

Original Research Article

Evaluation of adapalene alone versus combination therapy of adapalene with benzoyl peroxide and adapalene with clindamycin in treatment of acne vulgaris: a prospective, observational study

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Received: 14 July 2019

Revised: 13 September 2019

Accepted: 18 September 2019

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ABSTRACT

Background: Acne vulgaris is majorly affecting adolescent population with profound negative impact on the quality of life (QOL). The objectives of the present study was to evaluate adapalene 0.1% alone vs combination therapy of adapalene 0.1% with benzoyl peroxide (BPO) 2.5% and adapalene 0.1% with clindamycin 1% in the treatment of acne vulgaris and to analyse health related QOL using the cardiff acne disability index (CADI).

Methods: This prospective, observational study of 12 months duration involved patients who were being treated with adapalene alone and adapalene combined with either clindamycin or benzoyl peroxide in the normal course of treatment. Efficacy of treatment and QOL was assessed by the comprehensive acne severity system (CASS) and CADI respectively.

Results: A total of 180 patients were enrolled (n=60 in each group). Male: female ratio was 1: 2.52. 76.7% patients were of adolescent age with the Mean age of 21.17±3.28 years. Average age of onset was 18.03±2.80 years. Most patients had moderate grade of acne (51%) followed by mild grade (46%) and almost clear (3%). Face was the common site, followed by back and chest. There was a statistically significant improvement in both number of lesions and also QOL in all the three treatment groups (p<0.0001).

Conclusions: Topical adapalene 0.1% is efficacious in the treatment of acne vulgaris both alone as well as in combination with topical benzoyl peroxide 2.5% and topical clindamycin 1%. Adapalene also has positive influence on the QOL alone as well as in combination but no superiority of one group over the other was observed with regard to efficacy as well as QOL.

Keywords: Acne vulgaris, Adapalene, Benzoyl peroxide, CADI, Clindamycin

INTRODUCTION

Acne vulgaris is a skin condition affecting a large proportion of the population. It is characterized by black heads (open comedones), white heads (closed comedones), pimples, greasy skin and scarring.¹ Severity of acne is divided into four grades, with grade I being the

mildest and grade IV being the most severe form.² It is a multifactorial disorder of pilosebaceous unit. Clinical presentations vary from mild acne with comedones, erythematous papules, pustules, nodules or pseudocysts and sometimes scarring to systemic inflammatory disease.³ Acne is primarily considered an adolescent disease with maximum prevalence in 14-17 years age

group in females and 16-19 years age group in males. Four main factors involved in pathogenesis of acne vulgaris are increased production of sebum, increase in keratinocytes of pilosebaceous follicle, change in microbial flora of the skin (proliferation of *Propionibacterium acnes*) and inflammation. Impact of genetic factors has been proved.⁴

Many drugs are available for the treatment of acne both topical and systemic i.e., antimicrobials, vitamin A analogues (retinoids; isotretinoin) and hormonal preparations.⁵ Systemic antibiotics including doxycycline are used in treatment of moderate and moderate to severe acne. Oral broad spectrum antibiotics such as doxycycline and macrolides have been used in treatment of inflammatory acne.⁶ Azithromycin is preferred because it can be prescribed in less frequent doses.^{7,8}

Acne persists as an issue and has a profound negative impact on the QOL.^{9,10} Combinations of adapalene with clindamycin and adapalene with benzoyl peroxide (BPO) have shown efficacy in the treatment of acne.^{11,12}

Adapalene and BPO have complementary modes of action and synergistic activity.¹³ Adapalene has anti comedogenic, comedolytic, and anti-inflammatory properties. Adapalene inhibits micro comedone formation and leads to a reduction in both comedones and inflammatory lesions.¹⁴

BPO is a lipophilic oxidizing agent that has antibacterial activity and some keratolytic effects. A study comparing BPO 2.5% gel with 5% and 10% formulations of BPO showed that 2.5% BPO gel had similar efficacy to BPO 5% gel and 10% gel in patients with acne and it was better tolerated than BPO 10% gel.¹⁵ BPO 5% had bactericidal activity against *P. acnes* in vitro and significantly ($p < 0.01$) reduced the mean number of propioni bacteria recovered from the skin surface and from follicular casts after 2 days' application in patients with acne.¹⁶ BPO also demonstrated in vitro activity against antibiotic-resistant propioni bacteria.¹⁷ Significant ($p < 0.001$) reductions in *P. acnes* counts, including antibiotic-resistant *P. acnes* counts, occurred in volunteers with high levels of *P. acnes* at baseline who applied adapalene 0.1%/BPO 2.5% gel once daily for 28 days.¹⁸

