A Study of 5.5% Benzoyl Peroxide Microsphere Cream Versus 6% Benzoyl Peroxide Gel in the Treatment of Acne Vulgaris

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Benzoyl peroxide (BP) is among the most commonly prescribed topical treatments for acne vulgaris. To improve tolerability without adversely affecting efficacy, a novel formulation of 5.5% BP incorporated into synthetic polymer microspheres was developed. We conducted a pilot study comparing the efficacy and tolerability of this microsphere formulation to a leading formulation of 6% BP gel.

Forty-eight subjects at 2 research facilities were enrolled in a 12-week study. Subjects were required to have mild to moderate facial acne vulgaris with defined lesion counts and were randomized and blinded to receive either the 5.5% BP microsphere formulation or 6% BP gel for the entire study. Efficacy was measured using acne lesion counts, along with static scoring of acne severity and a global improvement score. Tolerability was determined by collecting adverse event reports during the study, as well as scoring local skin reactions. Subject satisfaction was measured by survey questionnaires.

Of the 48 subjects enrolled, 44 completed the study. One subject withdrew because of excessive irritation; all others tolerated the products well, experiencing infrequent (usually mild) redness, scaling, or dryness. The 5.5% microsphere formulation demonstrated a trend toward improved efficacy and tolerability compared with the 6% gel formulation. On average, subjects in the 5.5% microsphere formulation group showed substantially greater improvement in acne severity scores at each visit. Subject questionnaires demonstrated a preference for the 5.5% microsphere formulation because of perceived efficacy and cosmetic acceptance.

BP products continue to be useful in the management of acne. The irritation profile of BP products may limit their use or force a choice to a lower-strength product. This study demonstrates that 5.5% BP incorporated into synthetic polymer microspheres has a tolerability profile equivalent to or better than a traditional 6% gel formulation, with greater efficacy and higher patient preference.

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Dr. Smith has performed clinical studies and conducted professional training for SkinMedica. Dr. Kempers reports no actual or potential conflict of interest in relation to this article.

Benzoyl peroxide (BP) is a mainstay of topical treatment for acne vulgaris. It penetrates the pilosebaceous duct and, via its antibacterial activity, reduces the density of *Propionibacterium acnes* on the skin. It also induces keratolysis, which helps reduce follicular plugging.[1] Various concentrations and formulations of BP that balance efficacy, tolerability, and cosmetic acceptability are currently available. BP remains among the most cost-effective treatments without significant bacterial resistance. Its utility

is sometimes limited, however, by patient acceptance and tolerability.

A new form of BP has been developed using a patented microentrapped drug-delivery system. This technology originally was pioneered to create a slow or sustained-release drug-delivery system. This vehicle has proven to be of particular use in dermatologic drug treatments in which gradual release may have benefits.[2] Such benefits include either improved efficacy from prolonged concentrations of the active ingredient or lowered frequency or severity of side effects because of a reduced flux of the active ingredient though the skin.

Historically, it has been well known that BP produces dose-dependent irritation side effects that frequently limit its clinical utility. Consistent with this rationale, novel formulations with microsphere drug-delivery systems have been shown to be less irritating than conventional formulations with comparable BP concentrations.[3] These findings suggest the therapeutic value of a new BP product using this novel drug-delivery system. A pilot study was conducted to demonstrate the efficacy of this novel formulation compared with a 6% BP gel.

MATERIALS AND METHODS

Forty-eight subjects with mild to moderate facial acne vulgaris were recruited to participate in the study at 2 research centers. Subjects were eligible if they were 12 years of age or older, had 20 to 50 papules and pustules, 20 to 60 open and closed comedones (excluding those on the nose), and no more than 1 nodule in the facial treatment area. Subjects were required to be following a stable skin care regimen for 1 month before enrolling in the study. Female subjects of childbearing potential were required to produce a negative pregnancy test at the start of the study. Subjects were ineligible to participate if they had used topical antibiotics within 2 weeks; topical retinoids within 12 weeks; light treatment, photodynamic therapy, or chemical peels within 8 weeks; oral antibiotics within 4 weeks; oral antiandrogens within 8 weeks; or oral retinoids within 12 months of study commencement. Subjects using oral contraceptives were eligible provided they had been using the same medication for at least 2 months. Subjects underwent an informed-consent discussion and signed an institutional review board–approved consent form before the study.

