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A COMPARISON OF EFFICACY, SAFETY AND COST-EFFECTIVENESS BETWEEN COMBINATION THERAPY OF TOPICAL NADIFLOXACIN VERSUS CLINDAMYCIN WITH BENZOYL PEROXIDE IN TREATMENT OF ACNE VULGARIS.

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ABSTRACT

BACKGROUND: Acne vulgaris is a dermatological disorder in which anti-microbials, keratolytics are commonly prescribed in the treatment of acne.

Aim: The present study was undertaken with the aim of comparing the efficacy, safety, cost-effectiveness of combination of topical nadifloxacine-benzoyl peroxide and clindamycin- benzoyl peroxide in patients of acne vulgaris.

MATERIALS AND METHODS: 74 patients between 12 to 40 years having inflammatory and/or non-inflammatory lesions. Group 2 was prescribed nadifloxacin-benzoyl peroxide gel. There were 38 patients Group1 and 36 patients in Group 2.

RESULTS: A within group comparison of inflammatory lesion and non-inflammatory lesion count from baseline to different time points (4 and 8 weeks) showed a highly significant reduction of scores (P<0.0001). Nadifloxacine is effective, tolerable, safe and cost effective for mild to moderate facial acne.

CONCLUSION: Its clinical effectiveness is comparable to clindamycin when used as add-on therapy to benzoyl peroxide.

KEYWORDS : Acne vulgaris, clindamycin, nadifloxacin, topical treatment

INTRODUCTION:

Acne vulgaris is the most common skin condition which occurs most commonly during adolescence, affecting an estimated 80-90% of teenagers. The peak incidence is between 14-17 years in women and 16–19 years in men. [1]It is a self limiting disorder of the pilosebaceous unit that is seen primarily in adolescents. Most cases present with a pleomorphic array of lesions consisting of comedones, papules, pustules and nodules with varying extent and severity. [2] The pathogenesis is complex and multifactorial which includes abnormal sebum production, follicular hyperkeratinisation, bacterial proliferation and inflammation.[3]

Topical therapy is the standard of care for mild to moderate acne. Retinoids and antimicrobials such as benzoyl peroxide and antibiotics are the mainstay of topical acne therapy. Such treatments are active at application sites, and they can prevent new lesions. [4,5] In India various drugs are available for the treatment of acne vulgaris. This creates a lot of confusion for the physician to decide drug of choice for their patients. Literature search revealed very few studies which compared the cost-effectiveness of drugs for acne vulgaris. [6,7,8]

This randomized controlled assessor blind trial compared the efficacy, safety and cost effectiveness at the end of four and eight weeks therapy of nadifloxacine 1% versus clindamycin 1% as add-on therapy to benzoyl peroxide (2.5%) in mild to moderate grade acne.

MATERIALS AND METHODS

Aim of the study: To compare the efficacy and safety, cost-effectiveness between combination therapy of topical nadifloxacin and benzoyl peroxide versus clindamycin and benzoyl peroxide in acne vulgaris.

Ethical Consideration: The study was started after getting approval from the Institutional Ethical Committee. Written informed consent was obtained in the vernacular language from every patient before enrolment.

Study Design: Randomized, controlled, comparative, single blinded, single centre, prospective, parallel group study.

Study Centre: Dept. of Dermatology and Pharmacology, Andhra Medical College, Visakhapatnam.

Study Period: From May 2012 to October 2013

Subjects graded as mild to moderate (grade I and II) acne vulgaris attending the dermatology out-patient clinic were screened for study selection criteria.

Inclusion Criteria

1. Age group 12 yrs -40 yrs
2. Both genders
3. ≥ 2 but ≤ 30 total lesions - inflammatory and/or non-inflammatory lesions.