Clindamycin inhibits bacterial protein synthesis. A multicentre randomised study compared a topical combination of adapalene and clindamycin with clindamycin and vehicle in the treatment of mild to moderate acne vulgaris. A significantly greater reduction of total ($p < 0.001$), inflammatory ($p = 0.004$) and noninflammatory lesions ($p < 0.001$) was seen in the clindamycin plus adapalene group than in the clindamycin plus vehicle group however ADRs like scaling, dryness, stinging or burning were more in adapalene and clindamycin combination as compared to clindamycin plus vehicle.¹⁹

Acne persists as a problem in spite of many drugs being available both for systemic use as well as topical use. Though many studies have been done comparing various topical preparations no head to head comparison between adapalene gel 0.1% alone and adapalene 0.1% with clindamycin 1% gel and adapalene 0.1% with benzoyl peroxide 2.5% gel was found in literature in relation to efficacy and quality of life in mild to moderate acne vulgaris. No correlation between these drugs and QOL was also found in literature. This prompted us to take up this aspect in our study. We selected cardiff acne disability index (CADI) to evaluate QOL as it is a well-established scale.

METHODS

A prospective, observational study was carried out between August 2018 to May 2019 at Vadilal Sarabhai General Hospital which is a tertiary care teaching hospital. The study protocol was approved by institutional review board. All patients visiting the Dermatology OPD diagnosed with mild to moderate acne and fulfilling the inclusion criteria were included in the study. Informed consent of all patients was taken and the data of patients was recorded in a case record form. Cardiff acne disability index (CADI) questionnaire was utilized for evaluation of quality of life.²⁰ CADI was filled at the time of first contact and then after 30 days. Following were the inclusion and exclusion criteria:

Inclusion criteria

Age greater than or equal to 18 years, all patients attending dermatology OPD diagnosed with mild to moderate acne vulgaris and receiving topical treatment (adapalene alone, adapalene with benzoyl peroxide, adapalene with clindamycin only), patients should have history of acne vulgaris for at least one month and patients willing to give informed consent for the study and agreeing to answer questions related to their quality of life were included in the study.

Exclusion criteria

Patients suffering from grade IV nodular cystic acne vulgaris and on systemic therapy for acne vulgaris, presence of any other dermatological condition, presence of major medical disorders that may affect QOL, patients with severe psychiatric disorders and pregnant females, lactating females and females planning to get pregnant.

Patients were put on topical treatment for acne as deemed to be suitable by the dermatologist in the normal course of treatment. The patients were divided into three groups. One group received adapalene 0.1% alone, second group received adapalene 0.1% with benzoyl peroxide 2.5% and third group received adapalene 0.1% with clindamycin 1%.

Efficacy of treatment was assessed by comprehensive acne severity system (CASS).²¹ All patients were called for follow up after 30 days and comparative subgroup analysis was done with respect to efficacy and QOL. As grade IV acne vulgaris was not included none of the patients received any systemic drug for acne and evaluation of systemic drugs was not done. Efficacy of treatment was checked by observing the improvement in lesions according to their change in grading based on CASS.

The cardiff acne disability index (CADI) questionnaire analysed various aspects of QOL including psychological, social and professional life. CADI is specific for acne and consists of five questions that assess the patient’s attitude towards his/her condition. They are related to patient’s feelings about the disease interfering with his/her social life, interaction with opposite gender, avoidance of public places and perception of the severity of the condition in the last one month. Each question consists of four options and each question is graded with a maximum score of 3 and a minimum of 0. The CADI score is calculated by summing the score of each question resulting in a possible maximum of 15 and a minimum of 0.²⁰ The higher the score, the more the quality of life is impaired. Based on CADI score the QOL can be graded as not impaired (score 0), mildly impaired (score 1-5), moderately impaired (score 6-10) and severely impaired (score 11-15). The English and Hindi versions of the CADI were used in accordance with the patient’s choice of language.

Table 1: The cardiff acne disability index score.

