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Original Research Article

A Randomized Double-Blind Prospective Comparative Study on the Efficacy and Safety of Topical Nadifloxacin and Benzoyl Peroxide versus Clindamycin and Benzoyl Peroxide in Patients with Mild to Moderate Acne Vulgaris

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Conflict of interest: Nil

Abstract:

Background: Acne vulgaris is a chronic, self-limiting, inflammatory disease of the pilosebaceous unit, characterized by pleomorphic lesions such as comedones, erythematous papules, pustules, cysts, and nodules. Nadifloxacin, a topical fluoroquinolone, is used for acne vulgaris. Clindamycin has strong antimicrobial action and reduces follicular microbial colonization by inhibiting leukocyte chemotaxis or extracellular lipase production by Propionibacteria. Benzoyl peroxide is an effective topical agent indicated for mild-to-moderate acne vulgaris with anti-microbial, anti-inflammatory, and anti-comedogenic effects.

Methods: This is a randomized, double-blind, prospective, comparative, parallel-group study. Group A received topical Nadifloxacin 1% gel twice daily and Benzoyl peroxide 2.5% gel once daily at bedtime. Group B received topical Clindamycin 1% gel twice daily and Benzoyl peroxide 2.5% gel once daily at bedtime. All medications were masked with black tape to prevent identification and were labeled as A or B, dispensed by the nursing staff.

Results: Out of 81 randomized subjects, 37 in the nadifloxacin arm and 34 in the clindamycin arm completed the study. The mean reduction of lesions from baseline to the 8th week was statistically significant in both groups, with a P-value of < 0.0001 on a paired t-test. The mean reduction of CADI score from baseline to the 8th week was also statistically significant in both groups, with a P-value of < 0.0001 on a paired t-test. Adverse events were similar in both groups and not statistically different.

Conclusion: Our study concludes that nadifloxacin, a newer topical fluoroquinolone, is equally efficacious as clindamycin when used in combination with benzoyl peroxide.

Keywords: Acne Vulgaris, Nadifloxacin, Clindamycin, Benzoyl Peroxide.

Introduction

Acne vulgaris is a chronic, self-limiting, inflammatory disease of the pilosebaceous unit, characterized by pleomorphic lesions such as comedones, papules, pustules, nodules, and cysts, which may lead to scarring [1]. Acne vulgaris typically begins in adolescence, peaking between the ages of 14 to 17 years in women and 16 to 19 years in men, and generally resolves by the mid-twenties. Severe forms of acne vulgaris occur more frequently in males [2]. Acne presents with polymorphic eruptions, which may be non-inflammatory (open and closed comedones) or inflammatory (papules and pustules). It is a multifactorial disease, influenced by several factors [3]. Major factors responsible for the development of acne lesions include altered sebum production, abnormal keratinization within the pilosebaceous unit, Propionibacterium acnes proliferation, and perifollicular inflammation [4]. To assess the severity of acne, various grading systems are used, although no universally accepted quantitative system exists. Commonly used acne grading scales include the Global Evaluation Acne Scale, the US FDA's Investigator's Global Assessment for acne vulgaris, the Revised Leeds grad-

ing technique, and Plewig and Kligman's numerical grading of comedonal and papulopustular acne [5].

Topical therapy is the standard treatment for mild to moderate acne. Topical treatments act directly at the site of application, preventing the formation of new lesions. Topical therapies, including comedolytic agents such as tretinoin, benzoyl peroxide, antibiotics, and various anti-inflammatory drugs, are the first line of treatment for patients with non-inflammatory comedones or mild-to-moderate inflammatory acne [6].

Oral antibiotics such as doxycycline, minocycline, tetracycline, azithromycin, erythromycin, and sulfamethoxazole-trimethoprim are indicated for moderate and severe acne, acne resistant to topical treatment, and acne covering large body areas. These antibiotics exhibit both antibacterial action, by inhibiting P. acnes protein synthesis, and anti-inflammatory action, by decreasing the concentration of free fatty acids and pro-inflammatory products of P. acnes, inhibiting macrophage action, and modulating the host response to inflammatory stimuli [7].

