A Multicenter, Double-blind Study to Evaluate the Efficacy and Safety of 2 Treatments in Participants With Mild to Moderate Acne Vulgaris

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Acne treatment regimens have changed due to the recent over-the-counter (OTC) switch of all prescription benzoyl peroxide (BPO) topical preparations. The elimination of prescription single-agent BPO products means that dermatologists must select from a variety of OTC formulations to utilize the time-tested efficacy of BPO in the treatment of mild to moderate acne. Our research compared the efficacy and safety of an OTC BPO 5.5% formulation with lipohydroxy acid and tretinoin cream 0.025% with prescription clindamycin 1%–BPO 5% gel and tretinoin cream 0.025%. Parity was demonstrated between the 2 treatment regimens at 12 weeks.

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The paradigm for acne treatment has changed since the US Food and Drug Administration determined that preparations with 10% benzoyl peroxide (BPO) generally are regarded as safe and effective,[1] which led to the movement from the prescription realm to the over-the-counter (OTC) market. The movement has increased the need for quality OTC BPO preparations to use as sole therapy in individuals with mild acne and in combination with prescription therapy in individuals with mild to moderate acne. Most of the BPO preparations previously sold in the OTC market were based on the acne monograph,[1] but efficacy testing was not commonly performed. The preparations were assumed to be efficacious based on the active BPO ingredient, which plays an important role in the treatment of acne.

The most effective and most commonly used active ingredient in OTC acne preparations is BPO. Twenty-three percent of acne patients aged 13 to 27 years have used an OTC BPO product.[2] Benzoyl peroxide is a member of the organic peroxide family consisting of 2 benzoyl groups joined by a peroxide group. It has many properties pertinent to acne including antibacterial, anti-inflammatory, and comedolytic effects.[3] When BPO touches the skin, it breaks down into benzoic acid and oxygen, neither of which is problematic. It has antimicrobial properties against *Propionibacterium acnes* as demonstrated by a $\log_{10}$ 2 decrease in *P acnes* concentration following 2 days of topical BPO 5% application.[4] However, unlike topical antibiotics, BPO does not induce resistant organisms.[5] Even a BPO cleanser can suppress the development of resistant organisms.[6]

Benzoyl peroxide also acts as an anti-inflammatory agent by reducing oxygen radicals. Furthermore, its ability to reduce the *P acnes* population also

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reduces the activation of toll-like receptor 2 on the surface of monocytes, leading to reduced secretion of proinflammatory cytokines such as tumor necrosis factor α, IL-1β, and IL-8.[7] This anti-inflammatory effect is perceived by the consumer as reduced redness and pain.

Benzoyl peroxide is capable of producing a 10% reduction of comedones in clinical trials.[4] Higher-concentration BPO preparations were originally thought to provide superior antiacne effects; however, it now appears that even BPO 2.5% is effective in improving acne.[8]

Current trends in BPO formulations have focused on the use of less irritating hydrogel formulations and smaller particle size BPO.[9] Raw BPO is a large particulate that is not water soluble. The bulk of BPO in most formulations remains on the surface of the stratum corneum. It is only the dissolved BPO that reaches target areas in the skin and follicle where it is active in killing *P acnes*. Smaller particle size allows better skin coverage with less irritation, as it affords the opportunity to reduce the concentration of BPO. Careful creative formulation can minimize tolerability issues with OTC BPO formulations.

We conducted a 12-week, multicenter, double-blind study to compare the efficacy and safety of 2 acne regimen treatments (randomized in a 1:1 ratio) in patients with mild to moderate acne. One treatment regimen included an OTC formulation containing BPO 5.5% with lipohydroxy acid applied twice daily and tretinoin cream 0.025% applied at bedtime. The other treatment regimen consisted of prescription clindamycin 1%–BPO 5% gel applied twice daily and tretinoin cream 0.025% applied at bedtime.

Methods

Study Design and Treatment—Sixty-six participants aged 18 to 50 years were enrolled in this multicenter, double-blind, institutional review board–approved, 12-week study. There were 3 research sites: Dermatology Consulting Services, High Point, North Carolina; State University of New York, Brooklyn; and Pennsylvania State University College of Medicine, Hershey. Participants were randomized to treatment A or treatment B in a 1:1 ratio. Treatment A consisted of an OTC BPO 5.5% preparation with lipohydroxy acid applied twice daily and tretinoin cream 0.025% applied at bedtime. Treatment B consisted of the commonly prescribed clindamycin 1%–BPO 5% gel (BenzaClin) applied twice daily and tretinoin cream 0.025% applied at bedtime. Product labels were masked to conceal their identity from both the participants and the investigators. Following 12 weeks of product application, participants were asked to discontinue their acne treatment and enter a 4-week no-treatment phase known as a regression phase to determine the degree of acne relapse.

