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Original Research Article

A Comparative Study of Efficacy of Topical Nadifloxacin 1% with Clindamycin 1% in the Treatment of Acne Vulgaris with Benzoyl Peroxide 2.5% Being Used as Add-On Therapy in Both the Groups

Ramya K N[1], Harshavardhana K N[2], Harshitha C[3]

[1]Resident, Department of Pharmacology, Vydehi Institute Of Medical Sciences &Research Centre, Bangalore

[2]Associate Professor, Department of Dermatology, Kodagu Institute of Medical Sciences Madikeri

[3]Assistant Professor, Department of ENT, Sri Chamundeshwari Medical College & Research Institute Channapatna, India

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Corresponding author: Dr. Harshavardhana K N

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Abstract:

Background: Acne vulgaris is a common dermatological inflammatory disorder of the pilosebaceous unit presenting usually at puberty. It is characterized by the formation of open and closed comedones (non-inflammatory lesions), papules, pustules, and nodulocystic lesions (inflammatory lesions) generally affecting the face, arms, and back.

Objective: to compare the clinical efficacy and safety of eight weeks therapy of nadifloxacin 1% versus clindamycin 1% as add-on therapy to benzoyl peroxide (2.5%) in mild to moderate grade acne vulgaris

Methods: This Prospective, randomized, open label, comparative, efficacy study was carried out at Vydehi Institute of Medical Sciences and Research Institute, Bangalore. A total of 60 patients were included and were divided into two groups. One group was advised to apply clindamycin 1% gel and benzoy peroxide 2.5% gel twice daily (30 patients), while the other group was treated with nadifloxacin 1% gel and benzoyl peroxide 2.5% gel twice daily (30 patients) for 8 weeks. The efficacy parameters were changes in the total inflammatory lesion count and severity by Investigator Global Assessment (IGA) Scale from baseline to study end (eight weeks). All treatment emergent dermatological adverse events were evaluated for safety assessment.

Results: Reduction of total inflammatory lesion count from baseline were highly significant in both the groups ($P<0.0001$), but between the group difference was not significant. Significant improvement in IGA scales was noted in both groups. Between-group comparison showed no significant differences. The safety and tolerability profile of both regimens were good and comparable.

Conclusions: Topical nadifloxacin is a newer fluoroquinolone which is effective, tolerable, and safe for mild to moderate facial acne. Its clinical effectiveness is comparable to that of clindamycin when used as add-on therapy to benzoyl peroxide.

Keywords: Acne Vulgaris; Clindamycin; Nadifloxacin; Randomized Controlled Trial.

Introduction

Acne vulgaris is a common dermatological inflammatory disorder of the pilosebaceous unit presenting usually at puberty. It is characterized by the formation of open and closed comedones (non-inflammatory lesions), papules, pustules, and nodulocystic lesions (inflammatory lesions) generally affecting the face, arms, and back [1].

This disease being very common can cause significant emotional distress and physical scarring if left untreated [2]. Mild acne is typically limited to the face and is characterized by the presence of non- inflammatory closed and open comedones with few inflammatory lesions. Moderate acne is characterized by an increased number of inflammatory papules and pustules on the face and often mild truncal disease. It is considered to be severe when nodules and cysts are present. In these cases, facial lesions are often accompanied by widespread truncal disease [3].

Topical therapy is useful in mild and moderate acne, as monotherapy, in combination and also as maintenance therapy [4]. Benzoyl peroxide (BP) is an effective topical agent since many years and is available in different formulations like washes, lotions, creams, and gels and concentrations 2.5–10%. The drug has an anti-inflammatory, keratolytic, and comedolytic activities, and is indicated in mild-to-moderate acne vulgaris. BP

has the advantage to prevent and eliminate the development of P. acne resistance. Various trials have confirmed that efficacy and tolerability of BP is enhanced when combined with topical erythromycin or clindamycin. Benzoyl peroxide is lipophilic and when applied to the skin it is capable of penetrating into the pilosebaceous follicle. Within the skin, benzoyl peroxide releases free radical oxygen and benzoic acid. The free radicals oxidize bacterial proteins. Higher concentrations of benzoyl peroxide applied to the skin result in larger amounts of drug in the skin. The benzoic acid is cleared rapidly by the kidneys and excreted unchanged in the urine. Since the introduction of topical antibiotics in the mid-1970s, antibiotic-resistant strains of P. acnes have emerged and increased in numbers over the years.