On enrollment and at each visit thereafter, acne lesions were counted and acne severity scores assigned by a blinded investigator. Acne severity scores were based on a 6-point scale (Table 1). The blinded investigator assessed the facial skin of each subject for erythema, dryness, and scaling, and subjects evaluated stinging and burning. All tolerability assessments were based on a 4-point scale (0=none; 3=severe). At the study's end, the blinded investigator and the study participants assessed improvement in facial acne using a 5-point scale (0=no improvement or worsening; 4=complete clearing). Subjects also assessed overall treatment satisfaction.

Subjects were randomly assigned to receive either 5.5% BP microsphere (BP-MS) cream (NeoBenz™ Micro

Table 1

Acne Severity Scale

Score	Criteria
0	Normal, clear skin with no evidence of acne vulgaris
1	Skin is nearly clear; rare, noninflammatory lesions present with rare, noninflamed papules (papules must be resolving and may be hyperpigmented, though not pinkish red)
2	Some noninflammatory lesions present, with few inflammatory lesions (papules/pustules only; no nodules)
3	Noninflammatory lesions predominate, with multiple inflammatory lesions evident; several to many comedones and papules/pustules; may or may not be 1 small nodule
4	Inflammatory lesions more apparent; many comedones and papules/pustules; may or may not be nodules
5	Highly inflammatory lesions predominate; variable number of comedones, many papules/pustules/nodules

TABLE 2

Average Lesion Counts at Baseline*

	Inflammatory Lesions	Noninflammatory Lesions	Total Lesions
6% BP gel	29.8	44.7	74.4
5.5% BP-MS cream	26.3	36.2	62.5

*BP indicates benzoyl peroxide; MS, microsphere.

5.5%) or 6% BP gel (Triaz® 6% Gel). They were instructed to apply the product twice daily to the entire face for 12 weeks. The investigator remained blinded to treatment assignment throughout the trial. Photographs were taken at baseline and week 12. Concomitant treatments were recorded throughout the study period. Urine pregnancy tests were administered, if applicable, at baseline and at the study's end.

Descriptive statistics were planned only for data analysis in this pilot study. No power calculations were performed to determine sample size.

RESULTS

Demographics

Forty-eight subjects (24 per center) with mild to moderate facial acne were enrolled in the study. Subjects were divided equally into the 2 treatment groups. Four subjects withdrew from the study before week 12—1 from facial irritation attributable to the 6% BP gel and 3 for administrative reasons. Assessments that occurred outside protocol-specified windows were not included in individual analyses.

Twenty-six subjects (54%) were men, and 22 (46%) were women. Forty-three subjects (90%) were white, 4 (8%) were black, and 1 subject (2%) specified a race of black and white. The mean age was 17.1 years (range, 12–37 years). The treatment groups had similar average baseline lesion counts (Table 2). All but 3 subjects received an acne severity score of 3 at baseline.

EFFICACY

Acne Lesion Counts

After 4 weeks of treatment, subjects in both groups showed statistically significant reductions in inflammatory and total lesion counts ($P<.05$)(Figure 1). The greatest reductions were seen in inflammatory lesion counts (30% reduction in mean total acne lesion counts in the 5.5% BP-MS cream group and 12% in the 6% BP gel group). When assessed individually, the greatest reduction was seen in inflammatory lesion counts (40% decrease in the 5.5% BP-MS cream group; 26% decrease in the 6% BP gel group). More modest reductions in