Hormonal therapy is indicated in girls and women with acne due to ovarian or adrenal hyperandrogenism, recalcitrant acne, acne unresponsive to repeated courses of oral isotretinoin, acne tarda, polycystic ovary syndrome, or the presence of clinical signs of hyperandrogenism. Other treatment modalities include phototherapy, lasers, and surgery.

Nadifloxacin

Nadifloxacin is a topical fluoroquinolone and the first quinolone antimicrobial for topical dermatological use . Chemically synthesized, it is characterized as a 4-quinolone with a ketone group at position four and a fluorine atom at position six, broadening its spectrum of activity against both Gram-negative and Gram-positive pathogens. Nadifloxacin inhibits the enzyme DNA gyrase, preventing the negative supercoiling of bacterial DNA, essential for DNA replication, transcription, and recombination. It is used for the therapy of mild to moderate acne and was developed by Otsuka Pharmaceutical Company. It is widely used in Japan, other European countries, and has been recently introduced in India.

Nadifloxacin has shown good safety and efficacy against several bacteria, including aerobic Gram-negative, Gram-positive (including MRSA and coagulase-negative staphylococci), and anaerobic bacteria. Previous in vitro studies have demonstrated its potency against Propionibacterium species, Streptococcus species, and Staphylococcus species, which are important pathogens in acne. Its inhibitory effect on pro-inflammatory cytokines like interleukin (IL)-1α, IL-6, and IL-8, which play a significant role in the pathogenesis of acne, makes it effective in treating inflammatory acne lesions. The general side effects include erythema, itching, contact dermatitis, dryness, and skin irritation.

Benzoyl Peroxide

Benzoyl peroxide is an effective topical agent used for many years in various formulations (washes, lotions, creams, and gels) and concentrations (2.5–10%). It is indicated for mild-to-moderate acne vulgaris, with anti-microbial, anti-inflammatory, and anti-comedogenic effects. Benzoyl peroxide reduces the population of P. acnes by generating reactive oxygen species in the sebaceous follicle. Adverse effects include concentration-dependent cutaneous irritation or dryness and bleaching of clothes, hair, and bed linen. It can induce irritant dermatitis, characterized by burning, erythema, peeling, and dryness, which typically subsides with continued use. Combination therapy with benzoyl peroxide and topical antibiotics has been shown to be more effective and better tolerated than benzoyl peroxide alone.

Clindamycin

Clindamycin inhibits bacterial protein synthesis at the ribosomal level by binding to the 50S ribosomal subunit, affecting the process of peptide chain initiation. It exhibits strong antimicrobial action by inhibiting leukocyte chemotaxis and extracellular lipase production by Propionibacteria, thereby reducing follicular microbial colonization. Available in various formulations like solutions, lotions, and gels, clindamycin can cause adverse effects such as erythema, peeling, itching, dryness, and burning, with rare instances of pseudomembranous colitis. Development of bacterial resistance and cross-resistance is common with topical antibiotics.

This study aims to compare the efficacy and safety of topical nadifloxacin and benzoyl peroxide versus clindamycin and benzoyl peroxide in patients with mild to moderate acne vulgaris.

Materials and Methods

Based on the number of patients reporting to the outpatient unit of the Dermatology department with acne vulgaris, and according to the previous year's medical records, the expected sample size for this study was 80 patients.

The study was conducted at Rangaraya Medical College, Kakinada, from March 2017 and completed by March 2018. Patients who were irregular in using the study medication or during follow-up as per study procedures were not considered for the final analysis.

Study Medication: During the treatment and follow-up period, no concomitant systemic therapy was permitted. Patients were advised to apply the study medications after washing their face and pat-

ting it dry. They were instructed not to bathe, wash, or swim for at least 4 hours after applying the study medications.

Study Procedure: Patients who met the inclusion criteria and provided written informed consent were enrolled in the study and assigned a patient identification number (PID). Enrolled participants were randomly allocated into two groups through a randomization procedure. The treatment was administered in a double-blinded manner. The randomization code and blinding were unmasked at the end of the study or if any severe adverse drug reaction (ADR) occurred.

At the start of the study, general demographic information and medical history were collected in the case record form (CRF) for each patient. Acne lesions were examined, and a baseline evaluation of the Investigator Global Assessment (IGA) score was conducted. Patients were then given the respective trial medication. Follow-ups were conducted at the 4th and 8th weeks. During follow-ups, lesion count and Cardiff Acne Disability Index (CADI) scores were assessed, and any adverse events were recorded as per standard procedure in the CRF.