BP is a very effective broad-spectrum anti-bacterial agent. It was found to be more effective in reducing the concentration of free fatty acids in sebum than was systemic tetracycline, and efficacy was not affected by P. acnes resistance. BP has mild anti-inflammatory and comedolytic effects, thus, it influences three of the four factors involved in acne pathogenesis.[5]

BP is effective in controlling antibiotic-sensitive and antibiotic-resistant P. acnes. Significant reductions of P. acnes counts on the skin surface and in the follicle were noted after only 2 days of application of 5% benzoyl peroxide in an aqueous gel, with clinical improvement seen as early as 4 days.

Clindamycin and erythromycin are the commonly prescribed topical antibiotics for acne vulgaris with anti-inflammatory properties, among which the efficacy of clindamycin has remained better over a period of time [5]. Clindamycin acts by inhibiting Propionibacterium acnes at the 50S ribosomal subunit where they bind irreversibly to inhibit protein synthesis. P. acnes can thrive in an environment that combines sebum and desquamated cells, Topical antibiotics act against this organism, making these medications useful [6]. Nadifloxacin, a topical fluoroquinolone, is reported to have potent action against P. acne, S. epidermidis and methicillin-resistant Staphylococcus aureus (MRSA), with no cross-resistance with any other antibiotic or with another fluoroquinolone. Previous studies have reported that topical application of nadifloxacin cream exhibited excellent efficacy and tolerability and did not induce resistance in P. acnes strain[7].Nadifloxacin is highly active against aerobic and anaerobic bacteria isolated from patients with infected skin diseases. Investigations of the clinical efficacy of nadifloxacin 1% cream has demonstrated equal to clinical efficacy results of erythromycin 2% in the treatment of acne vulgaris [8].

Materials and Methods

A total of 60 patients diagnosed to have mild to moderate acne vulgaris, attending the dermatology OPD at Vydehi Medical college & research centre, Bangalore, were studied to know the safety and efficacy of clindamycin and nadifloxacin in the treatment of mild to moderate acne vulgaris. The study was conducted over a period of one year from August 2013 to July 2014.

Inclusion Criteria

1. Age 12-40 years
2. Either sex
3. Total lesion count 2-30
4. Grade I-II Lesions
5. Inflammatory lesions.
6. Willing to give informed consent.

Exclusion Criteria

1. Subjects with severe acne, nodulocystic lesions, acne conglobata, acne fulminans and purely comedones.
2. Subjects using any anti-acne medications in the last 30 days before study entry.
3. Secondary acne (drug induced).
4. Subjects diagnosed of having hormonal imbalances like PCOD, thyroid disorders.
5. Pregnant and lactating women.
6. History of drug allergy to nadifloxacin, clindamycin or benzoyl peroxide.

Methodology

The patients attending dermatology OPD with acne vulgaris were evaluated for the grade of acne and any other diseases. Patients were selected based on Inclusion and Exclusion criteria of our study. Written informed consent was taken from each individual before enrolling into our study and the importance of them for adherence to the treatment, schedule for follow up, dates for visits to hospital was told to them. The patients with mild to moderate grade acne vulgaris were randomly divided into 2 groups of 30 patients each. Group A received Clindamycin 1% gel twice daily for 8 weeks. Group B received Nadifloxacin 1% gel twice daily for 8 weeks. Both the groups recieved Benzoyl peroxide 2.5% gel as an adjuvant once daily at bedtime for 8 weeks. Patients were instructed to apply a thin layer of the study medications over the lesions at least 10 minutes after the skin was gently washed, rinsed with water and patted dry. The patients were asked not to bathe, shower, wash or swim at least 4 hours after the application of the study medications. Patients were adviced to restrict the use of medicated cosmetics in the entire study duration. The patients were followed up on 2nd, 4th and 8th week.