Assessments—A variety of assessments were made at baseline and weeks 2, 4, 8, and 12, with the regression phase assessment at week 16 in all enrolled study participants. The 3 board-certified investigators were asked to blindly assess the participants for tolerability (ie, erythema, edema, dryness, peeling) on a 4-point ordinal scale (0=none; 1=mild; 2=moderate; 3=severe). In addition, lesion counts were performed of the entire face including the nose for open comedones, closed comedones, papules, pustules, noninflammatory lesions, inflammatory lesions, and total lesions. The investigators also assessed the facial skin for skin tone (clarity), skin smoothness, skin brightness, appearance of pores, overall appearance, and global acne assessment on a 10-point visual analog scale with 0 indicating a favorable rating and 9 indicating an unfavorable rating. Participant irritation assessments (stinging, tingling, itching, burning) also were captured on a 4-point ordinal scale (0=none; 1=mild; 2=moderate; 3=severe) and standardized facial photography was conducted with a 3-point head restraint of the front, right, and left face to document the presence of participants at the research center. The photographs were not used for any efficacy assessments, as images cannot duplicate the accuracy of real-time acne counts.

Statistical Analysis—Data obtained from the efficacy and tolerability evaluations were collected from all of the testing centers and statistically compared between baseline and weeks 2, 4, 8, 12, and/or 16 using paired *t* tests or Wilcoxon signed rank tests. Changes from baseline were considered significant at $\alpha=.05$. Mean percentage change from baseline was reported for all attributes. Paired *t* tests or Wilcoxon signed rank tests were applied to determine the differences between the 2 treatments.

Results

Sixty-six participants were randomized and 60 participants completed the trial. Of the 60 participants, 26 received treatment A and generic tretinoin cream 0.025% and 34 received treatment B and generic tretinoin cream 0.025%. The study population was comprised of all ethnicities (32 white; 6 Hispanic; 2 Asian; 26 black); there were 54 female participants and 12 male participants enrolled. Following the 12-week active treatment period, treatment was discontinued. Participants refrained from other acne treatments and were reexamined after the

Table 1.

Mean Scores on the Visual Analog Scale for Clinical Grading for Efficacy Parameters[a]

Parameter[b]	Treatment	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16
Skin tone (clarity)	Treatment A	5.0	4.4	3.9	3.2	2.3	2.7
	Treatment B	5.3	4.6	4.1	3.3	2.6	2.7
Skin smoothness	Treatment A	4.9	4.5	3.5	2.7	2.1	2.3
	Treatment B	5.0	4.7	4.2	3.2	2.3	2.2
Skin brightness	Treatment A	4.6	4.1	3.6	2.8	2.4	2.6
	Treatment B	5.1	4.6	4.0	3.2	2.5	2.6
Appearance of pores	Treatment A	4.6	4.5	4.2	3.6	3.1	3.3
	Treatment B	4.6	4.3	4.1	3.5	3.2	3.1
Overall appearance	Treatment A	5.0	4.4	3.9	3.1	2.4	2.6
	Treatment B	5.1	4.7	4.3	3.2	2.6	2.5
Global acne assessment	Treatment A	3.1	2.7	2.3	2.1	1.7	2.0
	Treatment B	3.4	3.1	2.5	2.2	1.7	2.2

[a]Treatment A consisted of benzoyl peroxide 5.5% with lipohydroxy acid applied twice daily and tretinoin cream 0.025% applied at bedtime. Treatment B consisted of clindamycin 1%–benzoyl peroxide 5% gel applied twice daily and tretinoin cream 0.025% applied at bedtime.
[b]Rated using the visual analog scale with 0 indicating a favorable rating and 9 indicating an unfavorable rating.

4-week regression phase to determine how long the acne was controlled following cessation of treatment. A total of 57 participants completed the regression phase. The study was initiated in September 2010 and was completed in August 2011.

Efficacy—The mean ordinal scores for the investigator efficacy assessment are summarized in Table 1. There was statistically significant improvement compared with baseline in all scores for both acne treatment regimens at weeks 4, 8, and 12 ($P<.05$). Statistically significant improvement was maintained for both groups compared with baseline at the end of the 4-week no-treatment regression phase ($P<.05$). Some differences between treatment A and treatment B were noted at week 2. Treatment B showed statistically significant improvement in skin brightness ($P<.05$). Treatment B also showed a statistically significant reduction in the appearance of pores at week 2 when evaluated by the investigator ($P<.05$), while treatment A did not reach statistical significance. Parity between the 2 treatments was established from week 4 onward compared with baseline.

Mean scores of facial lesion counts are summarized in Table 2. Both treatment regimens produced a statistically significant reduction in noninflammatory and inflammatory lesion counts at treatment weeks 4, 8, and 12, and during the regression phase at week 16 as compared with baseline ($P<.05$). Treatment B showed a statistically significant reduction in open comedones at week 2 ($P<.05$) that was not observed with treatment A; however, treatment A showed a statistically significant reduction in pustules at week 2 ($P<.05$) that was not seen with treatment B. Again, parity was established by the 2 treatments from week 4 onward.