A total of 81 patients met the enrollment criteria and completed the follow-up with regular use of the study medications.

Assessment Parameters:

- Lesion counting
- Investigator Global Assessment (IGA) score
- Cardiff Acne Disability Index (CADI)

Outcomes:

The primary outcome was the measurement of efficacy, indicated by the change in total lesion count and CADI score from baseline to the end of the study/treatment period between the two treatment groups. Secondary outcomes included the assessment of safety and the response rate of each drug[7].

Statistical Analysis: Statistical analysis was performed using SPSS software version [insert version]. Continuous variables were expressed as mean ± standard deviation (SD).

The paired t-test was used to compare within-group changes from baseline to follow-up visits. An independent t-test was used to compare the mean changes between the two groups. A p-value of less than 0.05 was considered statistically significant. Adverse events were analyzed using descriptive statistics and compared between groups using the chi-square test.

Ethical Approval: The study was approved by the Institutional Ethics Committee of Rangaraya Medical College, Kakinada. Written informed consent was obtained from all participants before their inclusion in the study.

Results

Baseline Demographic Characteristics: The distribution of patients in each study group is detailed in Table 1. Group A consisted of 37 patients, while Group B included 34 patients. The distribution of sex in the study is shown in Table 2. Group A had 19 males and 18 females, whereas Group B had 13 males and 21 females, resulting in a total of 32 males and 39 females. The majority of patients were female, accounting for 54.92% of the total population.

Baseline features of the participants, including age distribution, are provided in Table 3. In Group A, 14 patients were in the 12–20 years age group, 14 in the 21–25 years age group, 6 in the 26–30 years age group, and 3 in the 31–40 years age group, with a mean age of 22.51 ± 6.04 years. In Group B, 11 patients were in the 12–20 years age group, 18 in the 21–25 years age group, 3 in the 26–30 years age group, and 2 in the 31–40 years age group, with a mean age of 22.5 ± 4.95 years. There were no significant differences in baseline demographic data and disease characteristics between the two treatment arms.

Efficacy

The mean lesion count in Group A at the 4th week and 8th week was 8.22 ± 3.86 and 2.46 ± 1.02, respectively. In Group B, the mean lesion count at the 4th week and 8th week was 9.32 ± 4.09 and 2.79 ± 1.09, respectively, as shown in Table 4. There was no statistically significant difference observed between the groups on an independent t-test.

Within-group comparisons (Table 5) showed that in Group A, the lesion count reduction from baseline (Day 0) to 4 weeks was 9.41 ± 2.90, and from baseline to 8 weeks was 15.16 ± 5.44. In Group B, the lesion count reduction from baseline to 4 weeks was 9.26 ± 1.58, and from baseline to 8 weeks was 15.79 ± 3.08. These reductions were statistically significant (p-value < 0.0001).

The mean Cardiff Acne Disability Index (CADI) score in Group A at the 4th week was 4.32 ± 2.03 and at the 8th week was 2.03 ± 0.80. In Group B, the CADI score at the 4th week was 4.74 ± 2.09 and at the 8th week was 2.58 ± 1.06, as indicated in Table 6. There was no statistically significant difference observed between the groups on an independent t-test at the 4th and 8th weeks.

Within-group comparisons of CADI scores (Table 7) revealed that in Group A, the reduction from baseline (Day 0) to 4 weeks was 2.54 ± 1.09, and from baseline to 8 weeks was 4.84 ± 2.37. In Group B, the reduction from baseline to 4 weeks was 3.50

± 0.75, and from baseline to 8 weeks was 5.65 ± 1.78. These reductions were statistically significant (p-value < 0.0001).

Safety Profile: The safety profile of the two intervention groups is presented in Table 8. The adverse effects observed included dryness, irritation, erythema, burning sensation, itching, and scaling. In Group A, 24.32% of patients (9 out of 37) experienced adverse events, while in Group B, 35.29% of patients (12 out of 34) experienced adverse events.

The adverse events were similar in both groups and were not statistically different.