Exclusion Criteria

1. Age less than 12 yrs and more than 40 yrs
2. Pregnant and lactating women
3. Severe grade of acne
4. Subjects using other anti-acne medications in the last 30 days before study.
5. Patients with h/o allergy to topical antibiotics
6. Total lesion count < 2 or >30,

Sample Size: The sample size was calculated considering the total lesion count as the primary efficacy parameter. After screening, 84 subjects fulfilled the subject selection criteria and were randomized (43 in Nadifloxacin group and 41 in clindamycin group) to the two study groups using an unstratified computer generated randomization list All enrolled subjects were instructed to apply a thin layer of the study medications over the lesions; benzoyl peroxide 2.5% gel once daily at bedtime and clindamycin 1% gel or nadifloxacin 1% gel twice daily. The patients were instructed to apply the study medications 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.

Efficacy parameter:

The primary efficacy parameter: It was change from baseline to study end of the total lesion count – both inflammatory and non-inflammatory lesions.

Secondary efficacy parameters: These were the validated IGA, [9] on a six-point scale: 0 - indicating clearance of inflammatory and non-inflammatory lesions, 1- almost clear, 2- mild severity, 3-moderate severity, 4-severe, and 5-very severe. Proportion of subjects in each group were considered as “improved” if there was at least two scale improvement in the IGA.

Safety: Safety was evaluated by vigilant follow-up of patients for adverse drug reactions (ADRs) and recorded in case report form

Cost effectiveness assessment: The cost effectiveness was calculated on basis of total expenditure on medicine (in INR) at the end of four and eighth week and cure rate (in %) and the two groups were compared on the basis of amount needed to treat one case successfully[10]

Statistical analysis : Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows (version 17, SPSS Inc., Chicago, IL, USA). The efficacy variables (total lesion, inflammatory, noninflammatory lesion counts, and CADI scores) were tested for normality using the Kolmogorov-Smirnov Z

test and were found to be normally distributed. Independent sample *t*-test was used to compare continuous parametric variables for between-group analysis while repeated measure ANOVA for within-group analysis with *Bonferroni* multiple comparison posthoc test. Categorical variables were analyzed using the χ test or Fisher's exact test, as appropriate. A *P* value of < 0.05 and <0.01 were considered as statistically significant and highly significant, respectively.

RESULTS:

Out of 74 randomized subjects (38-nadifloxacin arm) and (36-clindamycin) 37 in nadifloxacin (NADI) group, 34 in clindamycin (CLN) group completed the study. Two patients in the CLN group and one in the NADI group were lost to follow-up and did not attend any post baseline visit. Hence, there were 37 "evaluable subjects" in the NADI and 34 in CLN, respectively. Thus, the target number of evaluable subjects (32) in each group was achieved.

There were no significant differences in baseline demography and disease characteristics in the two treatment arms as shown in **Table 1.** At the end of 4 and 8 weeks, respectively, no statistically significant (P>0.05) difference of total lesion count was noted between two arms.

Table: 1 Between group comparison of total lesion count

TOTAL LESION COUNT (Mean ± SD)	Group 1: CLN+BZP (n=37)	Group 2: NADI+BZP (n=42)	P-Value
Baseline (0 weeks)	25.68±10.79	24.98±12.34	0.68
Follow-up (4 weeks)	19.36±7.30	17.61±7.42	0.42
Study end (8 weeks)	16.32±7.17	14.51±6.58	0.14
Values are mean ± standard deviation, CLN= clindamycin, BZP = benzoylperoxide, NADI= nadifloxacin			

Results show that 87.28% subjects in the NADI group while 61.26% in the CLN group had ≥ 50% reduction of baseline inflammatory lesion count at study end and this inter-group difference was statistically significant (*P*=0.009). However, similar comparison of the non-inflammatory counts showed statistically non-significant differences (*P*=0.636).

For both treatment groups, a progressive decline in the number of inflammatory and non-inflammatory lesion counts was observed. A between-group analysis of lesion counts at the first follow up (P=0.82 for inflammatory; P=0.38 for non-inflammatory) and at study end (P=0.24 for inflammatory; P=0.19 for non-inflammatory) did not show any statistically significant difference. A within group comparison of inflammatory lesion and non-inflammatory lesion count from baseline to different time points (4 and 8 weeks) showed a highly significant reduction of scores (P<0.0001).