Tolerability—Tables 3 and 4 summarize the tolerability assessments of both treatment formulations. Treatment B produced a statistically significant increase in investigator-assessed erythema compared with baseline at week 2 ($P=.042$) that was not seen in treatment A. Compared with baseline, a statistically significant increase in dryness and peeling was noted in both treatment A and treatment B as expected during the early phases of retinization (dryness: week 2, $P=.004$ and $P<.001$, respectively; peeling: week 2, $P=.001$ and $P=.002$, respectively; week 4, $P=.039$ and $P=.013$, respectively). By week 12, increase in dryness and peeling had resolved when assessed by the

Table 2.

Mean Scores on Facial Lesion Counts[a]

Parameter	Treatment	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16
Open comedones	Treatment A	8.3	4.8	3.6	3.5	0.9	0.8
	Treatment B	8.4	5.3	3.2	2.9	1.3	2.0
Closed comedones	Treatment A	23.0	14.8	13.7	9.8	8.4	10.0
	Treatment B	22.5	16.0	9.8	8.3	6.4	9.4
Papules	Treatment A	15.7	9.0	6.6	5.8	4.0	4.5
	Treatment B	17.4	12.0	8.0	6.4	5.3	6.8
Pustules	Treatment A	3.9	1.4	1.3	0.9	0.5	1.7
	Treatment B	3.6	2.3	1.4	0.8	0.5	1.0
Noninflammatory lesions	Treatment A	31.3	19.6	17.3	13.3	9.3	10.9
	Treatment B	30.9	21.3	13.0	11.2	7.7	11.4
Inflammatory lesions	Treatment A	19.6	10.4	7.9	6.7	4.4	6.2
	Treatment B	21.0	14.3	9.4	7.2	5.8	7.7
Total lesions	Treatment A	51.0	30.0	25.1	20.0	13.7	17.0
	Treatment B	51.9	35.6	22.5	18.5	13.5	19.1

[a]Treatment A consisted of benzoyl peroxide 5.5% with lipohydroxy acid applied twice daily and tretinoin cream 0.025% applied at bedtime. Treatment B consisted of clindamycin 1%–benzoyl peroxide 5% gel applied twice daily and tretinoin cream 0.025% applied at bedtime.

investigator. In addition, no increase in erythema was present as the facial skin had adapted to the acne treatment.

The participant-assessed tolerability presented in Table 4 showed a statistically significant increase with both treatment A and treatment B in stinging (both $P<.001$), tingling ($P=.007$ and $P=.001$, respectively), itching ($P=.027$ and $P=.007$, respectively), and burning (both $P<.001$) compared with baseline at week 2. The symptoms persisted at week 4, with the exception of an insignificant difference in itching in both treatments and in tingling for treatment A when compared with baseline. Participant-assessed irritation had largely resolved by week 8 in both groups.

The data demonstrated parity between the 2 treatments for investigator-assessed and participant-assessed tolerability.

Comment

The recent movement of all single-agent BPO products from the prescription realm to the OTC realm has created a need for quality OTC BPO formulations, which can be recommended by dermatologists and other healthcare providers. Many OTC formulations exist that can be purchased through mass merchandisers, direct sales, and infomercial marketing, yet few have been tested against prescription counterparts in treatments that include tretinoin cream 0.025%. Because dermatologists frequently combine the antibacterial benefits of BPO with the benefits of tretinoin to target noninflammatory and inflammatory lesions, this regimen seemed worthwhile to study in participants with mild to moderate acne. The OTC BPO and prescription BPO formulations demonstrated parity for efficacy and tolerability when used in a treatment regimen containing tretinoin cream 0.025%. Both BPO products were of similar particle size and composition.

There are several unique attributes of the OTC BPO formulation that merit further discussion. The BPO 5.5% formulation used in treatment A contained other antiacne ingredients, such as salicylic acid and lipohydroxy acid. Salicylic acid is an antiacne active ingredient that can be used in concentrations up to 2% according to the

Table 3.