Degree of impairment of QOL	CADI score
Not impaired	0
Mildly Impaired	1-5
Moderately impaired	6-10
Severely Impaired	11-15

Safety evaluation

At each visit, patients were asked about any complaints that might indicate an adverse drug reaction. Any such dermatological adverse reaction reported was recorded and analyzed.

Statistical analysis

We used descriptive statistics to summarize the baseline characteristics of the patient population. The analysis was performed using IBM® SPSS® Statistics v. 25. We compared the reduction in the number of lesions in all the three treatment groups by using unpaired t-test and also compared differences in individual groups before and after treatment by using paired t test. Similarly the quality of life was also analyzed by using paired and unpaired t test. P value<0.05 was considered statistically significant.

RESULTS

Population characteristics

A total of 180 patients visiting the dermatology department were diagnosed with mild to moderate grade of acne vulgaris and fulfilled the inclusion criteria during the study period from August 2018 to May 2019. The mean age of patients in our study was 21.17±3.28 years. Age distribution is shown in Figure 1. Female preponderance was observed as shown in figure 2. 129 (71.7%) Females observed as compared to 51(28.3%) males. Male: female ratio was 1:2.52. 167 (92.8%) patients belonged to lower socio economic group and 13 (7.2%) belonged to middle socio economic group. Majority of the patients were students. 51 (28.3%) were married and 129 (71.7%) were unmarried. 64 (35.6%) subjects were on mixed diet 116 (64.6%) were vegetarians. 7 (3.9%) persons had history of prior treatment with herbal medicines (Table 2).

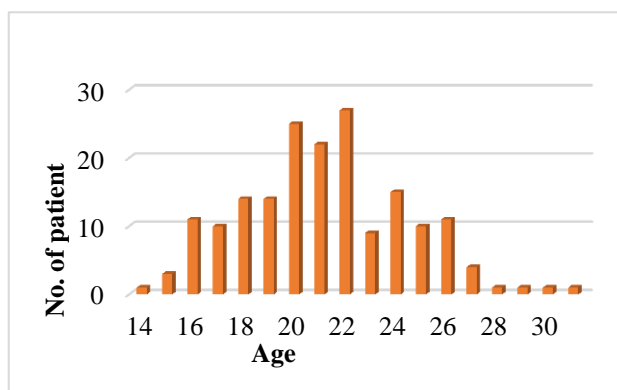


Figure 1: Age wise distribution of patients of acne.

Table 2: Demographic profile of patients.

Parameters	N (%)
Total patients	180
Men: women ratio	1:2.52
Mean age (in years)	21.17± 3.28
Married	51 (28.3)
Unmarried	129 (71.7)
Mixed diet	64 (35.6)
Vegetarian diet	116 (64.6)
Previous treatment with herbal medicine	7 (3.9)

Average age of onset of acne was 18.03±2.80 years. 85% patients had oily and 15% had dry skin type. Face was the common site in all the patients, followed by back and chest. 76.7% patients had acne from adolescent age and 10% patients had positive family history. Most of the females had regular menstruation (67%) out of that 28.3% female had worsening of acne before menses and 7.2% had worsening of acne after menses.

Severity of acne

On the basis of CASS patients were categorized into almost clear, mild and moderate as shown in Figure 3.

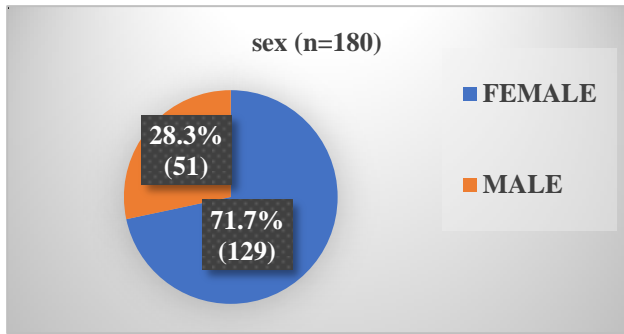


Figure 2: Sex distribution of patients of acne vulgaris.

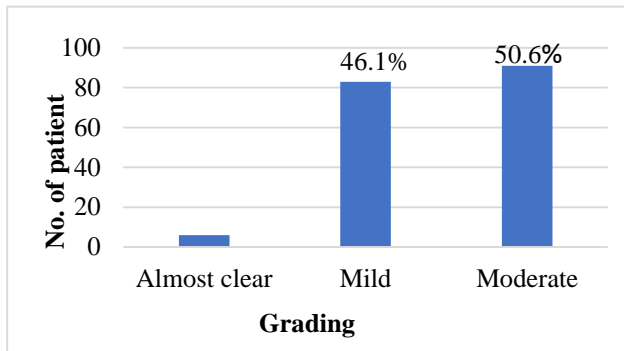


Figure 3: Distribution of patients according to severity of acne.

