Efficacy and tolerability of adapalene 0.1%-benzoyl peroxide 2.5% combination gel in treatment of acne vulgaris in Indian patients: A randomized investigator-blind controlled trial

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Background: Topical retinoid based combinations are recommended to enhance the outcome of acne treatment. Adapalene-benzoyl peroxide (BPO) combination gel was approved in 2009 for acne treatment. The aim of this study was to evaluate the efficacy and tolerability of adapalene 0.1%-benzoyl peroxide 2.5% combination gel compared to adapalene 0.1% gel monotherapy and benzoyl peroxide 2.5% gel monotherapy in treatment of acne vulgaris in Indian patients.

Methods: A randomized, parallel group, investigator-blind clinical trial was conducted from September 2014 to September 2015 in the Dermatology outpatient department. The patients were randomized into three groups of adapalene 0.1% gel, benzoyl peroxide 2.5% gel, and adapalene 0.1%-benzoyl peroxide 2.5% combination gel. The patients were asked to apply the allocated gel to the face in the evening for 12 weeks. Efficacy was evaluated using percent of reduction in total, inflammatory, and non-inflammatory lesions and success rate while tolerability was assessed by evaluating skin dryness, erythema, stinging or burning sensation and scaling at baseline and 1, 2, 4, 8, and 12 weeks.

Results: At the end of 12 weeks, the success rate reached 37.2% with adapalene-BPO combination gel compared to 23.3% and 19.4% for adapalene and benzoyl peroxide gel monotherapy respectively. Adapalene-BPO combination gel was significantly effective in the reduction of total, non-inflammatory and inflammatory lesions by 75.9%, 75.4%, and 74.7% respectively compared to the corresponding monotherapies. Side effects with adapalene–BPO combination gel were mild and transient.

Conclusion: Adapalene–BPO combination gel was more efficacious and better tolerated than adapalene and benzoyl peroxide gel monotherapy.

Keywords: acne vulgaris, adapalene, benzoyl peroxide, treatment

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INTRODUCTION

Acne vulgaris is a chronic skin disease of the pilosebaceous unit with a multifaceted pathophysiology mainly affecting the face, trunk, and back. The prevalence of acne vulgaris reported from various countries ranges to 87% of adolescents and up to 54% of adults [1].

Although acne is a self limiting disease, patients have social, psychological, and emotional

problems as reported in response to the 36-Item Short Form (SF-36) survey, a generic quality of life questionnaire [2].

Multiple pathophysiological factors are incriminated in acne involving hyperkeratinization, *Propionibacterium acne* proliferation, inflammation and excess sebum production [3]. Topical retinoid based combination therapy was first recommended in 2003 by global alliance to improve outcomes in acne [4] in the therapeutic algorithm, as this regimen acts on multiple pathophysiologic factors. Adapalene, a retinoid, reduces dyskeratosis at the pilosebaceous unit, inhibits the formation of microcomedones, and has mild anti-inflammatory effects [5]. Benzoyl peroxide (BPO) is a very effective broad-spectrum anti-bacterial agent and also has anti-inflammatory and comedolytic effects [6,7]. The fixed dose combination of adapalene 0.1% and benzoyl peroxide 2.5% gel was approved by US FDA in January 2009. Their complementary modes of action address three of four pathophysiologic processes of acne: abnormal keratinization leading to follicular plugging (comedo formation), proliferation of the bacterium *P. acne* within the follicle, and inflammation. So far, no Indian clinical data are available regarding the efficacy and tolerability of adapalene-benzoyl peroxide combination gel in acne vulgaris in Indian patients. We aimed to evaluate the efficacy and skin tolerability of adapalene-BPO combination gel compared to their corresponding monotherapies.

PARTICIPANTS AND METHODS

A single center, prospective, randomized, parallel group, investigator blind study with 12 weeks follow up was conducted to compare the efficacy and tolerability of adapalene 0.1%-benzoyl peroxide 2.5% (BPO) combination gel with adapalene 0.1% gel monotherapy and benzoyl peroxide 2.5% gel monotherapy in treatment of acne vulgaris in Indian patients.