Table 1: Distribution of Patients in Each Study Group

Study Group	Number of Patients
Group A	37
Group B	34

Table 2: Distribution of Sex in the Study

Study Group	Males	Females	Total
Group A	19	18	37
Group B	13	21	34
Total	32	39	71

Table 3: Baseline Features of the Participants

Age Category	Group A	Group B
	Male	Female
12 – 20 yrs	9	5
21 – 25 yrs	7	7
26 – 30 yrs	2	4
31 – 40 yrs	1	2

Table 4: Comparison of Total Lesion Count between Groups

Lesion Count	Group A (Mean ± SD)	Group B (Mean ± SD)	P value
Day 0	17.62 ± 6.76	18.59 ± 5.67	0.51
4 weeks	8.22 ± 3.86	9.32 ± 4.09	0.24
8 weeks	2.46 ± 1.02	2.79 ± 1.09	0.49

Table 5: Lesion Count Reduction within Each Group

Study Group	Lesion Reduction from (Day 0) to	Mean Difference ± SD	SE of Difference	P Value	95% Confidence Interval
					Lower Limit
Group A	4 weeks	9.41 ± 2.90	0.591	<0.0001*	8.21
	8 weeks	15.16 ± 5.44	1.143	<0.0001*	12.84
Group B	4 weeks	9.26 ± 1.58	0.564	<0.0001*	8.12
	8 weeks	15.79 ± 3.08	1.081	<0.0001*	13.59

***Extremely significant**

Table 6: CADI Scores within Each Group

Cardiff Acne Disability Index	Group A (Mean ± SD)	SEM	Group B (Mean ± SD)	SEM	P value
Day 0	6.86 ± 3.17	0.52	8.24 ± 2.84	0.49	0.06
4 weeks	4.32 ± 2.03	0.42	4.74 ± 2.09	0.38	0.46
8 weeks	2.03 ± 0.80	0.30	2.58 ± 1.06	0.28	0.17

Table 7: Comparison of Efficacy Parameters within Each Group

Study Group	CADI Reduction from (Day 0) to	Mean Difference ± SD	SE of Difference	P Value	95% Confidence Interval
					Lower Limit
Group A	4 weeks	2.54 ± 1.09	0.163	<0.001*	2.21
	8 weeks	4.84 ± 2.37	0.270	<0.001*	4.29
Group B	4 weeks	3.50 ± 0.75	0.216	<0.001*	3.06
	8 weeks	5.65 ± 1.78	0.307	<0.001*	5.02

***Extremely significant**

Table 8: Safety Profile of the Two Intervention Groups

Adverse Event	Group A (N=9)	%	Group B (N=12)	%
Dryness	2	5.40	4	11.76
Irritation	3	8.10	2	5.88
Erythema	1	2.70	1	2.94
Burning sensation	2	5.40	2	5.88
Itching	1	2.70	2	5.88
Scaling	0	0.00	1	2.94

