ORIGINAL ARTICLE

Prospective, open-label, comparative study of clindamycin 1%/benzoyl peroxide 5% gel with adapalene 0.1% gel in Asian acne patients: efficacy and tolerability

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Abstract

Background Used as individual agents, topical antibiotics and benzoyl peroxide are known to be effective in treatment of acne. Clindamycin phosphate 1% with benzoyl peroxide 5% (CDP/BPO) is a new combination gel, made by rationale, in that combination drug is more effective than either ingredients used alone. Adapalene 0.1% (ADA) is the third-generation retinoid, shown to be as effective as other topical retinoid with well tolerability.

Objectives To compare the efficacy and tolerability in combination of CDP/BPO in comparison with ADA in Asian patients with mild to moderate acne vulgaris.

Methods Total of 69 patients, including 31 patients for CDP/BPO group and 38 for ADA group, with mild to moderate acne vulgaris were enrolled for a 12-week prospective, randomized, open-label comparative study of topical agents. Efficacy was assessed by lesion counts, acne grading system, and global improvement. Adverse events were also evaluated in scale of 0 (none) to 3 (severe).

Results Both CDP/BPO and ADA were effective in reducing lesion counts and acne severity scale and showed significant global improvement. However, CDP/BPO offered greater efficacy against inflammatory lesions than ADA. Both drugs were well tolerated with minimal adverse drug reactions.

Conclusion Combination formulation of CDP/BPO and ADA were shown to be both effective in decreasing total, inflammatory, and non-inflammatory lesion counts along with well tolerability in Asian patients with mild to moderate acne vulgaris.

Received: 1 April 2008; Accepted 29 May 2008

Keywords

acne vulgaris, adapalene, benzoyl peroxide, clindamycin, combination

Conflicts of interest

None declared

Introduction

Topical therapy is generally considered as an appropriate first-line therapy in mild to moderate acne. Tretinoin, benzoyl peroxide, and topical antibiotics including clindamycin and erythromycin are the most frequently used topical agents.[1–5] Furthermore, significant synergy results when there is overlap in the mechanistic activities of the agents that are being used together.[5] Premixed combination product of clindamycin phosphate 1% with benzoyl peroxide 5% (CDP/BPO), which are currently being used as individual topical agents, is made by rationale, in that combination drug is more effective than either ingredients used alone. CDP/BPO was first introduced in Korea among Asian countries.

Funding sources: This study was supported by Medical Research Grant (2003–32) Pusan National University.

Adapalene (ADA) is third-generation retinoid gel, widely used as topical treatment of acne vulgaris. It is generally well tolerated with no known interactions with other drugs. Few studies have been conducted regarding the effectiveness CDP/BPO, but not in comparison with ADA in Asian population. The efficacy and tolerability of a combination formulation of CDP/BPO vs. ADA were evaluated in Asians.

Patients and methods

Patients

Total of 69 patients with mild to moderate facial acne vulgaris enrolled in the study in the Department of Dermatology at Pusan National University Hospital. Patients were at least 12 years of age with more than 12 inflammatory lesions, but no more than 3

nodules or cyst, and more than 12 non-inflammatory lesions and an acne grade of ≥ 2.0 and < 7.0 as in Leeds revised acne grading system[6] and ≥ 2.0 and < 4 as in KAGS-2.[7] A 'washout' period of at least 2 weeks of topical antibiotics and corticosteroid, 1 month of oral antibiotics and cortico-steroid, and 6 months of oral retinoid agent prior to the start of treatment was required. Patients were excluded if they had acne conglobata, acne fulminans, secondary and severe acne, and other dermatologic conditions requiring systemic treatments. Women were excluded if they were pregnant, planning pregnancy, or nursing. In addition, written informed consent was obtained from each patient.

Methods

This was a prospective, open-label, comparative study of CDP/BPO and ADA. Clinical assessment at baseline included demographic data, previous medical history, and total, inflammatory, and non-inflammatory lesion counts. Patients were randomly assigned to one of the two groups. Patients applied the study gels once daily for 12 weeks in the evening after washing face with cleanser and patting dry with soft towel. Pea-sized amounts of study gel were applied on whole face including non-lesional area, except periocular area and lip. Moisturizers were allowed if needed, but other lotions, creams, medicated powders, or solutions were restricted. Efficacy and tolerability were evaluated at baseline, weeks 1, 2, 4, 8, and 12. Photos were also taken from the front, left, and right oblique (45 degree) view.