The study was performed in an outpatient dermatology department during 1 year from September 2014 to September 2015. Male and female patients aged 12 to 35 years with grade 2, 3, and 4 of the Investigator's Global Assessment scale for acne vulgaris [8] were enrolled in the study. Patients with grade 5 of the Investigator's Global Assessment scale for acne, acne conglobata, acne fulminant, secondary acne, pregnant women, women with irregular menstruation, hirsutism, and those on oral contraceptive pills or other drugs with possible effects on the hormonal levels were excluded from the study. The patients who were already on treatment but discontinued treatment on their own for the last 3 months were also included in the study.

Written informed consent was taken from all patients (and parents/guardian if the patient was below 18 years of age) prior to entering the study. The study was conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice. This study was reviewed and approved by the Institutional Ethics Committee.

Three groups were assigned to adapalene 0.1% gel (A), benzoyl peroxide 2.5% gel (BP), and adapalene 0.1%-benzoyl peroxide 2.5% combination gel (ABP), respectively. The patients were instructed to apply the allocated gel once daily in the evening for 12 weeks. The patients were also asked to apply moisturizing cream daily in case of dryness throughout the study.

The efficacy of the allocated regimen was assessed and compared using mean percent change in total lesions (TL), non-inflammatory lesions (NIL), and inflammatory lesions (IL). The success rate, i.e. the percentage of patients rated clear (0) or almost clear (1) on the Investigator's Global Assessment scale for acne vulgaris, and the patients' assessment of the therapeutic efficiency (completely resolved, marked improvement, moderate improvement, mild improvement, no change, worsened) were also evaluated between study groups.

Safety and tolerability were assessed through evaluation of the clinical signs and symptoms like stinging and burning sensation, erythema, dryness and scaling using a four-point scale (0- absent, 1- mild, 2- moderate, 3- severe). Efficacy and tolerability were evaluated at baseline and 1, 2, 4, 8, and 12 weeks. To ensure the blinded design of the study, an investigator unaware of the treatment allocation performed the efficacy and tolerability evaluations.

The sample size was determined based on an estimated composite success rate of 50% [7] at the last evaluable time point, a power of 80%, and alpha error of 0.05 [9]. A total of 132 patients were randomized into three study groups.

Prior to the start of the study, a randomization

list was generated via simple randomization by a statistician using the Random Allocation software version 1.0.0. The randomization list was secured in a locked cabinet and electronic file to which the investigator/outcome assessor had restricted access. The allocation sequence was concealed from the investigator and outcome assessor using sequentially numbered, sealed, opaque envelops to enroll patients in the allocated groups. The investigator and outcome assessor did not have access to the randomization list and the study treatment was provided to the patients by a designated study drug dispenser. The study drug dispenser and subjects were instructed not to discuss the study treatment with the investigator or those assessing the outcomes.

Statistical analysis of the outcome variables was performed using paired *t*-test and one-way analysis of variance (ANOVA). Kruskal-Wallis test was used to compare side effects. The data were analyzed with SPSS 16.0 (SPSS Inc., Chicago, IL, USA) for windows. $P<0.05$ were considered significant.

RESULTS

A total of 132 patients were randomized and included in the intention to treat (ITT) analysis during the study period: 41 received adapalene-BPO combination gel, 45 received adapalene 0.1% gel monotherapy, and 46 received benzoyl peroxide 2.5% gel monotherapy. Among 132 enrolled patients, 90 (68.2 %) completed the study. Forty-two (31.8%) patients were excluded because of non compliance with the treatment regimen or the follow-up schedule and protocol violation. Thirty patients in each group who completed study were analyzed after 12 weeks of treatment (Figure 1).

