Research Paper

Efficacy and Safety of Nadifloxacin and Benzoyl Peroxide versus Adapalene and Benzoyl Peroxide in Acne Vulgaris: A Randomized Open-label Phase IV Clinical Trial

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Abstract

Objective: To compare the efficacy and safety of nadifloxacin and benzoyl peroxide versus adapalene and benzoyl peroxide in acne vulgaris. **Materials and Methods:** Patients fulfilling the inclusion criteria were divided into two groups. Patients in Group A received nadifloxacin and benzoyl peroxide. Patients in Group B received adapalene and benzoyl peroxide. Duration of treatment was 12 weeks. Changes in noninflammatory lesion count (NILC), inflammatory lesion count (ILC), total lesion count (TLC), investigator global assessment score (IGA) score, and Cardiff acne disability index (CADI) score was determined at weeks 0, 4, 8, and 12. **Results:** Combination of adapalene and benzoyl peroxide significantly decreased NILC, ILC, TLC, IGA score, and CADI score compared to the combination of nadifloxacin and benzoyl peroxide in acne vulgaris. **Conclusion:** Combination of adapalene and benzoyl peroxide is significantly more effective compared to the combination of nadifloxacin and benzoyl peroxide in the treatment of acne vulgaris.

Keywords: Acne, adapalene, benzoyl peroxide

Introduction

Acne vulgaris is a disorder of the pilosebaceous gland occurring usually at puberty but can also be seen in adult age.[1] The disease characterized by the formation of open and closed comedones (noninflammatory lesions), papules, pustules, and nodulocystic lesions (inflammatory lesions). The disease generally affects the face, arms, and back. The multifactorial pathogenesis of acne vulgaris includes follicular hyperkeratinization, abnormal sebum production, bacterial proliferation, and inflammation.[2] Acne vulgaris has been divided into four grades – 1, 2, 3, and 4. Grade 1 consists of comedones and occasional papules. Grade 2 consists of papules, comedones and few pustules. Grade 3 consists of predominant pustules, nodules, and abscesses. Grade 4 consists of mainly cysts, abscesses, and widespread scarring.[3] The aims of treatment are to control inflammation, decrease the activity of the sebaceous glands, normalize follicular proliferation, and decrease bacterial colonization. Drugs used for Grades 1 and 2 (mild-to-moderate case) of acne vulgaris are topical comedolytics, antibacterials, and retinoids as monotherapy or combination therapy. Grades 3 and 4 (severe cases) of acne vulgaris require systemic antibacterials along with topical agents.[4]

Nadifloxacin, topical fluoroquinolone antibiotic, is a relatively new drug for treatment of acne. Potent action of nadifloxacin against *Propionibacterium acnes*, *Staphylococcus epidermidis,* and methicillin-resistant *Staphylococcus aureus*, with no cross resistance with any other antibiotic or with another fluoroquinolone has been reported. The previous studies have reported that topical application of nadifloxacin cream exhibited excellent efficacy and tolerability and did not induce resistance in *P. acnes* strains.[5] Adapalene, a topical retinoid, is known to modulate keratinization and possesses anti-inflammatory action. The previous studies have reported adapalene to be safe and well tolerated as compared with

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other retinoids.[5] It is an agonist on the retinoid receptors and benefits the acne patients by inhibiting the keratinization and inflammation. It causes less irritation and shows better patient compliance because it binds to only selective subtypes of retinoic acid receptors. In addition, another advantage of adapalene is that it can be combined with other topical drugs for acne treatment, without causing significant side effects. Benzoyl peroxide is a common agent for treatment of acne vulgaris. It has comedolytic property and also contains potent antibacterial and mild anti-inflammatory actions. It is usually used alone or in combination with other topical anti-acne medications.[3]

The use of antibiotics alone may lead to resistance in coagulase-negative *Staphylococcus* and develop cross-resistant strains of *P. acnes*. Two-drug combination of clindamycin and benzoyl peroxide is an established regimen to mild-to-moderate acne as evident by meta-analysis reports and clinical trials.[6] Choudhury *et al*. reported that nadifloxacin and benzoyl peroxide together have comparable efficacy and safety with that of clindamycin and benzoyl peroxide.[2] On the other hand, Dubey *et al*. reported that adapalene is as efficacious as benzoyl peroxide-clindamycin combination to treat mild-to-moderate acne vulgaris; however, it is comparatively better tolerated than benzoyl peroxide-clindamycin combination.[3] Hence, the objective of the study is to compare efficacy and safety of nadifloxacin and benzoyl peroxide versus adapalene and benzoyl peroxide in acne vulgaris.

