baseline noninflammatory lesion count				
Open comedones	21.20 (12.81)	12.40 (11.38)	16.80 (12.63)	.1218
Closed comedones	33.80 (17.76)	27.90 (16.00)	30.85 (16.73)	.4452
Total (open + closed comedones)	55.00 (24.73)	40.30 (25.39)	47.65 (25.53)	.2062

Abbreviations: C/BPO HE, clindamycin 1%–benzoyl peroxide 5% topical gel with the hydrating excipients dimethicone and glycerin (tube gel); C/BPO, clindamycin 1%–benzoyl peroxide 5% topical gel that does not contain hydrating excipients (jar gel); SD, standard deviation.

[a]All combined.

[b]Chinese (n=1), East Indian (n=6), Mediterranean (n=1), Native American (n=1), Pacific Islander (n=2), and Portuguese (n=1).

C/BPO, respectively (*P*=.2162)(Figure 2). Lesion counts at baseline and week 12 are shown in Table 2. Similar results were seen when the number of papules and pustules were analyzed separately (Figure 2).

Noninflammatory Lesion Counts—The between-group comparisons in open comedone, closed comedone, and total noninflammatory lesion counts at week 12 were not significant (Table 2). There was considerable variability in open comedones between treatment groups. However, C/BPO HE appeared to be more effective than C/BPO in reducing open comedones at week 8 (−44.5% vs 2.6%; *P*=.480) and at week 12 (−60.8% vs 14.8%; *P*=.596) (Figure 3). There was less variability in closed comedones between treatment groups. Greater percentage reductions in closed comedones were observed with C/BPO HE compared with C/BPO at week 8 (−35.5% vs −26.3%; *P*=.501) and week 12 (−39.7% vs −24.0%; *P*=.286). Similarly, the percentage reduction in total noninflammatory lesions showed a trend toward greater efficacy with C/BPO HE compared with C/BPO at week 8 (−42.3% vs −26.1%; *P*=.1764) and week 12 (−52.3% vs −27.7%; *P*=.0668).

Investigator Assessment of Facial Signs and Symptoms—At baseline, no participant in either