Baseline characteristic of the ITT population are summarized in Table 1. At the end of 12 weeks, the success rate was 37.2% with adapalene-BPO combination gel compared to 23.3% and 19.4% with adapalene gel monotherapy and benzoyl peroxide gel monotherapy, respectively (Figure 2). Adapalene–BPO combination gel showed a significant mean percent reduction in total lesions,

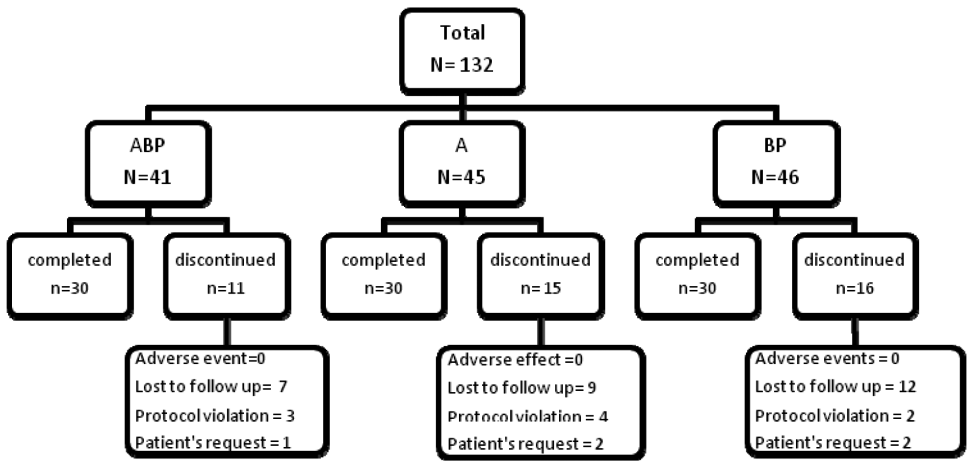

Figure 1. Patients' disposition.

Table 1. Demographic characteristics of the patients at baseline (intention to treat analysis approach).

	Adapalene-BPO* combination gel N (%)	Adapalene gel monotherapy N (%)	BPO* gel monotherapy N (%)	*P*
Patients	41	45	46	
Male	19 (46.3)	18 (40.0)	17 (37.0)	0.5
Female	22 (53.7)	27 (60.0)	29 (63.0)	0.4
Age (mean± SD†)	20.1±3.9	18.6±3.5	19.2±3.3	0.2
IGA‡ scale for acne				
2	17	21	22	0.7
3	13	14	16	0.6
4	11	10	8	0.6

BPO: benzoyl peroxide, SD: standard deviation, IGA: Investigator global assessment.

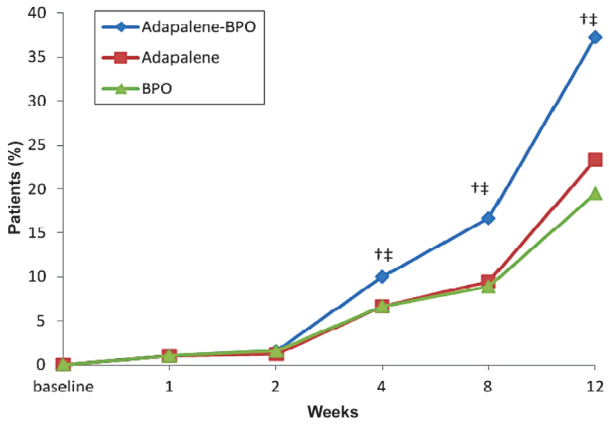

Figure 2. Success rate over time period (percentage of patients rated clear or almost clear on the IGA scale during the course of study) with statistical difference between three groups (P <0.05). Dagger indicates a statistically significant difference between adapalene-BPO combination gel and adapalene monotherapy (P<0.05). Double dagger indicates a statistically significant difference between adapalene-BPO combination gel and benzoyl peroxide gel monotherapy.

non inflammatory lesions and inflammatory lesions compared to adapalene and benzoyl peroxide gel monotherapy. Clinical response was seen earlier in patients who received adapalene-BPO combination gel starting after 2 weeks of treatment than monotherapy groups (Figure 3).