Table 2: Between group comparison of inflammatory and non-inflammatory lesion count

Lesions Count (Mean ± SD)	Visit	Group 1 CLN+BZP n=37	Group 2 NADI+BZP n=42	P-value
Inflammatory lesion count	Baseline	6.42±2.39	6.52±3.78	0.36
Non- inflammatory	(0 weeks)	20.15±7.67	19.57±8.59	0.95
Inflammatory	Follow-up	4.16±2.82*	3.46±2.32*	0.82
Non- inflammatory	(4 weeks)	13.43±5.80*	14.19±6.45*	0.38
Inflammatory	Study end	4.25±2.8*	2.63±1.71*	0.24
Non- inflammatory	(8 weeks)	12.92±6.43*	9.23±7.03*	0.19
SD= Standard deviation, CLN= clindamycin, NADI = Nadifloxacin, BZP = benzoylperoxide. P values are between group analysis.*P<0.0001 for within group comparision of inflammatory lesion count with respect to baseline,* P <0.0001 for within group comparison of non-inflammatory lesion count with respect to baseline.				

The percentage of subjects at study end who demonstrated at least two scale improvements in the IGA were 58.82% (20 out of 34) in the CLN group versus 81.08% (30 out of 37) 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.

Between groups comparison of CADI is shown **in Table 3**. The treatment groups were comparable at baseline and the first follow up scores also showed no significant differences (*P*=0.43), but at the study end visit a statistically significant difference (*P*=0.04) was observed in favour of the NADI group.

Table: 3 Between group comparison of Cardiff Acne Disability Index

Cardiff Acne Disability Index	Group 1: CLN+BZP (n=37)	Group 2: NADI+BZP (n=42)	P-Value
Baseline visit	6.7±2.58	7.21±2.32	0.35
First Follow-up visit	7.81±2.36	6.0±2.36	0.43
Study end visit	5.75±2.81	4.96±2.19	0.04
Values are mean ± standard deviation, CLN= clindamycin, NADI= Nadifloxacin, BZP = benzoylperoxide. P values are for between group analysis. *P<0.05 statistically significant			

Within group comparison of CADI at different time points (baseline, 1 follow-up and study end) showed a highly significant reduction (P<0.001) of scores for both the groups.

In the safety and tolerability assessment, both treatments were well tolerated with only minor differences 26.47% (9 out of 34) patients in CLN group and 13.51% (5 out of 37) in the NADI group experienced at least one treatment emergent adverse event (AE).

There were no serious side effects reported in both the groups. There was no statistically significant difference between the two groups (P > 0.05) [Table 4].

Table 4: Side effects of medications

Side effect	Clindamycin plus benzoylperoxide. n (%)	Nadifloxacin plus benzoylperoxide. n (%)	P value
hyperpigmentation,	1	0	0.3900
dryness,	2	1	
pruritus,	3	1	
burning sensation	3	3	

Cost-effective analysis: Average cost of nadifloxacin gel 10 gm – Rs. 70, average cost of clindamycin gel 10 gm – Rs. 90, average cost of benzyl peroxide 2.5% gel 10 gm – Rs. 32.

Table 5: Cost- effectiveness analysis of each drug at end of four week

Parameter	Group 1 CLN+BZP	Group 2 NADI+BZP
Cost in INR for 100 participants	122X100=12200	102X100=10200
Cure rate (%)	61	87
Cost to treat 100 cases	Rs. 12200 for 61 participants	Rs. 10200 for 87 participants
Cost (INR) to treat one case (Rs.)	200	117.24

Amount needed to treat 1 case of acne successfully using Group 1 (CLN+BZP) at the end of four week was Rs 200, for Group 2 (NADI+BZP) was Rs. 117.24.

