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A COMPARATIVE STUDY TO ASSESS THE EFFICACY OF CLINDAMYCIN WITH TRETINOIN VERSUS CLINDAMYCIN WITH NICOTINAMIDE IN MILD TO MODERATE ACNE VULGARIS

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ABSTRACT: Introduction: Acne is characterized by non-inflammatory follicular papules or comedones and by inflammatory papules, pustules and nodules and is estimated to affect 9.4% of the global population. Topical combination therapy is the first-line approach for facial acne. **Objectives:** To compare the efficacy and safety of topical clindamycin 1% with tretinoin 0.025% and clindamycin 1% with nicotinamide 4% in mild to moderate acne vulgaris. **Methods:** This was a comparative study conducted at BMCRI including seventy subjects who were randomized (1:1) into two groups. Group A received clindamycin with Tretinoin and Group B received clindamycin with nicotinamide. Efficacy was assessed by mean change in Acne Severity Index (ASI) from baseline and at the end of 4, 8 and 12 weeks. Safety was assessed by adverse events reported. **Results:** Both treatment groups showed statistically significant improvement. Baseline ASI of Group A was 86.48 ± 4.49 and of Group B was 88.05 ± 4.02, which were comparable. At end of 12 weeks, ASI of Group A and Group B was reduced to 25.65± 2.4 and 14.17 ± 2.7 respectively. Group B showed statistically significant reduction in ASI than Group A ($p<0.0001$). Both treatments were well tolerated. **Conclusion:** Both the combination therapies are effective in mild to moderate acne vulgaris however clindamycin with nicotinamide showed favourable efficacy.

INTRODUCTION: Acne vulgaris is a self-limited disorder of pilosebaceous units seen primarily in adolescents with a pleomorphic array of lesions characterized by comedones, papules, pustules, nodules with varying extent and severity [1]. The Global Burden of Disease Project estimates the prevalence of acne to be 9.4%, ranking as the eighth most prevalent disease worldwide [2].

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Acne mostly heralds the onset of puberty. The incidence of acne usually peaks during the middle to the late teenage period affecting more than 85% and then steadily decreases [3].

Topical therapy is the standard of care for mild to moderate acne, but one of the major limitations especially for facial acne, is the relatively high potential for tolerability reactions characterized by visible signs (i.e., erythema, scaling, peeling, edema, dryness, roughness) and/or symptoms (i.e., stinging, burning) of cutaneous irritation [4]. The Global Alliance to Improve Outcomes in Acne recommend combination treatment with topical retinoids and antimicrobials as the cornerstone in acne management and also as the first line

treatment for mild to moderate acne [5]. Since inflammation due to *Propionibacterium acnes* has been considered as a major causative factor, both topical and systemic antibiotics have been tried successfully through various studies [6]. In view of development of antibiotic resistance, the need for the development of new topical combinations against the conventional antibiotics becomes a necessity. Currently, a unique Fixed Dose Combination of Clindamycin with tretinoin is proven to be safe and effective.

Clindamycin being more lipophilic targets P. acnes and has anti-inflammatory and anti-comedogenic effect [7]. Whereas tretinoin, a key component in anti-acne therapy is comedolytic, anti-comedogenic with minimal anti-inflammatory properties [8] normalizes desquamation, facilitates penetration of the antibiotic into the subcutaneous follicle and potentially decreases the exposure to antibiotics, thereby reducing the antibiotic resistance. Clindamycin also reduces the irritant activity of tretinoin without influencing its immune-modulatory effects [9].

Nicotinamide a newly approved alternative therapy for acne, possesses a potent anti-inflammatory effect [10]. Reduction of inflammation plays a vital role in the management of acne. It also has a beneficial effect in reducing sebum production and is extremely well tolerated by facial skin. Studies of clindamycin with nicotinamide have not been extensively evaluated and limited studies comparing them versus clindamycin and tretinoin are available. Hence this present study was conducted to compare the efficacy and safety of topical clindamycin 1% with tretinoin 0.025% and clindamycin 1% with nicotinamide 4% in mild to moderate acne vulgaris.

METHODOLOGY: It was a prospective, open label, randomized, comparative study conducted for a period of two and half years on seventy patients diagnosed with mild to moderate acne vulgaris on the facewho attended dermatology outpatient department in Victoria Hospital attached to Bangalore Medical College and Research Institute. The sample size of sixty-four was calculated by keeping the power at 80% and 95% Confidence Interval and at 5% significance level under the two tailed test of significance adequate for the study. Expecting 10% dropouts, or lost to follow up, seventy is an adequate sample size. The study subjects were randomly assigned into two groups of thirty-five each.