Treatment groups

Out of the total 180 patients 60 patients received adapalene gel alone, 60 patients received adapalene + benzoyl peroxide gel and adapalene + clindamycin gel as shown in Figure 4.

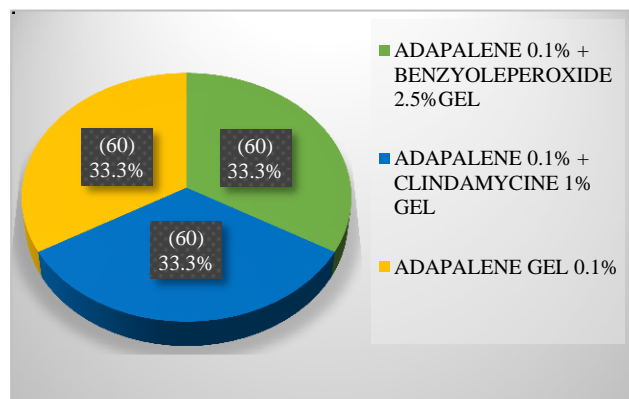


Figure 4: Treatment groups.

A total number of 180 patients were enrolled in the study (n=60 in each treatment group).

Efficacy

There was a significant improvement in the lesions in all the three treatment groups according to CASS. No superiority of one treatment over the other was seen pertaining to efficacy (Figure 5).

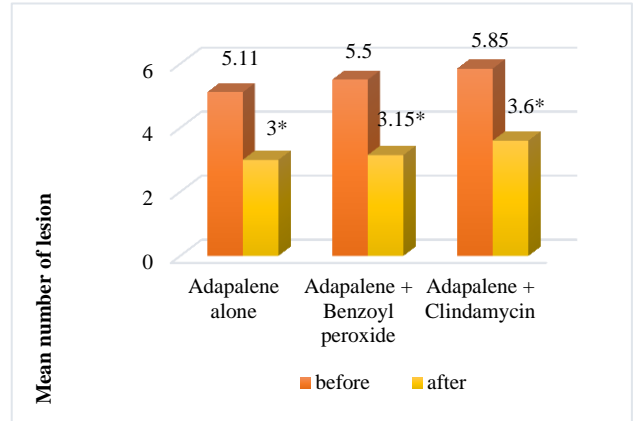


Figure 5: Efficacy of the three groups with respect to the mean of number of lesion.

*: p<0.0001.

QOL

There was a significant improvement in the QOL in all the three treatment groups according to CADI. No superiority of one treatment over the other was seen pertaining to QOL (Figure 6).

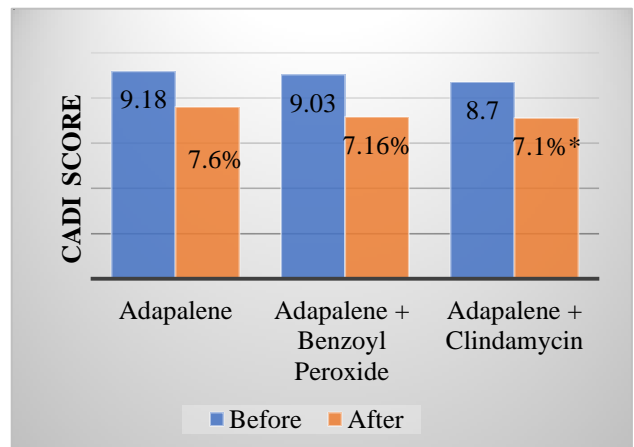


Figure 6: CADI score before and after treatment.

*: p<0.0001.

The improvement in mean scores for individual questions pertaining to QOL was observed (Table 3).

Quality of life variables

There was increase in anger, frustration and embarrassment due to acne in majority of the patients (86.7%). Acne also significantly affected social life, social events or relationships with members of the

opposite sex (86.6%). Due to acne patients were avoiding usage of public places (78.3%). A large amount of Acne patients were concerned regarding their appearance of

skin over the last month (91.7%). Patients of acne believed that acne was a major and significant health problem (93%).