The patients records were studied to compile the diagnostic and clinical data including age, sex,

duration and severity of acne, family history etc. The primary efficacy parameter was change from baseline to study end of the total lesion count - inflammatory lesions. Proportion of subjects in each group were considered as "improved" if there was at least two scale improvement in the IGA. Percentage of "improved" subjects in each group was compared for statistically significant difference if any. The Patients were also evaluated for safety of the drug on each follow up visit. The study was conducted in accordance with ethical principles originating from the Declaration of Helsinki and Good Clinical Practices, and in compliance with the regulatory requirements.

Statistical Analysis

Data was entered into Microsoft excel and analyses were done using the Statistical Package for Social Sciences (SPSS). Descriptive statistics such as mean and standard deviation (SD) for continuous variables, and frequency and percentage for categorical variables were determined. Unpaired 't' test was used to compare means between group A and group B for continuous variables.

Adverse event data were summarized in frequency tables by treatment group, but no statistical analysis was performed. For all the tests a p-value of 0.05 or less was considered for statistical significance.

Results

A total of 60 patients took part in this study, 30 received clindamycin and 30 received nadifloxacin as adjuvant to benzoyl peroxide. A total of 60 patients (100%) completed the study, none were withdrawn from the study.

In this study, out of 60 patients, half of the study population i.e.,30 (50%) patients were aged between 21-25years, 28% of the patients were <20years, 18% of the patients were aged 26-30years and 3% patients were aged above 30 years.

The mean age was 22.7 years and ranged from 14 to 33 years. Out of 60 patients, 42 (70%) were females and 18 (30%) were males. In this study majority of the patients i.e., 42 out of 60 had Grade I acne (70%) and the rest (30%)had Grade II acne (Table 1).

Table 1: Distribution of Cases of Acne Vulgaris – Grade

Grade of acne	Clindamycin Group	Nadifloxacin group	Total No. of Patients	Percentage
Grade I	19	23	42	70%
Grade II	11	7	18	30%

In this study, 25 (42%) patients weighed between 60-69kgs, 15 (25%) patients weighed between 50-59kgs, 14(23%) patients weighed between 70-79kgs and Only 6 (10%) patients weighed between 40-49kgs. Peak prevalence of weight was 66kgs. (Table 2)

Table 2: Distribution Of Cases of Acne Vulgaris –Weight

Weight of the Patients in kgs	Clindamycin Group	Nadifloxacin group	Total No. of Patients	Percentage
40-49	3	3	6	10%
50-59	10	5	15	25%
60-69	14	11	25	41.67%
70-79	3	11	14	23.33%

In this study it was found that majority of the patients were students i.e., 29 out of 60 (49%) were students, 12 Engineers (20%), 5 mechanics (8%) and 14 belonged to miscellaneous (23%) which included housewives, unemployed,businessmen,

Among the 60 patients, 22 had the H/o acne lesion since 1-2 years, 16 had from <6 months, 11of them had it for 6months-1year, and 11 had for > 2years. (Table 3)

Table 3: Distribution of Cases of Acne Vulgaris -Duration

Duration of Lesion	Clindamycin Group	Nadifloxacin group	Total No. of Patients	Percentage
<6 months	5	11	16	26.67%
6months – 1year	7	4	11	18.32%
1-2years	11	11	22	36.67%
2-3 years	3	1	4	6.67%
>3years	4	3	7	11.67%

In this study it was noticed that

- 16 (27%) patients denied of having any aggravating factors,
- 12 (20%) patients had H/o high glycemic diet such as chocolates, ice-creams, fried items, as the aggravating factor whereas
- 10 (17%) had stress as the reason for flaring up of acne
- 9 patients had summer and
- 3 patients had winter as the aggravating factors,
- 4 had menstrual flare and

- 6 had travelling and poor hygiene as the aggravating factor.

Family history of acne was reported in 13% of the patients, where as 87 % did not have family history of acne vulgaris.

Efficacy evaluation

For the primary end point, there was a significantly greater reduction of inflammatory lesions in the clindamycin 1% as well as nadifloxacin1% group at week 8.

The inflammatory lesion count were 10.86 at the baseline, 7.3 at 2 weeks, 4.33 at 4weeks, 1.36 at 8weeks respectively in the clindamycin group (Table 4).