Assessment of efficacy and tolerability

At each visit, the number of total, inflammatory, and non-inflammatory lesions on the face was counted by the same investigator. Acne severity was evaluated by Leeds revised acne grading system and Korean Acne Grading System (KAGS-2). Global improvement was rated by investigator in 6-point scale: very much improved (3), much improved (2), minimally improved (1), no change (0), minimally worse (–1), and much worse (–2). Tolerability was assessed through scale of peeling/desquamation, stinging/burning, redness/erythema, dryness, and itching/pruritus on none (0), mild (1), moderate (2), and severe (3). Patients were also asked of other adverse events.

Statistical analysis

The *t*-test was performed to compare number of inflammatory, non-inflammatory, and total lesions and change in acne grades between CDP/BPO and ADA. *P*-value < 0.05 was considered statistically significant.

Results

Demographic features

Total of 69 patients, 20 males and 49 females, were involved in the study with average age of 22.7 years (Table 1). Sixty-nine patients were randomized into one group: 31 patients in CDP/BPO group and 38 patients for ADA group. The average numbers of total, inflammatory, and non-inflammatory lesions were 48.2, 31.6, and 16.7 in CDP/BPO and 43.0, 26.6, and 16.4 in ADA, respectively. In addition, CDP/BPO and ADA had average acne grade of 3.4 and 3.2, respectively, in Leeds revised acne grading system and 2.6 and 2.8, respectively, according to KAGS-2.

Table 1 Demographics of patients

	CDP/BPO	ADA	Total
Subjects	31	38	69
Men/women	7/24	13/25	20/49
Age (mean, years)	24.5	21.1	22.7
Lesion counts (mean)			
Inflammatory	31.6	26.6	28.8
Non-inflammatory	16.7	16.4	16.5
Total	48.2	43.0	45.3
KAGS-2	2.6	3.4	
Leeds revised acne grading system	2.8	3.2	

Clinical efficacy

Number of total, inflammatory, and non-inflammatory lesions reduced after the initiation of therapy for both treatment groups (Fig. 1). Statistically significant more reduction of acne lesions was shown in CDP/BPO from week 8 for inflammatory and total lesions (Fig. 1a,c). Acne grade improved for both treatment groups according to Leeds revised acne grading system and KAGS-2 during the course of the study (Fig. 2). At week 2, the acne grade of combination gel significantly reduced when compared with ADA. The global improvement scale rated 2 (much improved) and 3 (very much improved) in 68% of CDP/BPO and 61% in ADA (Fig. 3). At the end of the treatment period, facial acne lesions dramatically improved (Fig. 4).

Tolerability

Both drugs were well tolerated with minimal adverse events, such as erythema, dry skin, desquamation, stinging/burning sensation, and pruritus (Fig. 5). Most adverse events occurred within a month and rarely lasted more than a month. CDP/BPO showed better tolerability on point of local irritability but allergic reaction was suspected in four patients, upon clinical manifestation.

Discussion

The combination formulation of CDP/BPO and ADA both effectively decreased total, inflammatory, and non-inflammatory lesions count. Difference in acne grade was apparent in week 2, with CDP/BPO being associated with greater improvement with sustained trend of 12 weeks, in favour of CDP/BPO. However, statistically significant decrease in number of total and inflammatory lesions count was evident in weeks 8 and 12. The difference