From baseline to week 12, patients treated with adapalene- BPO combination gel showed a mean reduction of 75.4% in total lesions compared to 60.5% in adapalene gel and 59.2% in benzoyl peroxide gel groups with a significant difference (P=0.0002) (Table 2). Adapalene-BPO combination gel caused a mean reduction of 74.8% in non-inflammatory lesions as compared to 61.0% in adapalene gel and 57.6% in benzoyl peroxide gel groups with a significant difference (P=0.001). The mean reduction in inflammatory lesions was 75.89% for adapalene- BPO combination gel compared to 58.6% and 53.4% for adapalene and benzoyl peroxide gel monotherapy respectively, which was statistically significant (P=0.008) (Table 2).

Adapalene-BPO combination gel showed tolerability comparable to adapalene and benzoyl peroxide monotherapy. A total of 42 patients experienced 56 adverse effects during 12 weeks of the study. None of the patients discontinued treatment because of adverse effects. More adverse effects were seen in adapalene–BPO combination gel as compared to adapalene and benzoyl peroxide gel monotherapy; however, no significant difference

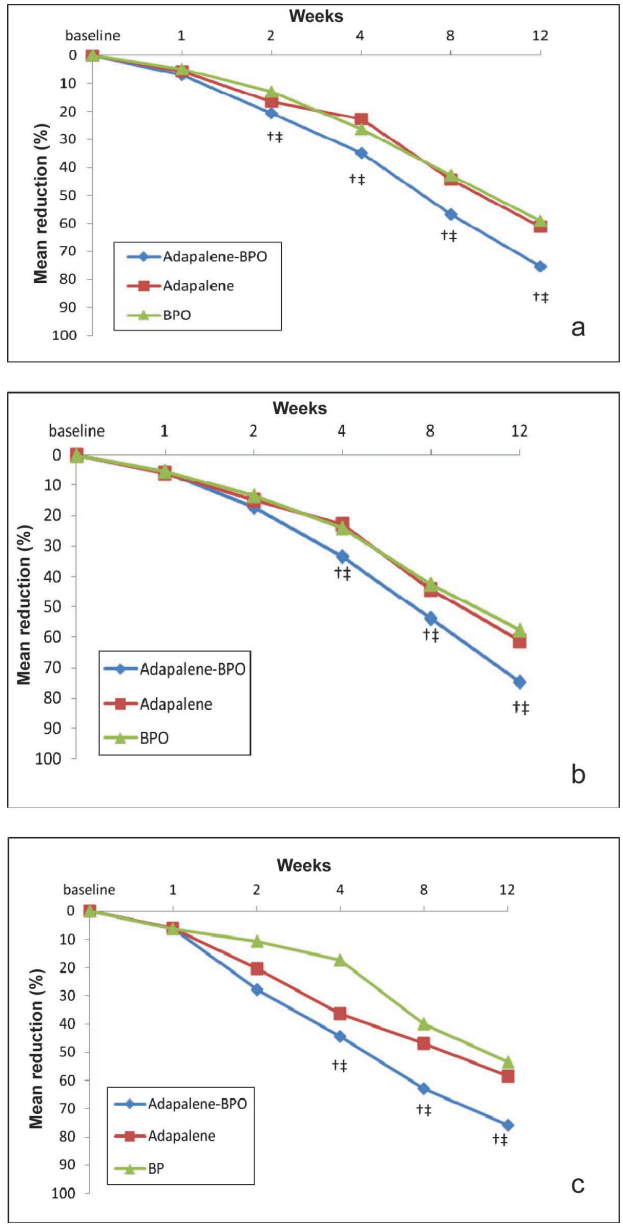

Figure 3. Mean percent reduction in total lesions **(3.a)**, inflammatory lesions **(3.b)**, non- inflammatory lesions **(3.c)** with P=0.0002, P=0.001, and P=0.008, respectively, after 12 weeks of treatment. Single dagger indicates a statistically significant difference between adapalene-BPO combination gel and adapalene gel monotherapy, and double dagger indicates a statistically significant difference between adapalene-BPO combination gel and benzoyl peroxide gel monotherapy (P<0.05).

was seen between these groups in each sign and symptoms of tolerability (Figure 4). The mean tolerability scores are presented in Table 3 For adapalene-BPO combination gel, dryness (46.0%) was the most common side effect followed by stinging and burning (26.9%), erythema (15.4%),

Table 2. Mean count of lesions before and after treatment and mean percentage of change of lesions in treatment groups.