Table 3: Mean scores in the three treatment groups according to CADI questionnaire.

Questions	Adapalene alone (mean score)		Adapalene + benzoyl peroxide (mean score)		Adapalene + clindamycin (mean score)	
	Before	After	Before	After	Before	After
Q1. Occurrence of frustration, embarrassment and aggression	1.82	1.65	1.73	1.61	1.76	1.53
Q2. Interference in social life and events	1.83	1.6	1.85	1.35	1.66	1.36
Q3. Avoidance of public places	1.65	1.28	1.73	1.65	1.68	1.35
Q4. Psychological state due to acne	1.9	1.5	1.86	1.1	1.63	1.48
Q5. Self- assessment of condition	1.93	1.56	1.85	1.45	1.95	1.36
Total mean score	9.18	7.60*	9.03	7.17*	8.70	7.10*

Safety and tolerability

A very low incidence of erythema was observed. 1 patient in adapalene alone group, 1 patient in adapalene with BPO group and 1 patient in adapalene with clindamycin group reported with erythema.

Mild irritation was observed in 4 (2%) patients from group receiving adapalene with BPO but no irritation was reported in adapalene alone group as well as adapalene with clindamycin group. No other adverse reaction was reported. There was no withdrawal from the study due to ADRs.

DISCUSSION

This study was carried out in 180 consenting patients visiting the Dermatology Outpatient Department at a tertiary care hospital. These patients were diagnosed with mild to moderately severe acne. They gave a history of acne vulgaris for at least one month or more. It was mandatory that the participating patients did not suffer from any other health condition or psychiatric disorder that would affect their health related quality of life.

Most acne patients were between 18-22 years of age with a female preponderance. Previous studies done by Wolf et al, Thiboutot et al, Reddy et al have also reported a female preponderance while an equal male to female ratio was seen in the study done by Jain et al.²²⁻²⁵ The peak incidence of acne seen in adolescent age group may be due to various factors like peak increase in hormones in this age group.²⁶ The psychosocial effects of acne also lead to an increased tendency of patients to seek treatment for this condition.

Efficacy

In our study all the three treatment groups i.e., adapalene 0.1% gel alone; adapalene 0.1% gel with BPO 2.5% gel and adapalene 0.1% gel with clindamycin 1% gel showed

a statistically significant improvement in lesions according to CASS. However no superiority of one group over the other was observed. We did expect a higher efficacy of adapalene in combinations with benzoyl peroxide and clindamycin as compared to adapalene alone because of synergistic interactions between these drugs but that was not observed in our study.

A greater efficacy of a combination of adapalene and BPO over adapalene alone has been reported in a study on a combination of adapalene 0.1% with BPO 2.5% gel. It was observed that the combination was more effective than adapalene 0.1% gel alone as well as more effective than BPO 2.5% gel alone; as well as more effective than vehicle gel alone in the treatment of moderate acne vulgaris in patients aged ≥ 12 years.²⁷

In another study done by Babaeinejad et al on efficacy, safety, and tolerability of adapalene versus BPO in the treatment of mild acne vulgaris the fixed-dose combination of adapalene and BPO was found to be safe, well tolerated, and significantly more efficacious for the treatment of acne vulgaris and with faster onset of action compared to adapalene and BPO monotherapy.²⁸

A comparative study of efficacy and safety of combination of topical clindamycin 1% and adapalene 0.1% with a combination of topical clindamycin 1% and BPO 2.5% in mild to moderate acne was done by Shwetha et al. The results of this study showed that the combination of topical clindamycin 1% and adapalene 0.1% is superior to the combination of topical clindamycin 1% and BPO 2.5% in the treatment of mild to moderate acne vulgaris.²⁹ We did not study the combination of clindamycin with BPO; however in our study combination of clindamycin with adapalene showed similar efficacy as adapalene alone.

Safety and tolerability

In our study a very low incidence of erythema was observed. 1 patient (0.5%) in adapalene alone 1 patient

(0.5%) in adapalene+BPO group and 1 patient (0.5%) in adapalene+clindamycin group reported with erythema.

Also mild irritation in 4 patients (2%) patient from group adapalene+clindamycin is reported in but there was no withdrawal from the study due to ADRs.