Materials and Methods

It was a prospective, randomized, open-label, parallel group Phase IV clinical trial. The study was approved by the Institutional Ethics Committee and conducted according to the National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 2017 of ICMR and the Declaration of Helsinki. Patients were recruited in the dermatology outpatient department of a tertiary care teaching hospital of a district headquarter, and the study was conducted between September and December 2017. The study was registered under Clinical Trials Registry-India (Registration Number-CTRI/2017/08/009280).

A total of 40 patients were screened initially. Out of 40 patients, 38 were included in the study. A total of 19 patients were included in each group. Patients in Group A received nadifloxacin and benzoyl peroxide. Patients in Group B received adapalene (Cipla Ltd) and benzoyl peroxide. Among these 38 patients, 37 completed the study. One patient was lost during follow-up [Figure 1]. The mean age of the patients were 19.1 and 21.6 years in Groups A and B, respectively. The difference of means to be detected was set at 10%. Considering the true mean difference between two treatment groups as zero and the expected standard deviation of 10% in the study population, 80% power, and $\alpha = 0.05$, the number of patients required in each treatment group was 17. Considering a 10% dropout rate, this translated to target recruitment of 19 patients in each group. The sample size was calculated using primer of Biostatistics software (version 5.0)(Appleton and Lange, New York, USA.

Patients of 12–40 years of age of either sex with ≥2 but ≤30 total lesions-inflammatory (papules and pustules) and/or non-inflammatory (open and closed comedones) lesions in the face which correspond to a baseline investigator global assessment (IGA) score of 2–4 (both inclusive) were included in the study. Exclusion criteria were as follows: age out of range, total lesion count (TLC) <2 or >30, very severe acne, Patients regularly using any anti-acne medications in the last 30 days before study entry, patients with nodulocystic lesions, acne conglobata, acne fulminans, acne fulminans, secondary acne (e.g., chloracne, drug-induced acne) and, any acne requiring systemic treatment.

Patients fulfilling the inclusion criteria were randomized to one of the two parallel arms of the study. Randomization was done by coin toss. Patients in Group A received nadifloxacin (Cipla Ltd., India) and benzoyl peroxide (Wallace Pharmaceuticals Ltd., India). Patients in Group B received adapalene (Cipla Ltd.) and benzoyl peroxide. All enrolled patients were instructed to apply a thin layer of the study medications over the lesions; benzoyl peroxide 2.5% gel once daily at bedtime, and adapalene 0.1% cream or nadifloxacin 1% gel twice daily. The patients were instructed to apply the study medications at least 10 min after the skin is gently washed, rinsed with water, and patted dry. The patients were asked not to bathe, shower, wash, or swim at least 4 h after application of the study medications.

For each enrolled participant, the total duration of the study was 12 weeks. Apart from the screening/baseline visit, three follow-up visits were scheduled at the end of 4th, 8th, and 12th week. Trial drug dispensing was done thrice, once at baseline visit for 4 weeks and subsequently at the first- and second follow-up visits for 4 weeks.

The primary efficacy parameter was change from baseline to study end of the TLC-both inflammatory (ILC) and non-inflammatory lesion count (NILC). Secondary efficacy parameters were the validated IGA,[7] on a six-point scale as mentioned in Table 1.

Change in the Cardiff acne disability index (CADI)[8] was also evaluated for assessing the impact of disease on their quality of life. The CADI included assessment on a five questions scale. Patients were monitored continuously throughout the study for

Table 1: IGA score

Score	Severity
0	Clearance of inflammatory and noninflammatory lesions
1	Almost clear
2	Mild severity
3	Moderate severity
4	Severe
5	Very severe

any adverse event (AE). Causality analysis of AE was done as per the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria.[9]

Statistical analysis

Data were analyzed as per modified intention to treat basis. Patients who reported for at least one follow-up visit were analyzed. All patients were included for safety analysis. Friedman's test (data in ordinal scale) and repeated measures ANOVA (data in numerical scale) were be used for intragroup comparison. *Post hoc* analysis was done by Tukey's honestly significant difference (HSD) test. Mann–Whitney U test (data in ordinal scale) and paired *t*-test (data in numerical scale) were used for intergroup comparison. Chi-square test was used for categorical data. $P < 0.05$ was considered statistically significant.