	Total lesions			
	Baseline (mean±SD)	**12 weeks (mean±SD)**	**Mean reduction (%) (95% CI) at 12 weeks**	***P***
ABP	42.2±18.5	11.0 ±9.2	75.4 (7.7 to 14.3)	
A	42.3±22.4	17.6±14.0	61.2 (12.6 to 22.6)	0.0002
BP	47.3± 18.5	21.2±16.9	59.2 (15.2 to 27.3)	
	Non-inflammatory lesions			
	Baseline (mean±SD)	**12 weeks (mean±SD)**	**Mean reduction (%) (95% CI) at 12 weeks**	***P***
ABP	35.2±15.1	9.5±8.8	74.8 (6.4 to 12.6)	
A	36.8±21.6	15.6±13.1	60.5 (11.0 to 20.3)	0.001
BP	39.4± 18.3	18.3± 15.9	57.6 (12.6 to 24.0)	
	Inflammatory lesions			
	Baseline (mean±SD)	**12 weeks (mean±SD)**	**Mean reduction (%) (95% CI) at 12 weeks**	***P***
ABP	6.6±5.1	1.5±1.9	75. 9 (0.8 to 2.2)	
A	6.6±3.8	2.2±2.0	58.6 (1.5 to 2.9)	0.008
BP	7.9±5.4	3.0±2.2	53.4 (2.2 to 3.8)	

ABP: Adapalene 0.1%-benzoyl peroxide 2.5% combination gel, A: Adapalene 0.1% gel, BP: Benzoyl peroxide 2.5% gel, SD: Standard deviation.

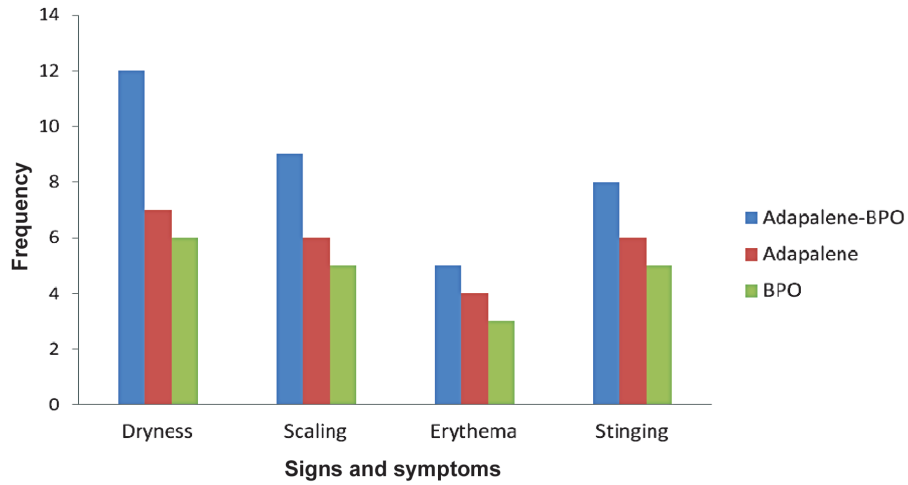

Figure 4. Frequency of local signs and symptoms experienced during study period.

Table 3. Average (mean ± standard deviation) score of the local tolerability signs and symptoms according to a four-point scale.

	Adapalene-BPO gel	**Adapalene gel monotherapy**	**BPO monotherapy**	***P***
Dryness	0.70±0.53	0.53±0.50	0.46±0.50	0.2
Scaling	0.46±0.67	0.30±0.53	0.26±0.52	0.5
Erythema	0.33±0.79	0.16±0.46	0.20±0.61	0.4
Stinging/burning	0.36±0.66	0.23±0.50	0.30±0.65	0.1

BPO: Benzoyl peroxide 2.5%.
ABP: Adapalene-benzoyl peroxide combination gel, A: Adapalene gel, BPO- Benzoyl peroxide gel

and scaling (11.5%) (Figure 4).