In a study done by Wolf et al using a combination of topical clindamycin 1% and adapalene 0.1%, in 120 patients it was reported that 25% of patients showed erythema and 5% of the patients reported with stinging and burning sensation of moderate to severe intensity.²² In our study 60 patients received this combination and occurrence of erythema was seen in only 1 (0.5%) patient and irritation was seen in 4 (2%) patients which is considerably less as compared to this study.

In an Indian study done by Prasad et al, moderate to severe erythema was seen in 9.9% of patients in the conventional gel formulation and in 0.8% of patients in the nano-emulsion gel formulation of adapalene 0.1% and clindamycin 1% combination.¹⁹ This indicates that with adapalene and clindamycin combination if the dosage form is altered it reduces the incidence of erythema. Our study was done using the conventional gel preparation.

In the study done by Babaeinejad et al on efficacy, safety, and tolerability of topical treatment in mild to moderate acne vulgaris in 60 patients; patients were divided into four groups.²⁸ One group received adapalene alone, one group received BPO alone, one group received combination of adapalene with BPO and one group received vehicle alone. This study reported that adverse events were minimal and self-limited (26.7% in adapalene group, 20% in BPO group). A majority of subjects in all of the groups experienced mild or no irritation. One (0.2%) subjects in the adapalene- BPO group, one (0.2%) subject in the adapalene group, six (1.4%) subjects in the BPO group and four (1.0%) subjects in the vehicle group discontinued due to an adverse event. Compared to this study ADRs in our study are considerably less and none of the subjects discontinued the treatment due to adverse effects.

A combination of topical clindamycin 1% and BPO 2.5% was studied by Thiboutot et al.²³ They reported irritation in 0.1% of patients who discontinued the study due to irritation. This shows that these patients had unbearable irritation. In our study mild irritation was observed in adapalene with BPO but there was no withdrawal from the study due to irritation.

Quality of life

A disease is not just characterized by its pathological manifestations, but also by its impact on the patient's quality of life. This crucial aspect, however, is very often overlooked by the physician while treating the patients. This study holds value because it not only evaluates the efficacy of three treatment groups in acne, but also

assesses the psycho-social impact of the disease using cardiff acne disability index (CADI). When we assess new therapies for a given condition the measurement of QOL becomes important. The impact on QOL, risk factors and preferences for a given therapeutic agent will help us design more targeted interventions.³⁰

In our study there was a significant improvement ($p < 0.001$) in the quality of life in all the three treatment groups.

In a study reported by Chandani et al on drug use pattern and quality of life in patients of acne; the mean CADI score was 6.34 ± 3.625 .³¹ This study analyzed QOL with regard to both systemic as well as topical treatment in all grades of acne. In our study total CADI score is 9.18 ± 2.23 before treatment and 7.60 ± 2.28 after treatment. We did not evaluate QOL with regards to systemic treatment; though there was improvement in QOL in the three treatment groups; the quality of life was moderately impaired.

CONCLUSION

Use of topical preparations is usually preferred for treating skin diseases as they have site specific action, less systemic absorption resulting in lesser side effects and they are convenient for patient use. Our study shows that topical adapalene 0.1% is as efficacious in the treatment of mild to moderate acne vulgaris as a combination of adapalene 0.1% with clindamycin 1% and adapalene 0.1% with BPO 2.5%. BPO and clindamycin are efficacious antimicrobial agents but here they do not seem to add to the efficacy of adapalene.

Adapalene also has positive influence on the QOL in patients of acne vulgaris alone as well as in combination with clindamycin and BPO. All the three groups were equally efficacious and no superiority of one group over the other was observed with respect to efficacy as well as QOL.

Limitations

We restricted our study to only topical treatment and did not evaluate systemic treatment for acne vulgaris. In topical treatment, we restricted our study to include adapalene gel, clindamycin gel and BPO gel only. Other topical treatments like topical erythromycin, azithromycin, clarithromycin, nadifloxacin, topical 2% zinc sulphate etc are also available for treatment of acne but we did not evaluate them and we also restricted our study to only 3 treatment combinations where as other combinations are also possible i.e., clindamycin with BPO, clindamycin alone, BPO alone.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Parikh NR, Sood SV, Rana D, Chaudhary R, Malhotra SD. Evaluation of adapalene alone versus combination therapy of adapalene with benzoyl peroxide and adapalene with clindamycin in treatment of acne vulgaris: a prospective, observational study. Int J Res Dermatol 2019;5:831-8.