Table 6. Cost- effectiveness analysis of each drug at end of eighth week

Parameter	Group 1 CLN+BZP	Group 2 NADI+BZP
Cost in INR for 100 participants	122X100=12200	102X100=10200
Cure rate (%)	57	81
Cost to treat 100 cases	Rs. 12200 for 57 participants	Rs. 10200 for 81 participants
Cost (INR) to treat one case	Rs. 214	Rs. 125.92

Amount needed to treat 1 case of acne successfully using Group 1 (CLN+BZP) at the end of four week was Rs 214, for Group 2 (NADI+BZP) was Rs. 125.92.

Thus, (NADI+BZP) is more cost-effective for treating one acne case successfully at the end of eight week regimen.

DISCUSSION:

The results from this study demonstrate a reduction in both the inflammatory and non-inflammatory lesions of acne over an eight-week treatment period with two topical therapies (clindamycin with

benzoyl peroxide and nadifloxacin with benzoyl peroxide). No differences between two therapies were observed in the total, inflammatory or non-inflammatory lesion counts. Nadifloxacin with benzoyl peroxide is more cost effective than clindamycin with benzoyl peroxide in treatment of acne, which is important factor in developing country like India.

Our findings were similar to previous published literature in this domain. Nadifloxacin inhibits activation of T cells and keratinocytes which could partly be responsible for its beneficial effects in inflammatory acne.[11] A phase III, regulatory trial (noninferiority study design), published from Japan with clindamycin (test drug) versus nadifloxacin (control) reported non-inferiority of clindamycin to nadifloxacin in terms of its efficacy in reducing inflammatory lesion count and improving global assessment scores.[12] Our study has shown similar effectiveness and safety of nadifloxacin with that of clindamycin.

A study by Veronnica *et al*., from Germany [13] was conducted to evaluate susceptibility of clinical isolates of *P. acnes* and the results have shown that nadifloxacin was superior to erythromycin and clindamycin as the MIC (minimal inhibitory concentration) values of nadilfloxacin against *P. acnes* were the least compared to the others.

A recently published randomized, vehicle controlled trial from Korea [14] has demonstrated that nadifloxacin 1% cream brought about a significant reduction of the inflammatory, non-inflammatory lesion counts in facial acne along-with a decrease in inflammation severities and IL-8 staining intensities in immunohistochemistry studies.

The medications of both the groups were well tolerated, cost-effective in our study, which was also illustrated by previous studies. There were no serious adverse effects reported in our study. [15] Results of our study were found to be comparable with studies of Anbarasi etal [16] found that between the clindamycin vs nadifloxacine there was no statistical difference in terms of efficacy and safety parameters ($p>0.05$). Similar results were found with IGA scores. Result of Anbarasi etal is comparable with finding of our study.

Kaur etal [17] fount that clindamycin-benzyl peroxide combination is more efficacious than Nadifloxacine-benzyl peroxide combination while Nadifloxacine-benzyl peroxide is safer than clindamycin-benzyl peroxide combination, this results are comparable to finding of our study.

Limitations of the study:
The limitations of our study was single blinded, small sample study. Further study with large sample size, double blinded, parallel studies are needed to find more cost-effective solution for treatment of acne vulgaris.

Advantages of the study:
Very few studies in past had compared the cost-effectiveness between these two regimen, we have throw the light on this new aspect, which will be helpful in selecting accurate regimen for treatment of acne in future. The results of this study might be helpful for manufacturers to consider undertaking pharmacokinetic feasibility studies for preparing combination formulation of nadifloxacin and benzoyl peroxide for treatment of acne.

CONCLUSION:

Topical nadifloxacin, a new fluoroquinolone is effective, tolerable, safe and cost effective for mild to moderate facial acne. Its clinical effectiveness is comparable to clindamycin when used as add-on therapy to benzoyl peroxide. Nadifloxacine-benzyl peroxide combination is more cost effective than clindamycin-ben-zyl peroxide combination. Nadifloxacin benzyl peroxide combination- is definitely a promising drug for the treatment of acne vulgaris.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee.

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