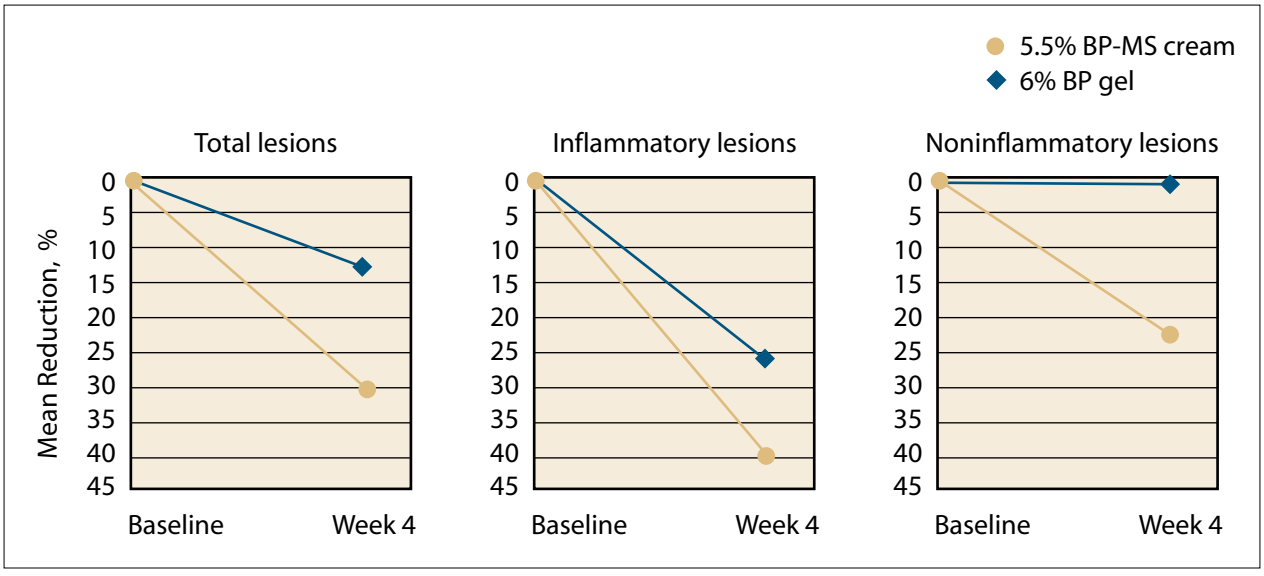

Figure 1. Mean lesion counts at week 4. BP indicates benzoyl peroxide; MS, microsphere.

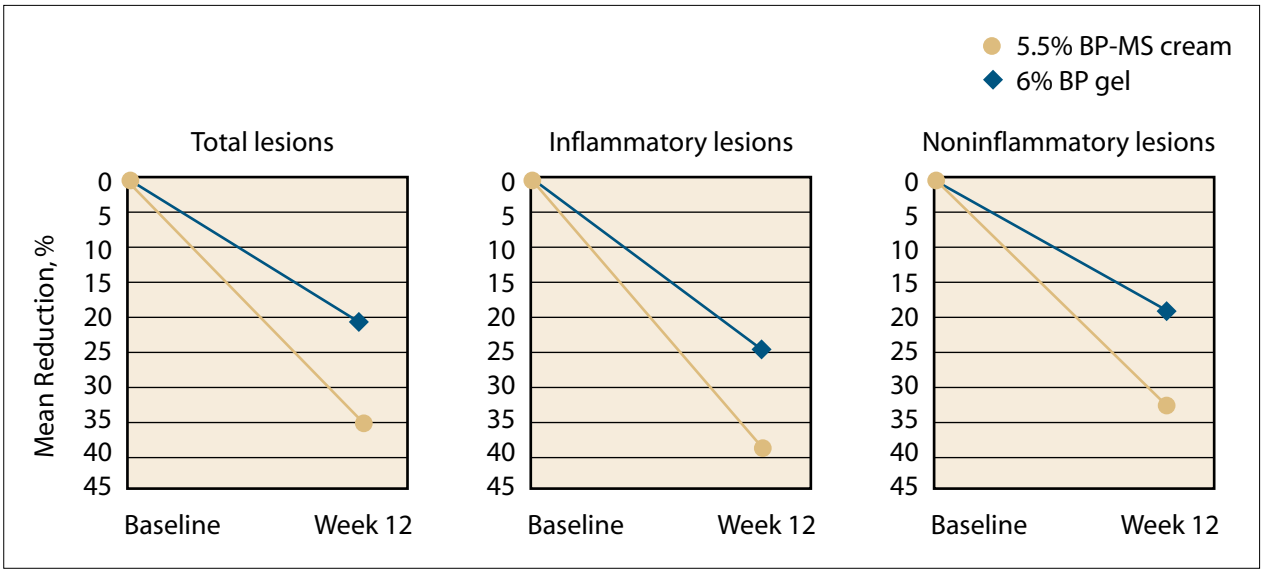

Figure 2. Mean lesion counts at week 12. BP indicates benzoyl peroxide; MS, microsphere.