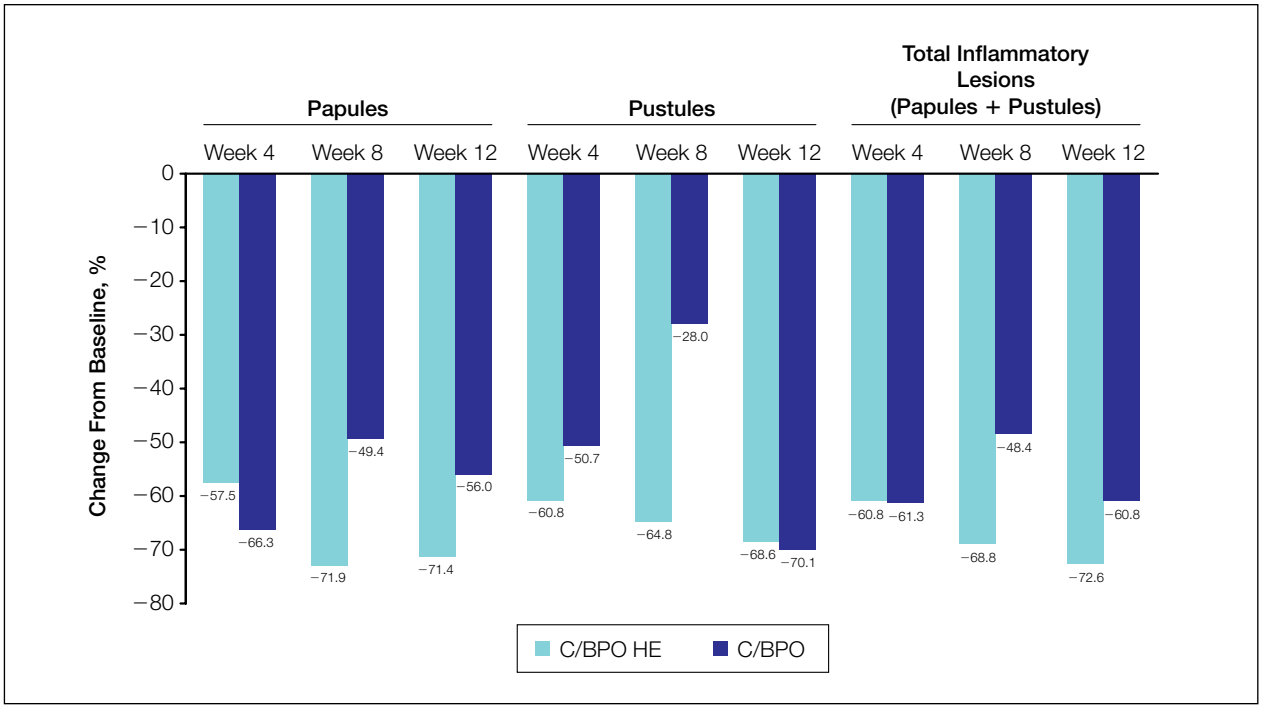

Figure 2. Mean percentage change from baseline in inflammatory lesions (papules, pustules, total [papules and pustules]) at weeks 4, 8, and 12. C/BPO HE indicates clindamycin 1%–benzoyl peroxide 5% topical gel with the hydrating excipients dimethicone and glycerin (tube gel); C/BPO, clindamycin 1%–benzoyl peroxide 5% topical gel that does not contain hydrating excipients (jar gel).

treatment group exhibited scaling, erythema, dryness, burning, or pruritus. None of the participants using C/BPO HE developed erythema or burning during 12 weeks of treatment, but 1 participant in this group had scaling at week 8, 1 had dryness at week 8, and 2 had pruritus at week 4. In all instances, these symptoms were rated as trace (score of 1). None of the participants in the C/BPO group had burning during 12 weeks of treatment. At week 4, 1 participant in the C/BPO group reported trace scaling, trace erythema, and trace dryness, and 3 reported pruritus (rated as trace in 2 participants and mild [score of 2] in 1 participant). At week 8, 1 participant in the C/BPO group had trace scaling and 1 had trace dryness, and at week 12, 2 participants had trace pruritus.

Participant Questionnaires—At weeks 4 and 12, 100% (10/10 and 9/9, respectively) of participants rated the ease of application of C/BPO HE as favorable or highly favorable compared with 80% (8/10) and 70% (7/10) of participants using C/BPO at weeks 4 and 12, respectively. Regarding the comfort of their skin, 90% (9/10) and 89% (8/9) of participants in the C/BPO HE group rated their skin as comfortable or very comfortable at weeks 4 and 12, respectively, compared with 50% (5/10) at weeks 4 and 12 in the C/BPO group.

At week 12, the participant-reported incidence of scaling was 70% (7/10) and 44% (4/9) in the C/BPO and C/BPO HE groups, respectively. Facial redness also was more common in participants receiving C/BPO versus C/BPO HE at week 12 (60% [6/10] vs 22% [2/9]). Similarly, dryness was more common in participants receiving C/BPO compared with C/BPO HE (90% [9/10] vs 70% [7/10] at week 4; 70% [7/10] vs 44% [4/9] at week 12). The incidence of burning was low and similar in the C/BPO HE and C/BPO groups: 30% (3/10) of participants in each group at week 4, and 22% (2/9) versus 20% (2/10), respectively, at week 12. Itching was reported by 70% (7/10) of participants at week 4 and 56% (5/9) at week 12 in the C/BPO HE group compared with 40% (4/10) at week 4 and 50% (5/10) at week 12 in the C/BPO group. Mean scores for the severity of each sign were similar in both treatment groups.

Participants were asked to compare the study medication with prior topical medications used. None of the participants using C/BPO HE reported being more dissatisfied at any time point compared with 1 participant using C/BPO at week 4 and 2 at week 12. Mean score (SD) for overall impressions on a scale from –2 (highly unfavorable) to +2 (highly favorable) at week 12 was 1.2 (0.8) for C/BPO HE and 0.8 (0.8) for C/BPO (P=.2834). At week 12, 100% (9/9) of participants in the C/BPO HE group reported that they would continue using the product compared with 80% (8/10) in the C/BPO group (P=.4737).

Safety

Both medications were well-tolerated. Adverse events that were possibly or probably related to

Table 2.