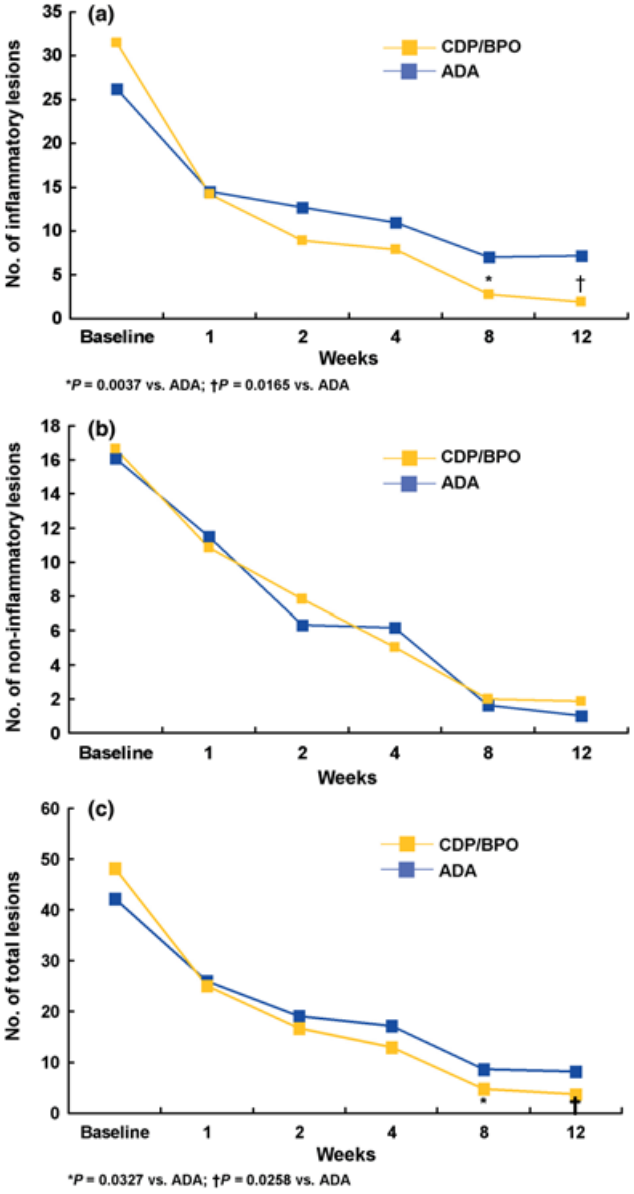

Figure 1 Lesions count A, inflammatory lesions. B, non-inflammatory lesions. C, total lesions.

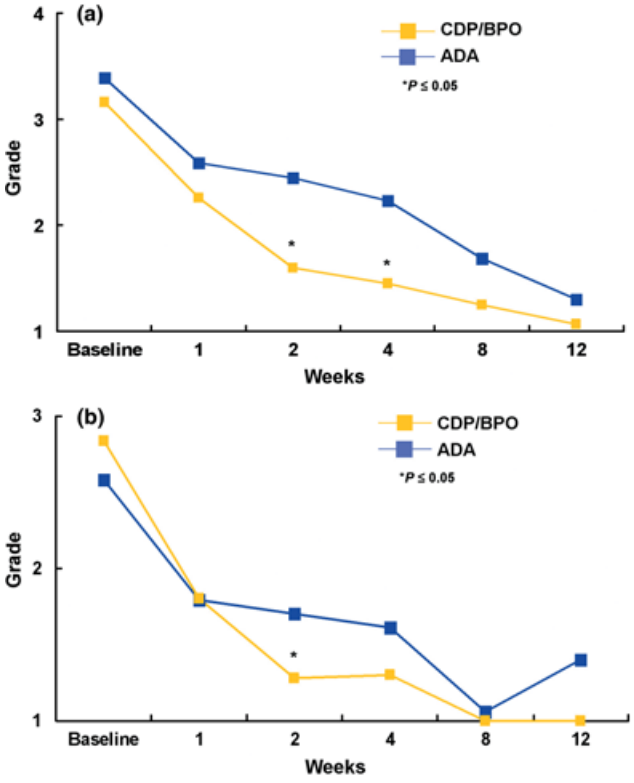

Figure 2 Acne grading system. A, Leeds Revised Acne Grading System. B, KAGS-2.

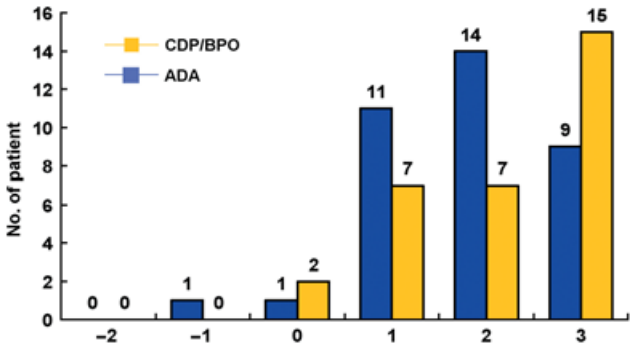

Figure 3 Global improvement scale.

between CDP/BPO and ADA was greatest for inflammatory lesions. Overall adverse events occurred less frequently in CPO/BPO.