The inflammatory lesion count were 10.1 at baseline, 6.96 at 2weeks, 4.03 at 4weeks, 1.16 at 8weeks respectively in the Nadifloxacin group. Lesion counts reduced after initiation of therapy in both groups, and there were significant greater reductions. Percentage of reduction in the lesion count is shown to be 32.78%, 60.12%, 87.47% at the end of 2, 4, 8th week respectively in the clindamycin group and 31.08%, 60.09%, 88.51% at the end of 2, 4, 8th week respectively in the nadifloxacin group.

Table 4: Percentage of Reduction in Inflammatory Lesions

Duration	2 weeks	4 weeks	8 weeks
Clindamycin	32.78	60.12	87.47
Nadifloxacin	31.08	60.09	88.51

Improvement in the severity of the lesions was considered if there was change in the IGA score by at least 2 scores. 19 out of 30 (63.33%) showed significant improvement in the clindamycin group and 22 out of 30 (73.33%) showed significant improvement in the nadifloxacin group (Table 5).

Table 5: Comparision of inflammatory lesions before and after

	Clindamycin 1%		Nadifloxacin1%	
Lesions at	Baseline	8week	Baseline	8week
Total no. of lesions	326	41	303	35

Safety Evaluation

Both treatment regimens were well tolerated during the study. Dryness was found in 10 out of 30 patients in the clindamycin group and 10 out of 30 patients in the nadifloxacin group. Erythema was found in 8 and 6 patients in the clindamycin and nadifloxacin groups respectively. Itching was present in 10 patients in the clindamycin group and only in 4 patients in nadifloxacin group. None of them complained of burning sensation or tingling sensation in both the groups.

Overall, more patients reported adverse events in the clindamycin 1% group than in the nadifloxacin1% group. As the events were only mild to moderate no patient withdrew from the study (Table 6).

Table 6: Comparision of improvement in the severity of the lesions

Treatmentgroup	< 2 score improvement	>2 score improvement	Total numberof patients	Percentage
Clindamycin group	19	11	30	63.33%
Nadifloxacin group	22	8	30	73.33%

Discussion

Cohen et al [9], in their study observed the prevalence in teenagers aged 15-17 years to be 85%. In the study by Thiobutot and Strauss [10], more number of patients were found to have acne during the middle to late teenage period.

Burton et al [11], reported the peak age of acne as between 14-17 years in females and 16-19 years in males which is in contrast to our study. The present study though shows teenagers as the second most common age of acne occurrence most prevalent is among the age group of 21-25 years, with the mean age being 22.7 which is in concurrance with the above study. In the present study 42 (70%) were females and 18(30%) were males in the ratio 2.3:1.

Lello et al [12], in their study observed the prevalence of acne to be 91% in male and 79% in female adolescents, which is in contrast to the observation of our study.

Out of the 60 patients, grade I acne was the most prevalent one (70%). Comedones, papules were present in all the patients and predominant lesions were comedones.

In the study by Adityan et al [2], grade I acne was the most prevalent (60.2%), grade II (27.5%),grade III (2.6%), grade IV (9.7%).

In the study by Supreethi Biswas et al [13], grade II acne was the most prevalent one (45%), grade III (16%) and grade IV (7%).

Hyuck Hoon Kwon et al [14]., observed in their study that acne was more common, found in students, 690 (50.3%) among 1370 patients.

Our study results favours the findings of the above study. Tan et al [15] in their study observed that 74% of patients had a duration of more than 1 year before seeking medical attention. 12% had between 6-12 months, 6% had between 3-6months and 7% had a duration less than 3 months. In all, 25% of patients had duration of disease < 1 year.

Thus the results of the present study were almost similar to the above study.

In our present study, 16 (27%) patients denied of having any aggravating factors,12 (20%) patients had H/o high glycemic diet such as chocolates, ice-creams, fried items, as the aggravating factor whereas 10 (17%) had stress as the reason for flaring up of acne 9 patients had summer and 3 patients had winter as the aggravating factors, 4 had menstral flare and 6 had travelling and poor hygiene as the aggravating factor.

In the study of Smith et al [16], there was a positive association between a high glycemic diet and acne severity.