Inflammatory and Noninflammatory Lesion Counts

	C/BPO HE		C/BPO		
	Baseline (n=10)	Week 12 (n=9)	Baseline (n=10)	Week 12 (n=10)	*P* Value[a]
Inflammatory Lesions, mean (SD)					
Papules	20.90 (9.99)	5.44 (2.30)	20.50 (2.51)	8.80 (4.80)	.0698
Pustules	11.90 (4.33)	3.33 (2.74)	9.30 (5.74)	3.00 (4.52)	.4503
Total (papules + pustules)	32.80 (12.79)	8.78 (3.19)	29.80 (4.54)	11.80 (8.43)	.3135
Noninflammatory Lesions, mean (SD)					
Open comedones	21.20 (12.81)	9.22 (11.01)	12.40 (11.38)	9.00 (12.29)	.5923
Closed comedones	33.80 (17.76)	20.44 (15.08)	27.90 (16.00)	18.40 (8.30)	.7148
Total (open + closed comedones)	55.00 (24.73)	29.67 (25.29)	40.30 (25.39)	27.40 (16.25)	.8170

Abbreviations: C/BPO HE, clindamycin 1%–benzoyl peroxide 5% topical gel with the hydrating excipients dimethicone and glycerin (tube gel); C/BPO, clindamycin 1%–benzoyl peroxide 5% topical gel that does not contain hydrating excipients (jar gel); SD, standard deviation.

[a] *t* Test for between-group comparison at week 12.

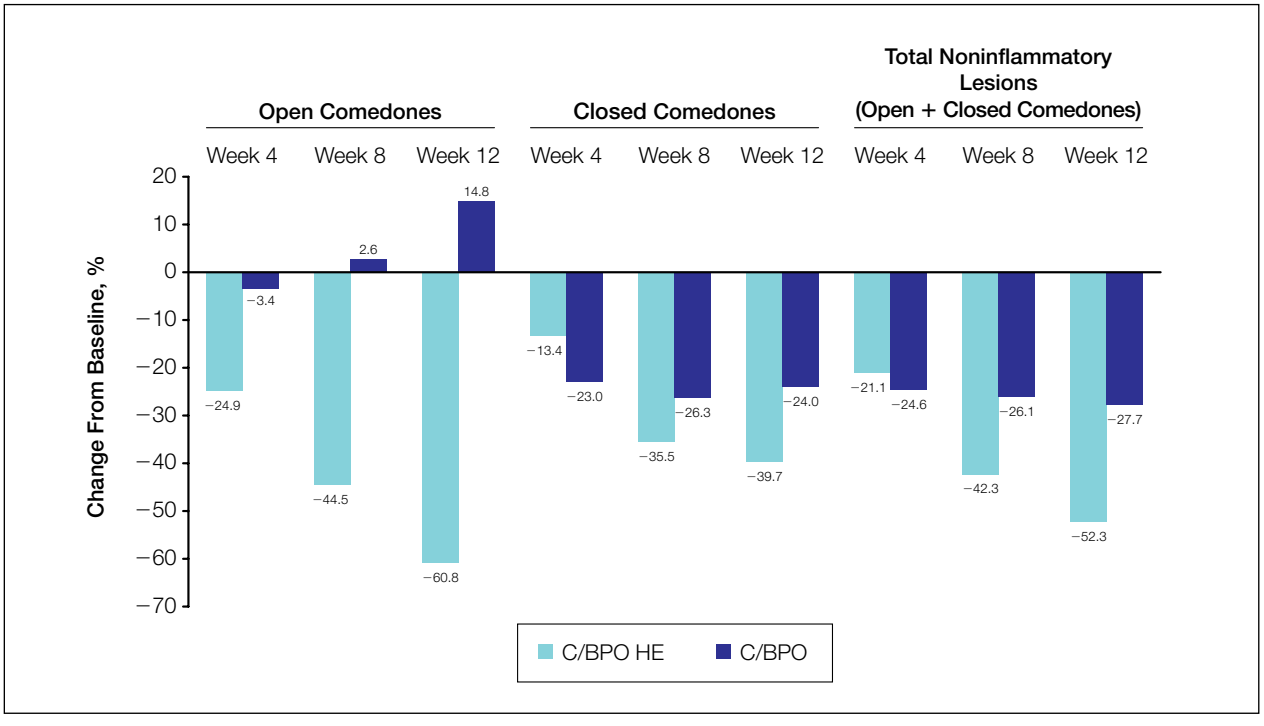

Figure 3. Mean percentage change from baseline in noninflammatory lesions (open comedones, closed comedones, total [open and closed comedones]) at weeks 4, 8, and 12. C/BPO HE indicates clindamycin 1%–benzoyl peroxide 5% topical gel with the hydrating excipients dimethicone and glycerin (tube gel); C/BPO, clindamycin 1%–benzoyl peroxide 5% topical gel that does not contain hydrating excipients (jar gel).

Table 3.