None of the patients in the three groups experienced any unintended adverse effects.

The patients' assessment of therapeutic efficacy showed that adapalene-BPO combination gel was significantly better than adapalene and benzoyl peroxide gel monotherapy (*P*=0.005). At 12 weeks, 79.8%, 57.5% and 58.0% of the patients reported

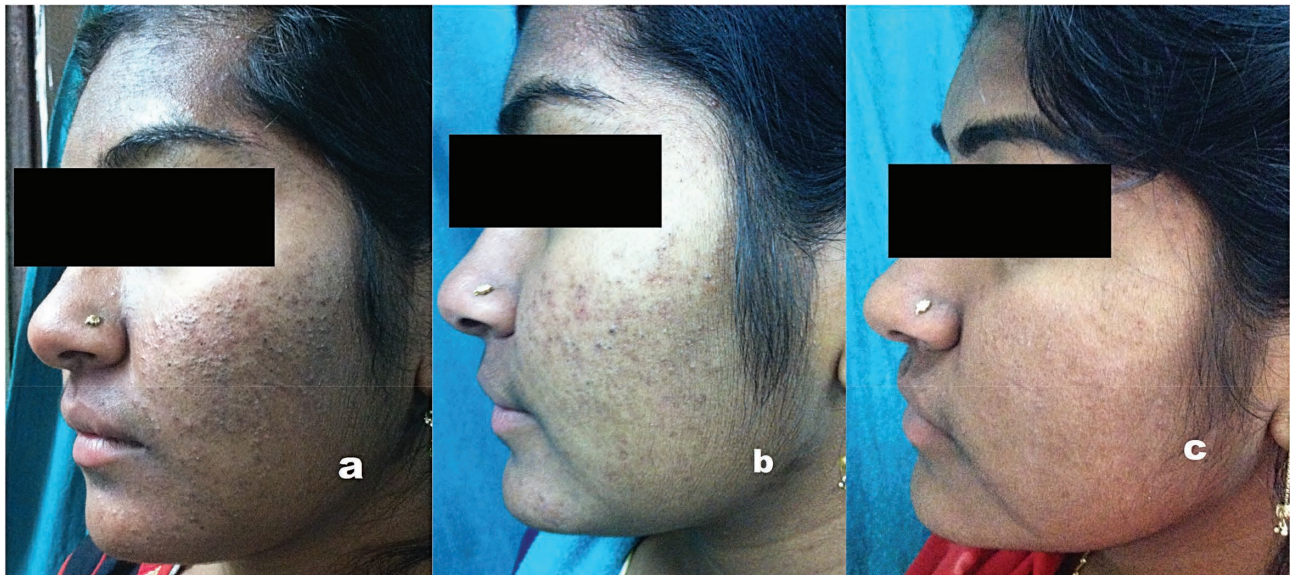

Figure 5. Clinical photographs of patients: **5.a.** at baseline, **5.b** after 8 weeks of adapalene-BPO combination gel treatment, and **5.c.** after 12 weeks of adapalene-BPO combination gel treatment.

a good therapeutic efficacy (completely resolved, marked improvement, moderate improvement of acne) for adapalene-BPO combination gel, adapalene monotherapy and benzoyl peroxide gel monotherapy, respectively.

DISCUSSION

Few studies have evaluated the efficacy and tolerability of adapalene 0.1%-BPO combination gel in acne vulgaris patients but according to our knowledge, this is the only study carried out on Indian patients. In this prospective, randomized, investigator blind, parallel group study, adapalene-BPO combination gel showed superior efficacy compared to adapalene gel monotherapy and benzoyl peroxide gel monotherapy in treatment of mild to moderate facial acne vulgaris.