Results

There was no statistically significant difference in baseline non-inflammatory [Figure 2], inflammatory [Figure 3], TLC [Figure 4], and IGA score [Figure 5] and CADI [Figure 6]. Total, NILC, and ILC decreased significantly in both groups at week 12 from their respective baseline values ($P < 0.05$). IGA and CADI scores also decreased significantly at week 12 from their respective pretreatment values ($P < 0.05$).

Intergroup analysis of data showed at every interval (weeks 4, 8, and 12) Adapalene and benzoyl peroxide combination significantly decreased TLC [Figure 4] and ILC [Figure 3], IGA, [Figure 5] and CADI [Figure 6] scores compared to nadifloxacin and benzoyl peroxide group. Whereas inflammatory lesion count decreased significantly in adapalene and benzoyl peroxide combination group at weeks 8 and 12 compared to the other group.

Safety analysis was carried as per intention-to-treat analysis. All patients who randomized were considered for safety analysis. Four patients in Group A and five patients in Group B reported adverse effects. Adverse effects were burning sensation, dryness, and pruritus. Adverse effects resolved spontaneously and none of the patients required any modification of treatment. Causality analysis of AEs was done as per WHO-UMC criteria. Analysis showed that they were in "possible" category.

Discussion

Acne vulgaris is a common disease encountered by the dermatologists. People of the adolescence age group are usually affected; however, it may be seen in adult age group also. Better understanding of pathogenesis of acne and new therapeutic modalities has led to various treatment options for acne. Drugs such as benzoyl peroxide, retinoids, and topical antibiotics are the mainstay of therapy and they are used alone or in combinations. The retinoid adapalene targets abnormal follicular epithelial hyperproliferation, decreases microcomedones, follicular plugging, non-inflammatory, and inflammatory lesions.[10] Adapalene is also tolerated better compared to other retinoids.[11] Topical benzoyl peroxide is one of the most common drugs used to treat acne and available in different concentration and formulations. Benzoyl peroxide is available as topical creams, gels, washes, or foams and can be used as leave-on or wash-off agents. Strength of different formulation ranges from 2.5% to 10%.[12]