noninflammatory lesion counts were observed (22% decrease in the 5.5% BP-MS cream group; 1% decrease in the 6% BP gel group). All lesion count reductions were statistically significant from baseline to week 4 in the 5.5% BP-MS cream group ($P<.05$). However, only the total and inflammatory lesion count reductions were statistically significantly for the 6% BP gel group ($P<.05$). The differences in lesion count reductions between the 5.5% BP-MS cream group and the 6% BP gel group did not reach statistical significance in this small pilot study.

Figure 2 shows the changes in lesion counts noted at week 12. Differences from baseline in inflammatory and noninflammatory lesion counts, as well as total lesion counts, are significant in both groups ($P<.05$). For each lesion type, the differences were greater for the 5.5% BP-MS cream group than for the 6% BP gel group, although the sample size was insufficient to show statistical significance.

Acne Severity Score

The differences between acne severity scores were tabulated (Figure 3). At week 4, 67% of subjects in the 5.5% BP-MS cream group experienced at least 1 grade of improvement compared with 31% in the 6% BP gel group. One subject in the 5.5% BP-MS cream group showed 2 grades of improvement.

At week 12, there was a shift to even greater responses in both groups. Forty-two percent of subjects in the 6% BP gel group showed an improvement of 1 grade and 5% showed an improvement of 2 grades. In the 5.5% BP-MS cream group, 48% of subjects showed an improvement of 1 grade and 19% showed an improvement of 2 grades. Two subjects in the 6% BP gel group and 1 subject in the 5.5% BP-MS cream group showed a worsening of 1 grade (data not shown).

Global Improvement Scores

Global improvement scores were assessed by the blinded investigator and subjects at the end of the study. The blinded investigator rated approximately 75% of the subjects in both treatment groups as showing some level of acne improvement. More subjects were graded as showing marked improvement or complete clearance in the 5.5% BP-MS cream group (33%) than in the 6% BP gel group (16%). The subjects treated with 5.5% BP-MS cream were more enthusiastic, with approximately 90% grading themselves as experiencing some level of improvement. More subjects in the 5.5% BP-MS cream group (38%) graded themselves as showing marked improvement or better compared with the 6% BP gel group (32%).

Overall Satisfaction

A similar number of subjects from both treatment groups rated their overall satisfaction as good or excellent (67% in the 5.5% BP-MS cream group and 68% in the 6% BP gel group). However, more subjects in the 5.5% BP-MS cream group rated their overall satisfaction as excellent compared with the 6% BP gel group (38% vs 11%, respectively)(Figure 4). A representative example of results obtained is shown in Figure 5.

Safety

Forty-six adverse events were reported by 48% of the subjects. Most were related to erythema, scaling, dryness, itching, and stinging and burning. One subject from the

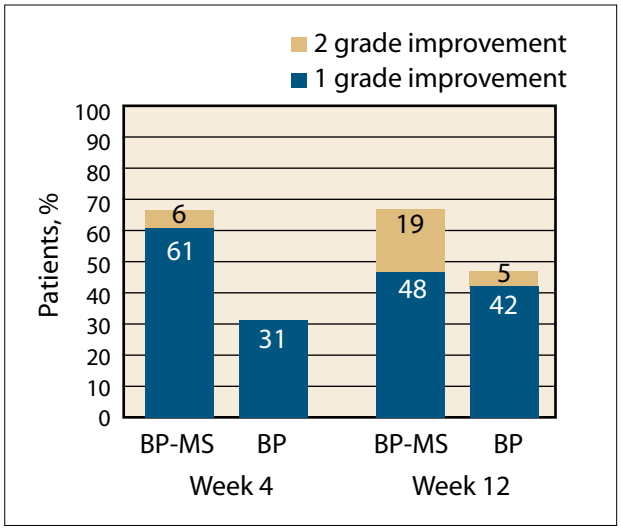

Figure 3. Improvement in acne severity scores. BP-MS indicates 5.5% benzoyl peroxide microsphere cream; BP, 6% benzoyl peroxide gel.