Adaplane-BPO combination gel was significantly effective in reduction of total lesions, non-inflammatory lesions, and inflammatory lesions by 75.9%, 75.4%, and 74.7%, respectively. This combination was equally effective in reduction of both non-inflammatory and inflammatory lesions. Our study results are in accordance with findings reported by Gold *et al.* [10] and Poulin *et al.* [11] that also observed the superiority of adapalene-BPO combination gel in acne vulgaris. However, Korkut and Paskin [12] did not find any significant difference in efficacy between adapalene-BPO combination gel, adapalene gel, and benzoyl peroxide gel.

The success rate of adapalene-BPO combination was 37.2%, which is comparable with 30.1% reported by Gold *et al.* and 44.1% reported by Poulin *et al.* [10,11]. A significant early treatment response was seen in as early as 2 week in patients receiving adapalene-BPO gel combination compared to monotherapies. A similar response has been reported in other studies [10-11].

Although the signs and symptoms of local tolerability were more common in combination therapy, no statistically significance difference was observed in adapalene-BPO combination gel compared to adapalene and benzoyl peroxide gel monotherapy. The majority of the adverse effects appeared within the first 2 weeks of the treatment, although they were transient, and mild to moderate in severity. Dryness was the most common side effect, which is expected in retinoid containing combination therapy and can be easily treated by non-comedogenic moisturizers from the beginning of therapy. Our findings are supported by other similar studies [10,11,13-15].

Gollinick [11] and Poulin *et al.* [14] reported that long term treatment with adapalene-BPO combination gel is efficacious, safe, and well tolerated, prevents relapse, continues to reduce acne lesions, and further increases the treatment success [11,14].

International consensus recommendations emphasize the importance of aggressive

combination therapy for acne because of the complex multifactorial pathophysiologic features of the condition [8]. Various other combination regimens have been studied and part of acne treatment strategy includes combination of topical retinoids with oral or topical antimicrobial agents. The superior efficacy of adapalene–BPO combination gel compared to monotherapies may be due complimentary mode of action which addresses three out of four pathophysiologic features of acne. Thus, benzoyl peroxide eliminates *P. acne* by its strong anti-bacterial action [16] while adapalene downregulates the cell surface receptors [17] used by *P. acne* for the induction of inflammatory cytokine production [18]. Adapalene also alters the follicular microclimate, thus enhancing the penetration of benzoyl peroxide [4]. Adapalene is a rational choice among retinoids as previous studies have shown that combination therapy with adapalene 0.1% may be more tolerable and associated with a lower rate of adverse events relative in comparison with other topical retinoids [19-23]. Unlike other retinoids, adapalene is stable when combined with benzoyl peroxide in the presence or absence of light [24]. Being anti-biotic free, neither adapalene nor benzoyl peroxide is known to develop bacterial resistance; hence, their combination may be appropriate for short-term as well as long-term use [25,26]. Efficacious, well-tolerated, fixed-dose combination may reduce the number of medications patients have to apply and once daily application improves the patient's compliance.

We acknowledge the following limitations of our study. We studied the efficacy and tolerability of adapalene-BPO combination gel with 12 weeks follow-up. More clinical studies are needed to evaluate the long term efficacy and tolerability of this combination in Indian patients with acne vulgaris. We did not compare the efficacy and adverse effects of adapalene-BPO combination gel in different Fitzpatrick skin types in Indian patients and elaborative Indian clinical trial are required in the future.

Treatment selection in acne vulgaris depends on multiple factors, including acne history, prior treatment, patient preferences, compliance, and grading. Such a decision is facilitated by various comparative efficacy studies between different available treatment options. According to our findings, adapalene-BPO combination gel can be an alternative to other therapies in non-inflammatory as well as inflammatory acne lesions in adolescent to middle-aged patients of both sexes with better efficacy and compliance.

Adapalene-BPO combination gel is superior in efficacy and is well-tolerated compared to adapalene and benzoyl peroxide gel monotherapy in mild to moderate acne vulgaris in Indian patients. This combination is stable, reduces dosing, and provides early response that improves the patients' compliance. It can be used for short-term as well as long-term acne care.

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