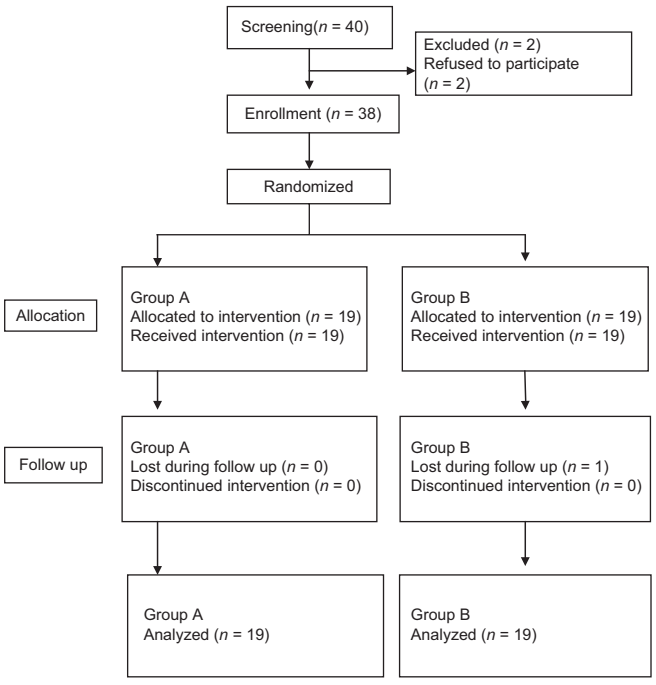

Figure 1: The consort flow chart

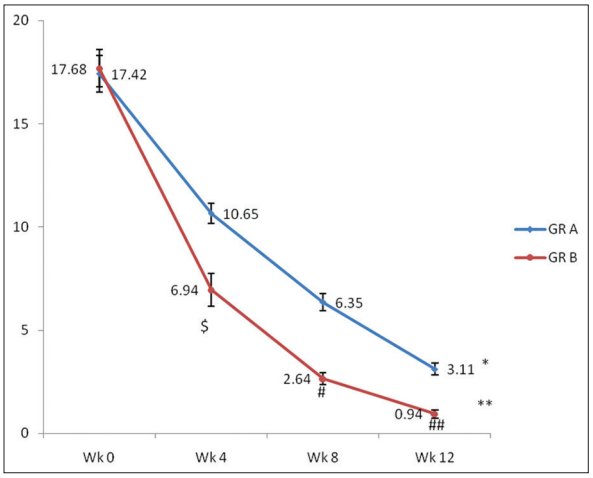

Figure 2: Changes in noninflammatory lesion count in groups A and B. Noninflammatory lesion count (mean ± standard deviation) in Group A are 17.42 ± 0.9, 10.65 ± 0.5, 6.35 ± 0.4, 3.11 ± 0.3 at weeks 0,4, 8, 12 respectively; in Group B are 17.68 ± 0.9, 6.94 ± 0.8, 2.64 ± 0.3, 0.94 ± 0.2 at weeks 0,4, 8, 12 respectively. *$P < 0.05$ and **$P < 0.05$-weeks 4, 8,12 versus week 0 in Groups A and B respectively. Intergroup comparison of noninflammatory lesion count levels at weeks 4, 8, and 12: $^{\$}P < 0.05$ - Group A versus B at week 4. $^{\#}P < 0.05$ - Group A versus B at week 8. $^{\#\#}P < 0.05$ - Group A versus B at week 12

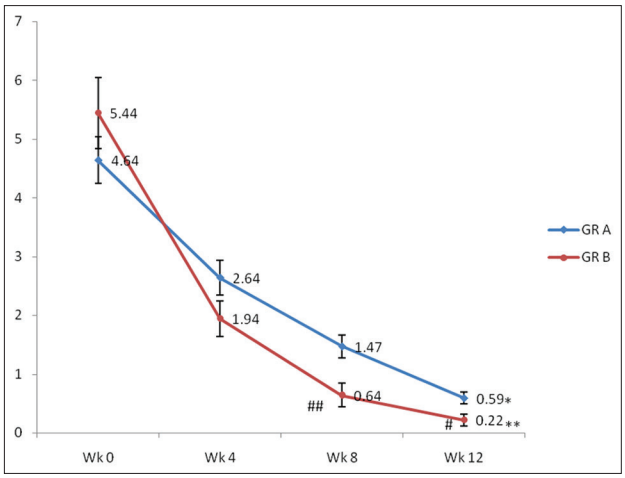

Figure 3: Changes in inflammatory lesion count in Groups A (nadifloxacin and benzoyl peroxide) and B (adapalene and benzoyl peroxide). Inflammatory lesion count (mean ± standard deviation) in Group A are 4.64 ± 0.4, 2.64 ± 0.3, 1.47 ± 0.2, 0.59 ± 0.1 at weeks 0, 4, 8, 12 respectively; in Group B are 5.44 ± 0.6, 1.94 ± 0.3, 0.64 ± 0.2, 0.22 ± 0.1 at weeks 0, 4, 8, 12 respectively. *P < 0.05 and **P < 0.05-weeks 4, 8,12 versus week 0 in Groups A and B respectively. Intergroup comparison of noninflammatory lesion count levels at weeks 4, 8, and 12: ##P < 0.05 - Group A versus B at week 8. #P < 0.05 - Group A versus B at week 12