In mild to moderate acne, topical treatments, including tretinoin, benzoyl peroxide, and antibiotics, are considered to be the first-line therapy.[1–5] Since one of the major contributing factor in acne is the hyperkeratinization of the pilosebaceous follicles, topical retinoid have been well accepted.[8,9] On the other hand, topical antibiotics eliminate *Propionibacterium acne* and suppress the production of free fatty acid and chemotactic factor, thus allowing the inflammation to subside.[10,11] Unfortunately, with an increased use of topical and oral antibiotics, emergence of erythromycin-resistant strain of *P. acne* along with cross-resistance of erythromycin and clindamycin is widespread among *P. acne*.[12,13] Due to the emergence of erythromycin-resistant strain of *P. acne*, single therapy of topical antibiotics has lost its preference as the first-line therapy.[14] Nonetheless, when topical antibiotics are used with other topical agents such as zinc, tretinoin, or benzoyl peroxide, concomitant use of both drugs would work in synergy, giving better outcome.[15,16]

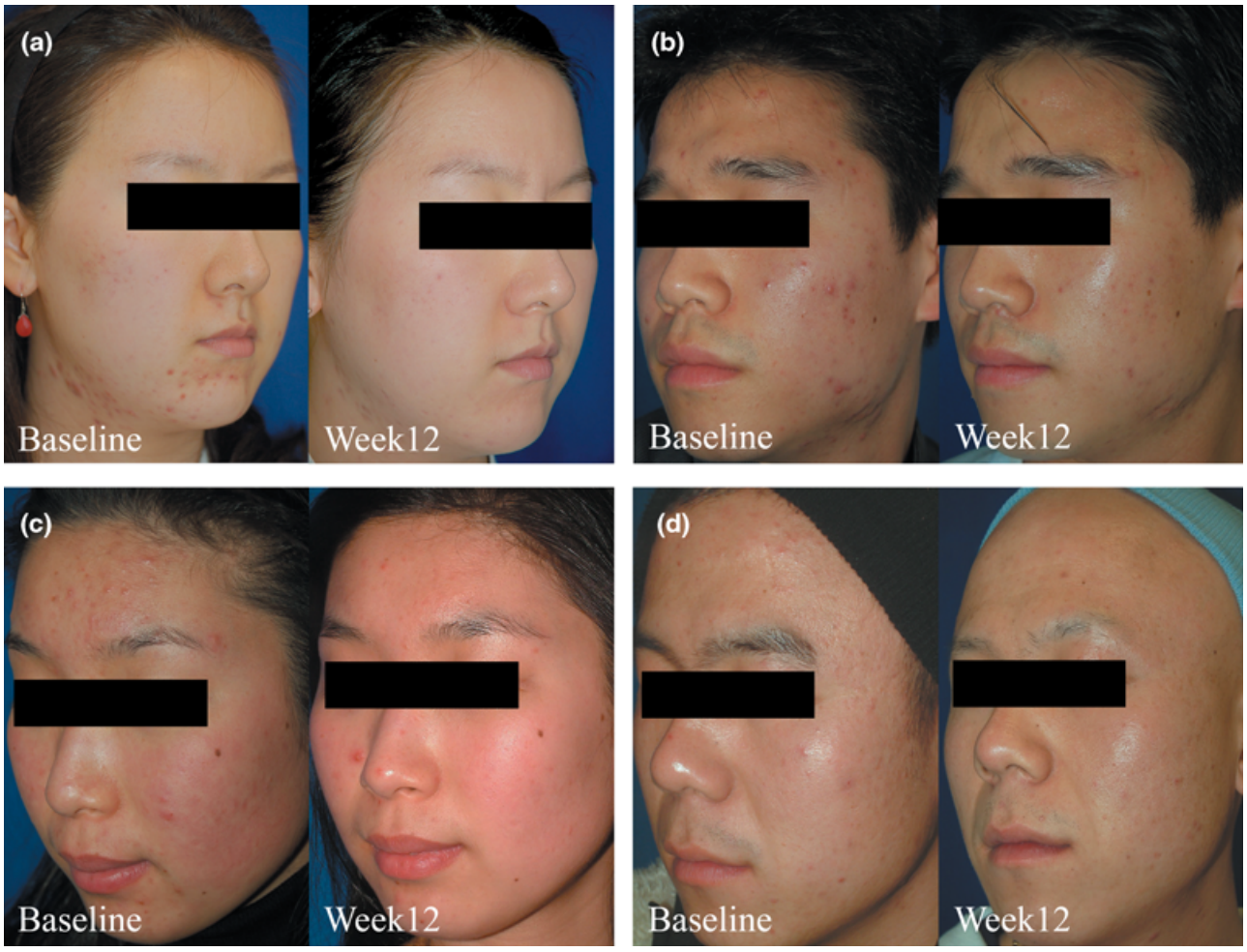

Figure 4 Clinical improvement of moderate acne patient; at baseline and 12 weeks after application of CDP/BPO gel (A, B) and ADA gel (C, D).