Mean Scores of Objective Tolerability (Investigator Assessed)[a]

Parameter[b]	Treatment	Baseline	Week 2	*P* Value[c]	Week 4	*P* Value[c]	Week 8	*P* Value[c]	Week 12	*P* Value[c]	Week 16	*P* Value[c]
Erythema	Treatment A	0.4	0.4	.652	0.4	.813	0.2	.438	0.2	.375	0.1	.125
	Treatment B	0.3	0.6	.042	0.3	.844	0.1	.188	0.2	.313	0.1	.063
Edema	Treatment A	0.1	0.2	.750	0.2	1.000	0.1	1.000	0.0	.375	0.0	.500
	Treatment B	0.1	0.2	.500	0.1	1.000	0.0	.500	0.0	.500	0.0	.500
Dryness	Treatment A	0.2	0.7	.004	0.3	.578	0.2	.844	0.2	.844	0.0	.063
	Treatment B	0.4	0.9	<.001	0.6	.211	0.2	.547	0.2	.175	0.0	.039
Peeling	Treatment A	0.0	0.6	.001	0.3	.039	0.2	.188	0.1	.500	0.0	1.000
	Treatment B	0.1	0.5	.002	0.5	.013	0.1	.813	0.1	.844	0.0	.250

[a]Treatment A consisted of benzoyl peroxide 5.5% with lipohydroxy acid applied twice daily and tretinoin cream 0.025% applied at bedtime. Treatment B consisted of clindamycin 1%–benzoyl peroxide 5% gel applied twice daily and tretinoin cream 0.025% applied at bedtime.
[b]Rated on a 4-point scale (0=none; 3=severe).
[c]Compared with baseline.

Table 4.

Mean Scores of Subjective Tolerability (Participant Assessed)[a]

Parameter[b]	Treatment	Baseline	Week 2	*P* Value[c]	Week 4	*P* Value[c]	Week 8	*P* Value[c]	Week 12	*P* Value[c]	Week 16	*P* Value[c]
Stinging	Treatment A	0.0	0.8	<.001	0.4	.016	0.5	.031	0.3	.094	0.2	.375
	Treatment B	0.1	0.8	<.001	0.4	.042	0.3	.083	0.2	.365	0.1	.563
Tingling	Treatment A	0.1	0.7	.007	0.3	.313	0.3	.547	0.3	.469	0.1	.813
	Treatment B	0.2	0.6	.001	0.4	.020	0.3	.206	0.1	.547	0.0	.063
Itching	Treatment A	0.1	0.5	.027	0.4	.084	0.3	.301	0.3	.195	0.3	.469
	Treatment B	0.2	0.5	.007	0.4	.123	0.3	.641	0.2	.000	0.1	.438
Burning	Treatment A	0.1	1.0	<.001	0.4	.049	0.5	.074	0.4	.098	0.1	1.000
	Treatment B	0.2	1.1	<.001	0.6	.013	0.5	.054	0.3	.588	0.0	.063

[a]Treatment A consisted of benzoyl peroxide 5.5% with lipohydroxy acid applied twice daily and tretinoin cream 0.025% applied at bedtime. Treatment B consisted of clindamycin 1%–benzoyl peroxide 5% gel applied twice daily and tretinoin cream 0.025% applied at bedtime.
[b]Rated on a 4-point scale (0=none; 3=severe).
[c]Compared with baseline.

US Food and Drug Administration acne monograph.[1] It is a colorless, crystalline, oil-soluble, phenolic compound originally derived from the willow tree.[10] Salicylic acid, a β-hydroxy acid also known as 2-hydroxybenzenecarboxylic acid, can penetrate into the follicle where it acts as a comedolytic agent. Although it does not kill *P acnes* and does not prevent the development of antibiotic resistance, it can be combined with BPO to deliver these benefits, as in the formulation tested.[11]

The third unique ingredient in our study was lipohydroxy acid. Lipohydroxy acid is a β-hydroxy acid also known as 2-hydroxy-5-octanoyl benzoic acid. It is a salicylic acid derivative containing an 8 carbon acyl fatty acid chain linked to the fifth carbon of the benzene ring. The added fatty group makes the lipohydroxy acid more lipophilic than salicylic acid, thus increasing its ability to cause corneodesmosome dissolution in the follicle, which can lead to increased comedolytic activity. This ingredient was not present in the prescription BPO regimen and might account for some of the efficacy results obtained with the OTC BPO formulation.

The limitations of this study include the small sample size; however, enough participants were included to reach statistical significance. It might be interesting to undertake another study that does not include the tretinoin cream 0.025% in combination with the 2 test BPO formulations to eliminate the retinoid effect. The combination therapy was used because it represents a standard topical therapy for acne.

Conclusion

In our study of 66 participants with mild to moderate acne, statistically significant improvement in acne compared with baseline was noted in a treatment regimen combining an OTC BPO 5.5% formulation with lipohydroxy acid and tretinoin cream 0.025% and in a treatment regimen combining prescription clindamycin 1%–BPO 5% gel and tretinoin cream 0.025%. The improvement of acne and the tolerability were comparable in both treatments.

This study demonstrates that a treatment regimen for mild to moderate acne can be constructed using an OTC BPO formulation and a prescription retinoid to achieve statistically significant acne improvement. This formulation has the additive benefit of lipohydroxy acid, which may provide enhanced comedolytic effects over the BPO alone.

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