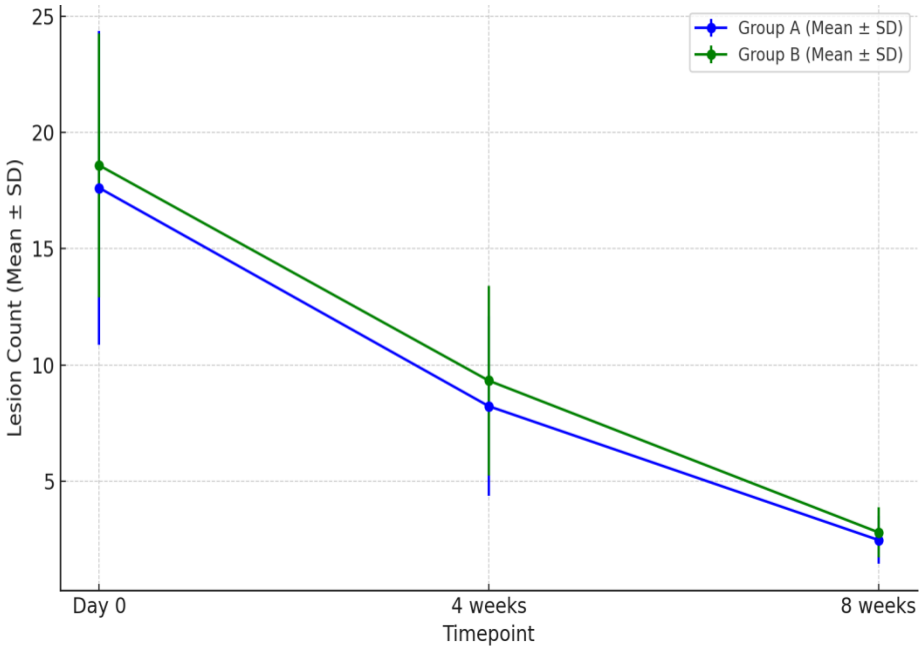

Figure 1: Comparison of Total Lesion Count between Groups

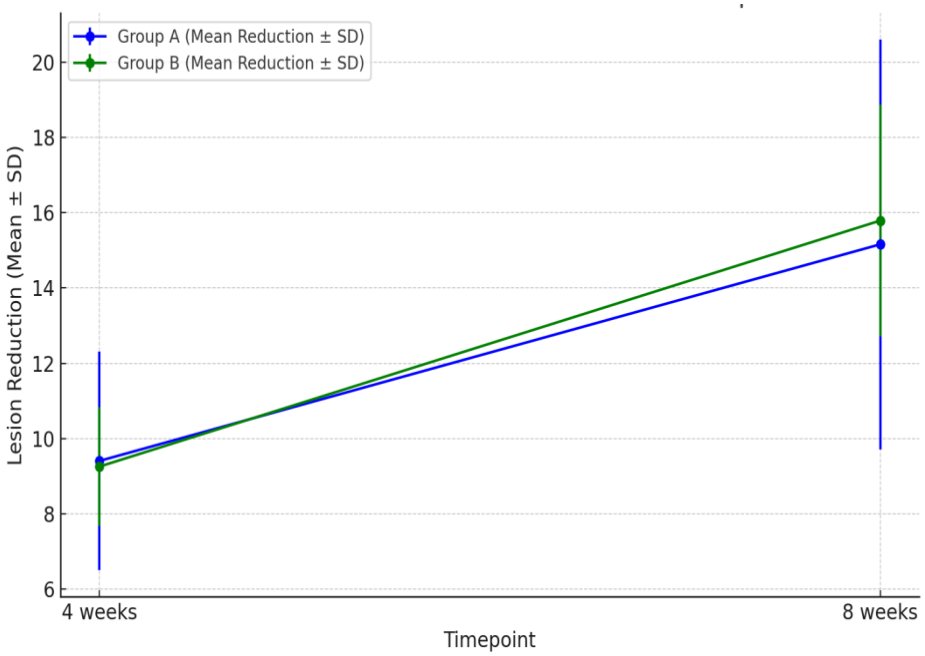

Figure 2: Lesion Count Reduction within Each Group

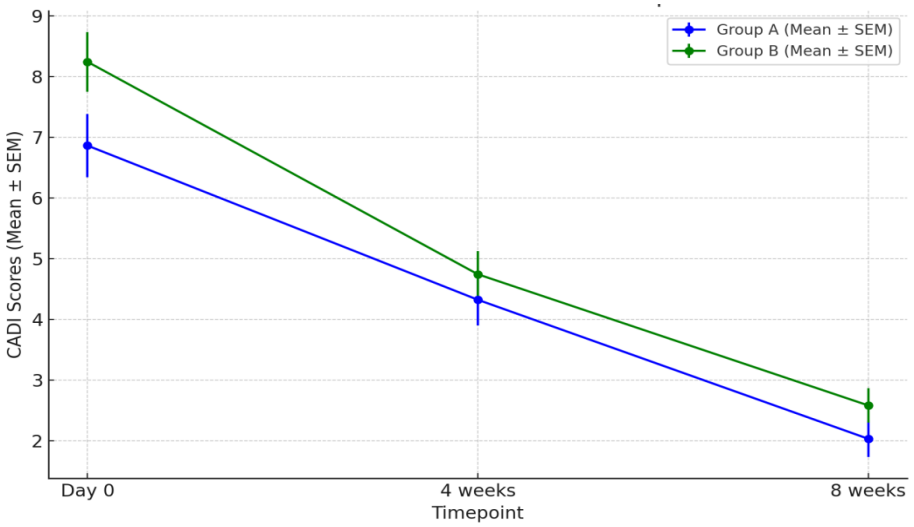

Figure 3: CADI Scores within Each Group

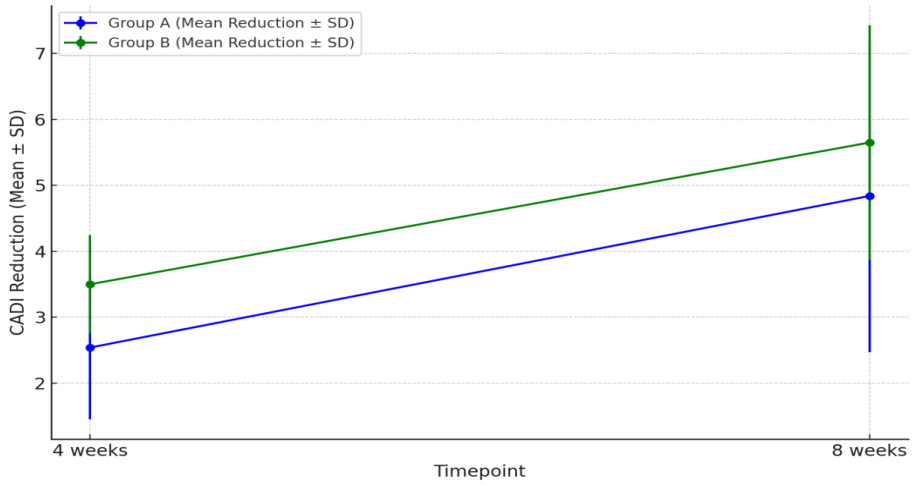

Figure 4: Comparison of Efficacy Parameters within Each Group

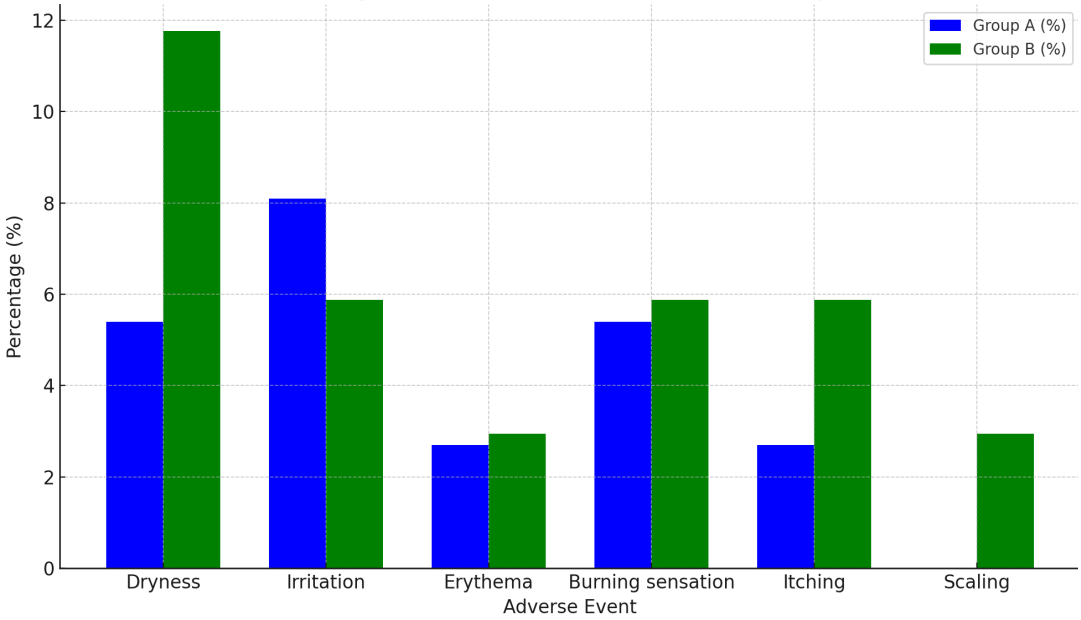

Figure 5: Safety Profile of the Two Intervention Groups

Discussion

The present study was conducted to evaluate the efficacy and safety of topical Nadifloxacin compared to topical Clindamycin in combination with Benzoyl Peroxide among patients with mild to moderate acne vulgaris. Acne is a chronic relapsing disease. For some acne patients, their condition may not be objectively severe, but they perceive it as severe, and this psychological impact must be taken seriously.