Group A: Patients treated with topical clindamycin 1% with tretinoin 0.025% (n=35).

Group B: Patients treated with topical clindamycin 1% with nicotinamide 4% (n=35).

The following patients were included – Subjects of either of sex, aged 18 to 35 years, subjects with mild to moderate acne vulgaris on face grade 2 and 3 of Investigator's Global Assessment Scale (IGAS) and Subjects willing to give written informed consent. The exclusion criteria were the subject who have used topical antibiotics or topical steroids on the face, facial procedures, or any investigational therapy within the past 4 weeks or systemic retinoids within the past 6 months, drug induced acne, pregnant and lactating mothers, and history of hypersensitivity to any of the study medication.

After obtaining approval and clearance from the institutional ethics committee, patients fulfilling the inclusion and exclusion criteria were enrolled in the study after obtaining informed consent. (Ethical committee approval was from the Institutional ethics committee attached to Bangalore Medical College and Research Institute and the approval number is BMC/PGs/289/2017-18).

Patients were randomized into two groups of thirty-five each. Patients were advised to apply pea-sized amount of medication into a thin layer on the face once daily in the evening/night after facial cleansing, avoiding the eyes, lips and mucous membrane. Treatment was continued up to 12 weeks and follow up was done at the end of 4 weeks, at the end of 8 weeks, at the end of 12 weeks for evaluation of efficacy and safety of the study drug.

Visit 1: Each patient was given a unique identity number. Demographic data, medical history, concomitant medications, physical examination, clinical examination including recording of vital signs and details of drug prescription by the treating doctor was recorded in the study proforma and relevant clinical assessment was done.

Follow-up visits was done at the end of 4 weeks (visit 2), at the end of 8 weeks (visit 3) and at the end of 12 weeks (visit 4) after administering the study medication. A deviation of ±2 days for first follow-up and ±1 week for subsequent follow-ups was accepted.

At follow-up visits clinical assessment was recorded. Concomitant medications that are necessary was given at the discretion of the doctor and was recorded. Adverse events were recorded using CDSCO-ADR form and graded according to severity. Efficacy was assessed by using Acne Severity Index (ASI), Total lesion counts (Inflammatory lesions and non-inflammatory lesions) and Patients satisfaction score by Turkish academy of dermatology. Safety was assessed by erythema, scaling, pruritus, and burning sensation. Each being assessed using a five-point scale.

RESULTS: A total of seventy patients were included in the study who were diagnosed with mild to moderate acne. The efficacy and the safety of both groups were analysed. The demographic data of the study groups were matched concerning demographic characteristics as shown in **Table 1.**

TABLE 1: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS WITH ACNE VULGARIS AT BASELINE

Characteristics		Group A (n = 35) Clindamycin +Tretinoin	Group B (n = 35) Clindamycin + Nicotinamide	p value**
Age in years (mean)		26.74(1.8)	25.57(1.18)	0.202
Gender	Male	15	16	1#
	Female	20	19	
Residence	Urban	18	20	0.81#
	Rural	17	15	
Mean ASI*		86.48 ± 4.49	88.05 ± 4.02	0.59
Mean TLC$		28.85 ± 1.29	30.17 ± 1.33	0.15

**-t test showing p value where p<0.05 is significant, *- Acne Severity Index = papules + (pustules x 2) + (comedones x 4), $- Total lesion counts= Inflammatory lesions + Non inflammatory lesions, #-chi square test.

Gender Distribution: The gender distribution in the present study groups is depicted in **Fig. 1.**