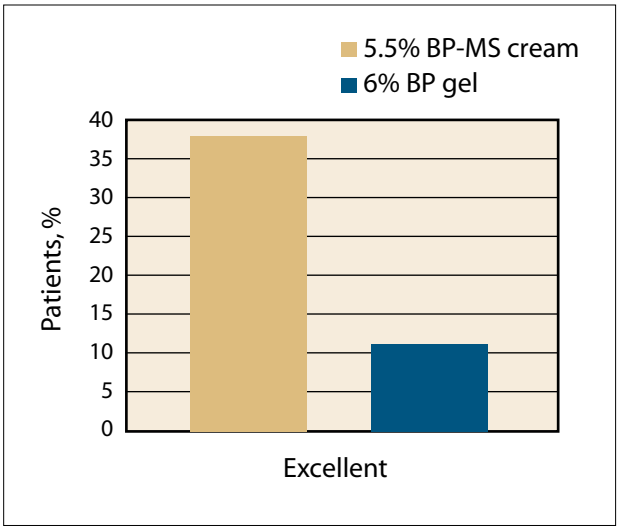

Figure 4. Overall subject satisfaction at week 12. BP indicates benzoyl peroxide; MS, microsphere.

6% BP gel group withdrew from the study because of irritation that occurred after 4 days of use. This reaction may have been due to true allergic contact dermatitis to BP or another ingredient in the product. The subject refused further analysis. For the other subjects, most tolerability issues were reported at week 4 (Figure 6).

Subjects in the 5.5% BP-MS cream group reported fewer adverse events than those in the 6% BP gel group. Overall, subjects in the 6% BP gel group reported greater frequency in all categories except for scaling. In nearly all cases, adverse events were rated as mild (excluding the subject who discontinued the study because of skin irritation). In most cases, irritation had resolved considerably by week 12, with 16% of subjects reporting local adverse events, all of which were rated as mild.

COMMENT

In this pilot study, both 5.5% BP-MS cream and 6% BP gel were effective in treating acne vulgaris. Lesion counts revealed that both products demonstrated significant activity against inflammatory and noninflammatory lesions ($P<.05$). Subjects in the 5.5% BP-MS cream group trended toward greater improvement than those in the 6% BP gel group at weeks 4 and 12. Global scores for the subjects reiterated these findings, but differences between the groups were less dramatic. It should be noted, however, that subjects in the 5.5% BP-MS cream group showed a 2-point increase in global improvement. As all but 3 subjects had a severity score of 3 at baseline, a 2-point improvement indicates a score of almost clear.

It is not surprising that there were no statistically significant differences in safety and efficacy between the 2 groups. This trial was planned and executed without an expectation of such findings; it was a pilot study only. Differences between topical acne products are relatively small, and trials that demonstrate statistically significant differences between such products may require hundreds or even thousands of participants.[4]