AEs Experienced by Participants Over 12 Weeks

	C/BPO HE (n=10)	C/BPO (n=10)
AEs, n (%)	3 (30)	8 (80)
Coldlike symptoms	1 (10)	3 (30)
Sore throat	0 (0)	2 (20)
Headache	0 (0)	1 (10)
Asthma	1 (10)	0 (0)
Pityriasis alba[a]	1 (10)	0 (0)
Facial burning and dryness[b]	0 (0)	1 (10)
Hives[a]	0 (0)	1 (10)
Serious AEs, n (%)	0 (0)	0 (0)
AEs possibly or probably related to treatment, n (%)	1 (10)	2 (20)

Abbreviations: AE, adverse event; C/BPO HE, clindamycin 1%–benzoyl peroxide 5% topical gel with the hydrating excipients dimethicone and glycerin (tube gel); C/BPO, clindamycin 1%–benzoyl peroxide 5% topical gel that does not contain hydrating excipients (jar gel).
[a]Possibly treatment related.
[b]Probably treatment related.

treatment occurred with a similar frequency in both treatment groups (Table 3).

COMMENT

In this pilot study, C/BPO HE produced a consistent reduction in total inflammatory lesions throughout 12 weeks of treatment, whereas the effect of C/BPO appeared to wane between weeks 4 and 8. For C/BPO, the effect at week 12 was similar to the initial week 4 effect, whereas the effect of C/BPO HE incrementally improved at each 4-week assessment. Greater reductions in noninflammatory lesions occurred in the C/BPO HE group, though none of the comparisons reached statistical significance.

Both formulations contained similar concentrations of active ingredient in an aqueous gel; however, C/BPO HE also contained the emollient dimethicone and glycerin. The inclusion of these excipients in topical acne therapies has been associated with a significantly reduced incidence of erythema and dryness relative to the standard formulation, at least during the initial 14 days of treatment ($P<.05$).[11] We noted a similar trend, though none of the comparisons reached statistical significance. For example, C/BPO HE was associated with a lower incidence of scaling, erythema, and dryness as assessed by both the investigator and participants.

It has been suggested that poor patient adherence can cause treatment failure in acne.[12] A large-scale analysis of dermatology outpatients indicated that patient satisfaction with care was a major determinant of patient adherence. Although physician interpersonal skills and access to care were the major determinants, treatment factors, such as an overly complicated regimen or AEs, also impacted adherence.[13] Specifically for acne therapy, treatment factors that impact adherence include efficacy, regimen simplicity, choice of treatment for individualized therapy, and tolerability.[12]

In the current study, while both C/BPO formulations were effective, well-tolerated, and easy to use, there was a trend in favor of the agent with the hydrating excipients. Overall, 100% of participants in the C/BPO HE group and 80% in the C/BPO group reported that they would continue using the product. The participant preference questionnaire revealed a small and nonsignificant difference in favor of C/BPO HE in scores for satisfaction and

overall impressions, and a higher proportion of participants reporting treatment as comfortable or very comfortable (89% vs 50%). The once-daily administration schedule also may improve patient adherence by simplifying treatment application. As noted for nondermatologic indications, once-daily treatment regimens improve adherence relative to more frequent administration schedules.[14]

The current study has a number of limitations. First, as a pilot study, the number of participants was small (N=20), so many of the between-group comparisons did not reach statistical significance. Therefore, no firm conclusions can be drawn regarding the comparative efficacy of these 2 formulations, particularly regarding their effects on noninflammatory lesions, as these were variable. Second, although our study was randomized and the treatment groups comparable, the treatments were administered open label, thereby introducing the potential for bias. The objective nature of the primary end point (number of total inflammatory lesions) and investigator blinding probably helped to minimize bias in the efficacy analysis, but we cannot rule out the possibility that some degree of bias was introduced in the participants' subjective analyses, as they were not blinded. In addition, the C/BPO jar gel in our study is indicated for twice-daily treatment and was applied once daily, as often is prescribed in clinical practice. Therefore, there is the potential to underestimate the efficacy and to possibly overestimate the tolerability of C/BPO jar gel relative to its approved use. Lastly, the demographic composition of our small study group (particularly the racial mix) may not be representative of the acne population seen in typical clinical practice. The findings from this pilot study warrant replication in a larger patient population.

CONCLUSION

The results of this pilot study indicate that, when applied once daily, a gel formulation of C/BPO HE and C/BPO is effective in the treatment of inflammatory and noninflammatory acne lesions, but C/BPO HE produced a more consistent reduction in lesion counts over 12 weeks. The addition of hydrating excipients in the C/BPO HE formulation appears to improve patient tolerance and acceptance, which will likely help patients to comply with therapy.

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