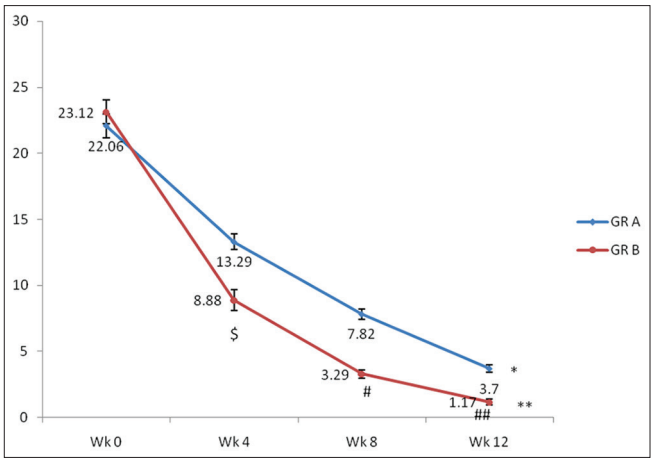

Figure 4: Changes in total lesion count in Groups A (nadifloxacin and benzoyl peroxide) and B (adapalene and benzoyl peroxide). Total lesion count (mean ± standard deviation) in Group A are 22.06 ± 0.9, 13.29 ± 0.6, 7.82 ± 0.4, 3.7 ± 0.3 at weeks 0, 4, 8, and 12, respectively; in Group B are 23.12 ± 0.9, 8.88 ± 0.8, 3.29 ± 0.3, 1.17 ± 0.2 at weeks 0,4, 8, and 12, respectively. *P < 0.05 and **P < 0.05-weeks 4, 8, and 12 versus week 0 in Groups A and B respectively. Intergroup comparison of total lesion count levels at weeks 4, 8, and 12: $$P$ < 0.05 - Group A versus B at week 4. #P < 0.05 - Group A versus B at week 8. ##P < 0.05 - Group A versus B at week 12

Figure 5: Investigator global assessment scores (mean±standard deviation) at different intervals in Groups A (nadifloxacin and benzoyl peroxide) and B (adapalene and benzoyl peroxide)

Interval	Mean±SD		*P*
	Group A	Group B	
Week 0	3.59±0.2	3.17±0.3	0.2
Week 4	2.59±0.2	1.76±0.2	0.02*
Week 8	1.64±0.1	1.17±0.1	0.016*
Week 12	0.88±0.1	0.4±0.1	0.006*
P	<0.001*	<0.001*	

SD=Standard deviation. *P<0.05

Figure 6: Cardiff acne disability index scores (mean±standard deviation) at different intervals in Groups A (nadifloxacin and benzoyl peroxide) and B (adapalene and benzoyl peroxide)

Interval	Mean±SD		*P*
	Group A	Group B	
Week 0	6.64±0.4	5.76±0.4	0.14
Week 4	3.7±0.3	2.01±0.2	<0.001*
Week 8	1.7±0.2	0.89±0.1	0.012*
Week 12	0.88±0.1	0.23±0.1	0.002*
P	<0.001*	<0.001*	

SD=Standard deviation*P<0.05

Topical fluoroquinolone nadifloxacin has been reported to have good efficacy and tolerability in acne.[5] Combination therapy is a preferred approach in treatment of acne vulgaris as it target three different aspects of pathophysiology of acne vulgaris–proliferation of *P. acnes*, inflammation, and hyperkeratinization.[13] Various meta-analysis reports and clinical trials suggest that combination of clindamycin and benzoyl peroxide is an established regimen for the treatment of acne vulgaris.[6] Data from our study suggest that the combination of adapalene and benzoyl peroxide significantly decreased NILC, ILC, TLC, IGA score, and CADI score compared to combination of nadifloxacin and benzoyl peroxide in acne vulgaris.

Few studied have evaluated different two-drug combinations in the treatment of acne vulgaris. Clinical trial conducted by Kaur *et al*. compared the combinations of benzoyl peroxide-clindamycin, nadifloxacin-benzoyl peroxide, and tretinoin-clindamycin. Their study showed significant decrease of TLC in benzoyl peroxide and clindamycin group; however, tolerability was significantly better in nadifloxacin and benzoyl peroxide group.[14] Another study by Choudhury *et al*. suggests that nadifloxacin and benzoyl peroxide combination have comparable efficacy and safety with that of clindamycin and benzoyl peroxide.[2] Dubey *et al*. reported that adapalene is as efficacious as and better tolerated than benzoyl peroxide-clindamycin combination in the treatment of acne vulgaris.[3] Data from our study are also in agreement with these studies.

Conclusion

The result of this randomized, open-label phase IV clinical trial showed that the combination of adapalene and benzoyl peroxide is significantly more effective compared to the combination of nadifloxacin and benzoyl peroxide in acne vulgaris. The combination therapy is also safe.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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