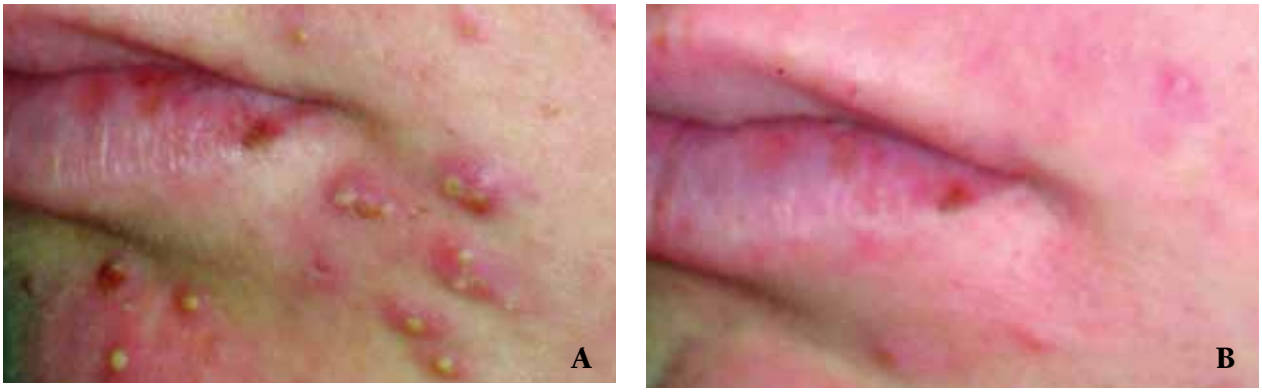

Figure 5. Subject before treatment with 5.5% benzoyl peroxide microsphere cream (A) and at week 12 (B).

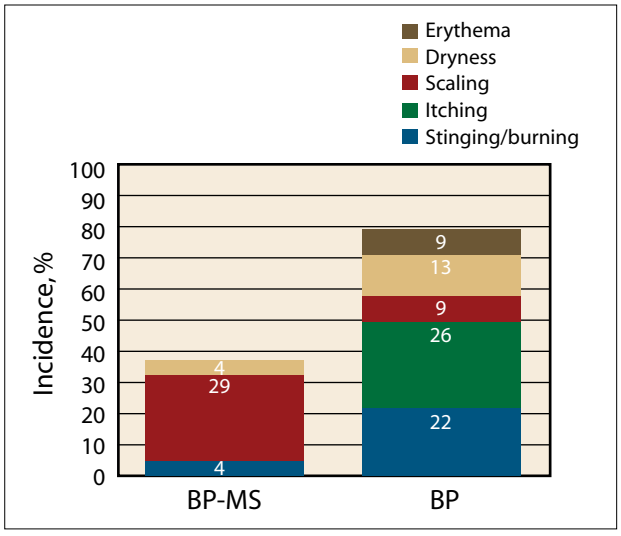

Figure 6. Tolerability assessments at week 4. BP-MS indicates 5.5% benzoyl peroxide microsphere cream; BP, 6% benzoyl peroxide gel.

When selecting a topical acne treatment, it is critical to choose a therapy that is likely to result in optimal product use and compliance. For example, it is well known that once-daily treatments are associated with greater compliance than treatments requiring more frequent application.[5] More subjects in the 5.5% BP-MS cream group rated their overall satisfaction as good or excellent compared with the 6% BP gel group. It may be inferred that greater satisfaction will lead to improved compliance and better disease control.

The 5.5% BP-MS cream product is formulated with a proprietary microsphere drug-delivery system that allows prolonged release at the skin surface with low transdermal penetration. This delivery system is expected to reduce the known irritation issues associated with BP. It is interesting to note that results from this pilot study support a possible benefit from 5.5% BP-MS cream compared with a traditional 6% gel formulation; however, one of the irritation parameters (ie, scaling) was actually greater with the 5.5% BP-MS formulation. A presumed therapeutic action of BP is keratolysis, which is thought to relieve some of the follicular plugging that is part of the triad of acne pathogenesis. Chemical peeling and exfoliation have long been advocated as treatments for acne vulgaris.[6,7] Thus, it is possible that the increased scaling noted in the 5.5% BP-MS cream group is due to better epidermal exposure to BP and more of its keratolytic effect. The fact that the blinded investigator did not observe associated increases in erythema or dryness and subjects did not report increased itching or burning further corroborates this notion.

Despite the differences shown in Figure 6, both products were well tolerated, with a low but expected rate of irritation. Subjects were asked to report their impressions of the feel and odor of the products; all reports were quite favorable, with no distinct differences (data not shown). The 6% BP gel has enjoyed considerable popularity in the marketplace, and the data from this study confirm its utility. Given the similarity in this data, one might expect the same results from the 5.5% BP-MS cream as well.

Statistically significant improvement from baseline was observed in both the 5.5% BP-MS cream group and the 6% BP gel group ($P<.05$). From a trend perspective, improvements were greater with 5.5% BP-MS cream at weeks 4 and 12. The irritation profile in both groups was low, with more favorable data reported in the 5.5% BP-MS cream group in all categories except scaling. Data from this study indicate that 5.5% BP-MS cream is effective, well tolerated, and well liked by users.

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