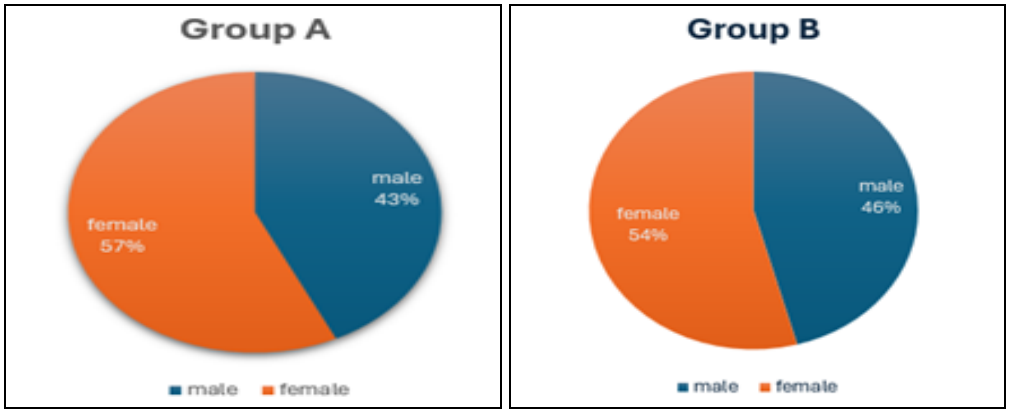

FIG. 1: SHOWS GENDER DISTRIBUTION OF BOTH GROUPS

Efficacy Parameters:

TABLE 2: COMPARISON OF ASI IN GROUP A AND GROUP B AT THE END OF 4, 8, 12 WEEKS

Visit	Groups	Mean ± SD	P *value
Baseline	Group A (C+T)	86.48 ± 4.49	0.59
	Group B (C+N)	88.05 ± 4.02	
At the end of four weeks	Group A (C+T)	52.34 ± 3.48	0.09
	Group B (C+N)	48.51 ± 3.06	
At the end of eight weeks	Group A (C+T)	36.71 ± 3.5	<0.0001
	Group B (C+N)	26.65 ± 2.56	
At the end of twelve weeks	Group A (C+T)	25.65± 2.4	<0.0001
	Group B (C+N)	14.17 ± 2.7	

*-t test showing p value where p<0.05 is significant.

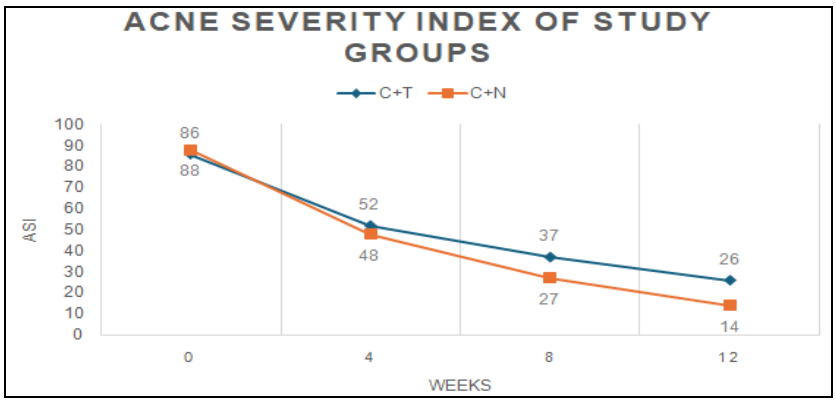

FIG. 2: ACNE SEVERITY INDEX SCORES OF THE STUDY GROUPS

TABLE 3: COMPARISON OF TLC IN GROUP A AND GROUP B AT THE END OF 4, 8, 12 WEEKS

Visit	Group	Mean ± SD	P* value
Baseline	Group A(C+T)	28.85 ± 1.29	0.15
	Group B(C+N)	30.17 ± 1.33	
At the end of four weeks	Group A (C+T)	16.6±0.97	0.93
	Group B(C+N)	16.54±0.92	
At the end of eight weeks	Group A(C+T)	11.4±1.01	<0.0001
	Group B(C+N)	8.71±0.81	
At the end of twelve weeks	Group A(C+T)	7.14±0.77	<0.0001
	Group B(C+N)	4.25±0.99	

*-t test showing p value where p<0.05 is significant.