In Asia, Korea was the first to be introduced to combination formulation for CDP/BPO. In Korea, as a topical retinoid gel, ADA is also available. ADA, a derivative of napthoic acid, became available and has been widely accepted by Korean dermatologist. In a comparative study of CDP/BPO and ADA among Caucasians, CDP/BPO showed rapid onset of action and favourable safety profile, therefore improving compliance and efficacy.[17] Few research has been conducted to know about the specific treatment responsiveness and adverse events in topical management of acne vulgaris among Asians. We studied the efficacy and tolerability of CDP/BPO in comparison with ADA in Asian population because there is certain degree of racial differences in skin structure and physiology and susceptibility between Asians and Caucasians.

In general, Asians frequently complain about sensitive, stinging skin after application of chemical or physical trauma, giving question whether or not there actually is a racial/ethnic difference in susceptibility of human subjects to skin reaction. There are still controversies over the matter that Asian population may be more susceptible to irritant or just that self-report skin sensitivity is higher than Caucasians.[18–22] However, cumulative irritation test and acute irritant test have shown to be larger and more severe in Caucasians than Japanese.[20] This is probably caused by increased percutaneous absorption of chemical due to high permeability of water.[21] Additionally, Asian skin was significantly more sensitive to stripping than Caucasians, indicating the easy alternation of stratum corneum barrier function by physical trauma.[22] For that reason, a major challenge encounters in clinical practice in patients with acne vulgaris to provide topical medication with least adverse events such as erythema, dryness, sting and irritability, especially in Asian population.

Tadaki reported a higher level of intolerance among Japanese subjects to topical tretinoin cream than in Caucasians.[23] In a comparative study of ADA gel 0.1% and tretinoin gel 0.025% in Chinese patients, overall 45.7% of the tretinoin patients and 32.4%

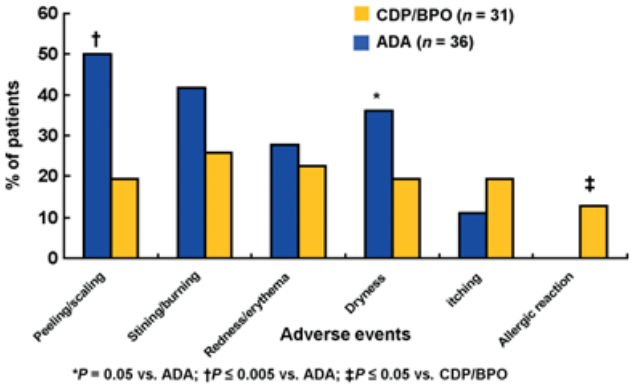

Figure 5 Adverse events and tolerability; CDP/BPO gel showed better tolerability on point of local irritability, but it may induce allergic reaction.

of ADA experienced some forms of irritation, which encounters much higher incidence of adverse events in both tretinoin and ADA, than those reported in Caucasians.[24]

BPO is also generally regarded as a strong irritant and a weak allergen. However, the combination of CDP/BPO has shown to be well better tolerated in our study. It may be related to the moisturizers and direct inflammatory action of CDP, which could alleviate the irritancy of BPO.[25] Maintenance of epidermal barrier integrity and function is vital component of successful topical treatment. CDP/BPO contains unique formation of glycerin, a humectants, and dimethicone as emollient to obviate the need for supplemental moisturizers to minimize irritation. Such ingredients maintain barrier integrity and reduce skin irritation. As a result, CDP/BPO was well tolerated for Asians as well.

Recent guidelines have promoted the use of topical retinoid as first-line and maintenance therapy for the treatment of acne vulgaris with or without topical antimicrobials in mild acne.[8,9] Oral antibiotics are recommended to be used in combination for moderate acne.[2] With there being a greater concern regarding the use of oral or systemic antibiotics alone, being associated with development of resistance, CDP/BPO could be indicated as a first line therapy for mild to with or without topical retinoid for the treatment of mild to moderate acne vulgaris. Although ADA effectively inhibits the formation of microcomedones and reduces in numbers, the greater anti-inflammatory activity of both CDP and BPO promotes an earlier response to treatment with better tolerability in Asian population.

For acne is a multifactorial condition, combination therapy is well suited, and is rational to formulate acne therapy regimens that target as many factors as possible.[5] It could be hypothesized that concomitant use of ADA with CDP/BPO would be superior to the two individual agents in global improvement and reduction in inflammatory, non-inflammatory lesions, including microcomedones. In fact, combination uses of CDP/BPO and ADA have shown to further enhance the therapeutic results.[26,27] Further study should be conducted in comparing the therapeutic efficacy and tolerability of combination of CDP/BPO and ADA in Asian acne patients.

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