The management of acne begins with educating patients about the origin of the disease, proper skin hygiene, and the appropriate application of medications. The initial treatment phase aims to reduce inflammatory lesions and comedones. After achieving an acceptable clinical result, maintenance therapy aims to prevent relapses by reducing the formation of microcomedones.

It is generally accepted that antibiotics play a key role in the therapy of acne vulgaris. For moderate to severe cases of acne, systemic antibiotics are used, while topical antibiotics are very effective in mild to moderate stages of acne vulgaris [8].

Topical therapy is usually the first attempt for patients with non-inflammatory comedones or mild to moderate inflammatory acne. Any topical anti-acne treatment should be chosen based on the type of predominant lesion and the overall severity of the disease [9]. Topical antibiotics reduce the population of P. acnes on the skin surface and within the follicles, thereby reducing free fatty acids on the skin surface lipids—a marker of P. acnes lipase activity—and an indirect anti-comedogenic effect can be observed.

Topical antibiotics should generally not be used as monotherapy because of a dramatic increase in bacterial resistance. Therefore, combinations therapies of topical antibiotics are now favored, as combination therapy with different topical agents can improve efficacy, reduce the toxicity of topical monotherapy, decrease application frequency, and thereby increase compliance. Topical antibiotics have a relatively low cutaneous irritant profile [10].

Topical combination therapy includes the use of several medications together, such as Benzoyl Peroxide, retinoids, and antibiotics or they may be available as fixed-dose combination therapies [11]. The results showed a reduction in the total number of acne lesions throughout the eight-week treatment period with both treatment regimens. No significant differences were observed between the two treatment regimens in the total lesion counts.

The findings suggest that Nadifloxacin is as effective as Clindamycin in treating patients with acne vulgaris, but Nadifloxacin was slightly more tolerated than Clindamycin. However, the sample size in this trial is too small to conclusively determine the safety and tolerability profiles of Nadifloxacin and Clindamycin.

Baseline Characteristics: In the current study, no statistical difference was observed regarding baseline characteristics among the two groups, ensuring the internal validity of the data.

Efficacy Parameters: During the study period, there was a significant decrease in lesion counts and CADI scores within both the Nadifloxacin and Clindamycin groups, but there was no significant difference between the groups.

Choudhury et al [12]. Conducted a randomized single-blind study comparing the efficacy of two combinations of Benzoyl Peroxide: Nadifloxacin and Benzoyl Peroxide vs. Clindamycin and Benzoyl Peroxide. Results showed that both drugs are equally effective, with no statistically significant difference between the groups. Anbarasi et al [13]. Conducted a study showing that topical Nadifloxacin 1% cream is non-inferior to topical Clindamycin 1% gel and is as effective as Clindamycin in the treatment of mild to moderate acne vulgaris.

Another study by Plewig et al [14]. a phase III multinational study, compared Nadifloxacin 1% cream and Erythromycin 2% cream. They reported that in 474 European patients, during 12 weeks of treatment, both Nadifloxacin and Erythromycin caused a significant reduction in the number of inflamed papulopustular lesions (66.7% and 64.7%, respectively) and open and closed comedones. Swetha et al [15] concluded that the combination of topical 1% Clindamycin and 0.1% Adapalene is superior to the combination of topical 1% Clindamycin and 2.5% Benzoyl Peroxide in the treatment of mild to moderate acne vulgaris.

Miwa Kobayashi et al [16] conducted a Japan-based multicentric study comparing the efficacy of the combination of Adapalene gel and Nadifloxacin cream with Adapalene monotherapy in patients with moderate and severe inflammatory acne. The combination therapy improved inflammatory acne as early as two weeks with less irritation than Adapalene monotherapy.

Conclusion

This prospective, double-blind, randomized study evaluated the efficacy and safety of Nadifloxacin 1% and Clindamycin 1%, both combined with Benzoyl Peroxide, in treating acne vulgaris. Among 81 participants, 71 completed the study. Both treatment groups showed a statistically significant reduction in total lesion count and CADI scores from baseline to the 8th week, indicating efficacy. Nadifloxacin and Clindamycin were well-tolerated, with no significant difference in adverse effects, though Nadifloxacin was slightly better tolerated. Further large-scale, multi-centric studies are recommended to confirm these findings and explore

different drug combinations for optimal acne treatment.

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