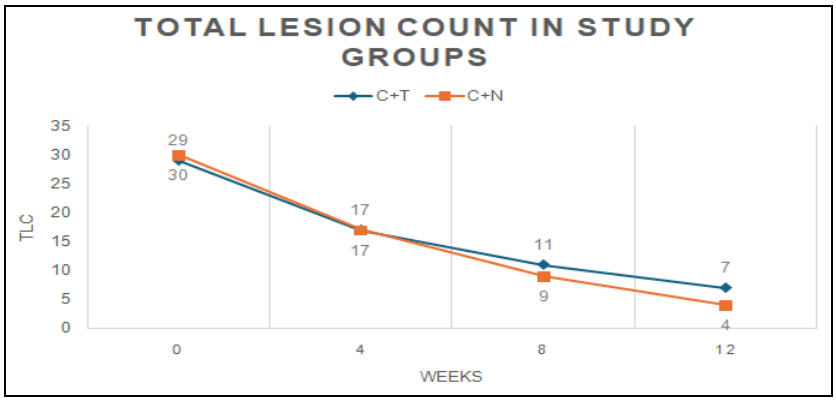

FIG. 3: TOTAL LESION COUNT IN STUDY GROUPS

TABLE 4: DIFFERENCES IN MEAN ASI WITHIN THE GROUPS ACROSS DIFFERENT TIME PERIODS

Group	Baseline	At the end of 4th week	At the end of 8th week	At the end of 12th week	p value
Group A (C+T)	86.48 ± 4.49	52.34 ± 3.48	36.71 ± 3.5	25.65± 2.4	< 0.001
Group B (C+N)	88.05 ± 4.02	48.51 ± 3.06	26.65 ± 2.56	14.17 ± 2.7	< 0.001

Repeated Measures ANOVA: Post hoc Tukey's analysis showed a statistical significance between each visit in both the groups.

TABLE 5: DIFFERENCES IN MEAN TLC WITHIN THE GROUPS ACROSS DIFFERENT TIME PERIODS

Group	Baseline	At the end of 4th week	At the end of 8th week	At the end of 12th week	p value
Group A (C+T)	28.85 ± 1.29	16.6±0.97	11.4±1.01	7.14±0.77	< 0.001
Group B (C+N)	30.17 ± 1.33	16.54±0.92	8.71±0.81	4.25±0.99	< 0.001

Repeated Measures ANOVA: Post hoc Tukey's analysis showed a statistical significance between each visit in both the groups.

Safety Parameters:

Adverse Effects: During the study period, mild adverse drug reactions were seen in both groups.

The most frequently seen adverse effect was mild itching followed by burning, scaling, redness. None of the participants discontinued the application in the study period.

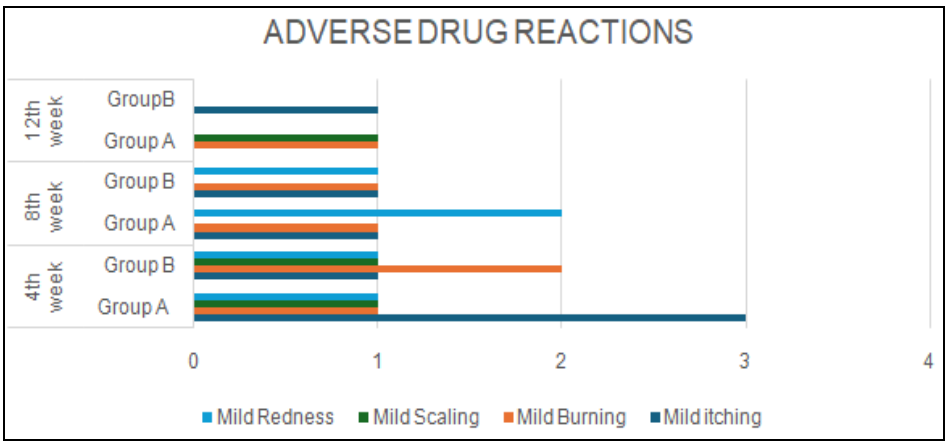

FIG. 4: ADVERSE DRUG REACTIONS

DISCUSSION: Acne vulgaris is a very common skin disease worldwide. It is associated with the high possibility of adverse cosmetic and psychosocial effects. Even in its milder form, acne can have lingering impact on mental health as it affects social interaction, self-confidence, self-esteem and employment opportunities [11]. Although the use of successful drugs and adjunctive procedures have dramatically improved outcomes in many patients with severe acne, improvements in much larger population with mild to moderate acne remains elusive. Therefore, individualization of therapy and persistence by both patients and clinicians is the key.Acne therapy aims at reducing sebum production and colonization of *Propionibacterium acnes*, thus correcting the abnormal ductal keratinisation and preventing the release of inflammatory mediators that are basically responsible for the pathogenesis of acne [12].