Our study showed high glycemic diet being one of the most common aggravating factors.

In the study by Pearl et al [17], 57.4% patients believed stress to be a contributing factor to acne. Green and Sinclair [18], observed that 67% of students believed that stress played a role in acne exacerbation. The present study is in contrast with the study by Pearl et al [17].

Emotional factors presumably affect acne by altering the adrenal pituitary axis. Stress may be associated with increased adrenal androgen production and subsequent increased sebum production[9].

In the study by Sardana et al [19], 28.5% of patients noted an aggravation in summer. The results were varied. This could be due to the fact that several factors influence the exacerbation of acne. The increased temperature marked humidity and sweating may be responsible for the summer aggravation.

Cunliffe and Cotterill [20]., observed that 60-70% of women noticed a deterioration in acne in the premenstrual period.

Premenstrual flare is possibly related to a premenstrual change in the hydration of the pilosebaceous epithelium [20].

Schofer conducted a study to evaluate the efficacy of nadifloxacin as monotherapy, the results showed that the topical antibiotic nadifloxacin, investigated in this non-interventional trial, was shown to be very effective as a monotherapy as confirmed by 82.1% of “very good/good” efficacy ratings. Dermal symptoms as well as the psychological disposition of the patients improved considerably over the treatment period. In our study also there is 88.51% reduction in the lesion count showing that it effective in the treatment of acne vulgaris [8].

While comparing both the regimens, there was a significantly greater reduction of inflammatory lesion count in the clindamycin 1% as well as nadifloxacin1% group at week 8.

Lesion counts reduced after initiation of therapy for both treatment groups, but these were significantly greater and faster reductions for both the groups (p=0.001). But inter group variation was not significant (p=0.453). Percentage of reduction in the lesion count is shown to be 32.78%, 60.12%, 87.47% at the end of 2, 4, 8th week respectively in the clindamycin group and 31.08%, 60.09%, 88.51% at the end of 2, 4, 8th week respectively in the nadifloxacin group. There was no much difference between the efficacy of both the regimen. Choudry. S et. al., conducted a similar study with clindamycin and Nadifloxacin as adjuvants tobenzoyl peroxide which clearly showed that at baseline the two groups were comparable withrespect to the total lesion count. At the end of 4 and 8 weeks, respectively, no statistically significant difference of total lesion count was noted between two arms. Results show that 88.18% subjects in the NADI group while 62.16% in the CLN group had ≥ 50% reduction of baseline inflammatory lesion count at study end and this inter-group difference was statistically significant [1].

Improvement in the severity of the lesions was considered if there was change in the IGA score by at least 2 scores. 19 out of 30 (63.33%) showed significant improvement in the clindamycin group by the end of 8 weeks and 22 out of 30 (73.33%) showed significant improvement in the nadifloxacin group by the end of 8 weeks.

In a similar study done in kolkatta, the percentage of subjects at study end who demonstrated at least two scale improvements in the IGA were 54.05% (20 out of 37) in the CLN group versus 73.8% (31 out of 42) in the NADI group at the study end visit. Though the proportion of subjects in the NADI group showed better improvement, the difference did not reach statistically significant (*P*=0.067) values. No subjects in either group demonstrated worsening of the scores [1]. Our present study results correlate with the result of the above study [1].

Safety evaluation

Both treatment regimens were well tolerated during the study.

In a similar study done by Choudhury. S et. al., In the safety and tolerability assessment, both treatments were well tolerated with only minor

differences 24.3% (9 out of 37) patients in CLN group and 14.3% (6 out of 42) in the NADI group experienced at least one treatment emergent adverse event (AE). The adverse events were dryness, pruritus, burning sensation, and erythema. None of the patients needed treatment modification for the AEs and they resolved spontaneously. Treatment compliance was comparable in both the treatment arms [1].

Conclusion

Overall, this study showed that nadifloxacin has a similar clinical efficacy as clindamycin with benzoyl peroxide in the treatment of mild to moderate acne vulgaris. The results support the existing published data showing the efficacy of nadifloxacin similar and comparable to that of clindamycin with benzoyl peroxide in the treatment of mild to moderate acne vulgaris.

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