In the current study, the efficacy of topical combination therapy of clindamycin + tretinoin versus clindamycin + nicotinamide in the treatment of the mild-moderate acne vulgaris was compared. In the present study female: male ratio was 39:31 depicting an overall female preponderance. The pathogenesis of adult female acne is very complex and remains incompletely elucidated. The study on adult acne prevalence done by Cunliffe *et al.*, demonstrated that acne incidence was higher among adolescent men than adolescent women[13]. However, Cunliffe and colleagues found that, in adults 18 years of age and older, this prevalence decreases for both sexes, but becomes more prevalent in adult women than adult men [13]. Adult female acne involves an interplay of excess sebum production, abnormal keratinization within the follicle, and bacterial colonization of the pilosebaceous duct by *Propionibacterium acnes* [14]. Furthermore, hormones, use of cosmetics and/or drugs, and chronic stress have been put forward as possible etiological factors [15]. The mean age in our study was found to be 26.15 years and was in accordance with the study done by P. K. Rao *et al* and Goulden *et al* [16, 17]. The efficacy of the study drugs was evaluated by Acne Severity Index (ASI) and Total Lesion Count (TLC). The mean ASI of Group A (C+T) and Group B (C+N) was 86.48 ± 4.49 and 88.05 ± 4.02 respectively and mean TLC of Group A (C+T) and Group B (C+N) was 28.85 ± 1.29 and 30.17 ± 1.33 respectively at baseline and were comparable as shown in the **Table 2** and **3.**

At the end of 4 weeks, the mean ASI and mean TLC of both the groups were reduced and were equivalent in efficacy, with no statistical significance. The drugs used in both the study groups were novel topical therapies that included combination products of antibiotic, retinoids and nicotinamide which are the current standard of care in treatment of acne. These combination products act by addressing multiple pathogenic factors, covering the spectrum of acne symptoms and severity and thus provide a quicker and more efficacious treatment outcome than monotherapy [18]. At the end of 8 weeks, the mean ASI and mean TLC of both the groups were reduced from baseline. However, the reduction in mean ASI and

mean TLC in Group B (C+N) was more than Group A(C+T). The results of this analysis of data demonstrate that in Group A comprising of Clindamycin and Tretinoin, the comedolytic and anti-comedogenic action of tretinoin and the anti-inflammatory and anti-comedogenic action of clindamycin together contribute to the effect of C+T against non-inflammatory lesions whereas antibacterial and anti-inflammatory actions of clindamycin are the primary contributors to the effect of C+T against inflammatory lesions of acne [19]. Group B showed a better reduction of lesions than Group A as nicotinamide, a potent anti-inflammatory agent, was added to clindamycin. The precise mechanisms by which nicotinamide exerts a therapeutic effect in acne vulgaris is unclear. Nicotinamide may exert an anti-inflammatory action through inhibition of mast cell histamine release, blockade of histamine receptors, suppression of lymphocyte transformation and neutrophil chemotaxis and inhibition of secretion of inflammatory mediators [20].

Both Group A and Group B had a positive therapeutic effect on acne, after the evaluated 12 weeks of application. At the end of 12 weeks, the mean ASI and mean TLC reduced to a greater extent in Group B (C+N) than in Group A(C+T) and was found to be statistically significant ($p<0.0001$) as shown in **Table 9** and **Table 10**. The efficacy of Group B, a combination product of Clindamycin and Nicotinamide was significantly more than Group A. Studies done by Sardesai *et al* [21] and Dos SK *et al* [22] in evaluation of clindamycin phosphate monotherapy versus combination therapy of clindamycin phosphate with nicotinamide in the treatment of acne vulgaris, showed that both treatments produced a statistically similar reduction in the number of acne lesions and their severity. In the current study both treatment regimens were well tolerated, although patients did experience mild local side effects as shown in **Fig. 4**. Mild itching, mild burning, mild scaling and mild redness were the adverse effects which were tolerable. The Strength of the present study are, it is Prospective, randomized, comparative study evaluating the efficacy and safety of clindamycin with tretinoin versus clindamycin with nicotinamide in mild to moderate acne vulgaris among south Indian patients on which the data is limited. The limitations of our study were, it was not blinded which could have led to biased results. As the study was conducted at only one tertiary care centre, the results of the study cannot be generalized like a multicentre study.

CONCLUSION: Topical formulations are the most widely used treatment for Acne vulgaris to target one or more steps in the pathogenesis of acne .It was concluded from the results of the present study that the combination of Clindamycin with nicotinamide has a better efficacy than Clindamycin with tretinoin in mild to moderate acne vulgaris. Participants of both the intervention groups had a significant improvement in acne lesions after12th week of topical application and were satisfied with the therapy. No major adverse effects were observed in both groups. Hence, topical Clindamycin with nicotinamide represents a potential alternative to first line combination therapies in mild to moderate acne vulgaris. Further large-scale studies are needed to establish the same.

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