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Original Article

Pharmacology Section

Efficacy and Safety of Topical Adapalene (0.1% w/w) and Clindamycin (1% w/w) versus Topical Adapalene (0.1% w/w) and Benzoyl Peroxide (2.5% w/w) in Inflammatory Acne Vulgaris: A Phase-IV Open-label Comparative Study

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ABSTRACT

Introduction: Acne vulgaris, a chronic inflammatory condition, is characterised by open and closed comedones, erythematous papules and pustules. In current treatment guidelines, topical retinoids, such as adapalene, are commonly prescribed in combination with antimicrobials, including clindamycin. This combination has been proven to reduce acne lesions more quickly and prevent antimicrobial resistance. Benzoyl Peroxide (BPO) has a synergistic effect that enhances the penetration of adapalene in the skin and prevents the growth of *Propionibacterium* acnes. No published studies have compared topical adapalene and clindamycin versus topical adapalene and BPO.

Aim: To compare the efficacy and safety of a combination of topical adapalene (0.1% w/w) and clindamycin gel (1% w/w) with a combination of topical adapalene (0.1% w/w) and BPO (2.5%w/w) gel for the treatment of inflammatory acne vulgaris .

Materials and Methods: This study was a prospective randomised, open-label, parallel group interventional trial, which was conducted in the Departments of Pharmacology and Dermatology at NRS Medical College and Hospital, Kolkata, West Bengal, India, from January 2023 to August 2023. The total sample size was 34, with 17 in each group. Patients fulfilling the inclusion criteria were assigned to one of the two study groups in a parallel-arm design. Patients in Group A had received topical adapalene (0.1% w/w) and clindamycin (1%w/w) and patients in Group B had received topical adapalene (0.1% w/w) and BPO (2.5%w/w). Randomisation was done by the coin-toss method. Changes in Total Lesion Count (TLC), Investigator Global Assessment (IGA) score and Cardiff Acne Disability Index (CADI) score were recorded at weeks 0, 4, 8, and 12. Friedman's test and repeated measure Analysis of Variance (ANOVA) test were used for intragroup comparison and Mann-Whitney U test and Unpaired t-test were applied for intergroup comparison. Chi-square test was used for categorical data. A p-value<0.05 was considered statistically significant.

Results: No statistically significant intergroup differences existed at baseline in TLC, IGA score and CADI score. Intragroup comparisons in both groups showed a significant decrease in TLC, IGA and CADI scores at week 12 from their respective baseline values (p-value<0.05), but intergroup comparison showed no statistically significant difference at week 12.

Conclusion: It was observed that consecutive topical treatment with clindamycin and adapalene appears to possess additive effects that can be of valuable therapeutic benefit for acne patients. It has been observed that topical treatment with adapalene and BPO has good efficacy and tolerability. It has been found that both treatment therapy is beneficial and safe for mild to moderate acne vulgaris patients.

Keywords: Fixed dose combination, Pilosebaceous gland, Randomised controlled trial

INTRODUCTION

Acne vulgaris is a chronic skin disease of the pilosebaceous gland, characterised by seborrhoea, development of open and closed comedones, papules and pustules. Four main factors have been thought to be responsible for acne: hypersecretion of sebum, abnormal keratinocyte proliferation and differentiation, bacterial colonisation and host inflammatory response [1]. In 2019, acne vulgaris caused 4.96 million (95% CI 2.98-7.85) Disability Adjusted Life Years (DALYs) globally. Of these, 3.52 million (95% CI 2.11-5.64) DALYs occurred in those aged 15-49 years [2].

Recent guidelines recommend combination treatment with topical retinoids and antimicrobials as a frontline treatment option for the management of acne. Adapalene, a third-generation synthetic retinoid, is more stable with less molecular photodegradation, allowing daytime use [3]. Adapalene (0.3%) plus BPO (2.5%) are found to be effective in patients with severe acne, whereas the fixed combination with a lower concentration of adapalene (0.1%) is no more effective than vehicle. Clindamycin inhibits bacterial protein synthesis. Clindamycin phosphate (1.2%) plus tretinoin (0.025%) shows similar efficacy in severe acne, but with little benefit over individual monads [4]. In the literature search, no comparative studies exist between topical adapalene and clindamycin with topical adapalene and BPO in the Eastern India zone. Common oral antibiotics used for acne include doxycycline (100 mg twice daily), minocycline (50-100 mg once or twice daily), TMP-SMZ (Trimethoprim - Sulfamethoxazole) (one double-strength tablet twice daily), or a cephalosporin (cefadroxil or cephalexin 500 mg twice daily), which should be used in combination with BPO to reduce antimicrobial resistance. In general, discontinuing antibiotics immediately without adjunctive topical therapy results in prompt

recurrence [5]. Local drug delivery is better than oral medications for a few reasons; like targeted drug delivery at the lesion, reduced systemic side effects, safe for special populations (e.g., pregnant women, adolescents, and patients with co-morbidities) and avoidance of resistance concerns.

Under these circumstances, it was planned to compare the efficacy and safety of the combination therapy of topical adapalene and clindamycin with topical adapalene and BPO in inflammatory Acne vulgaris.

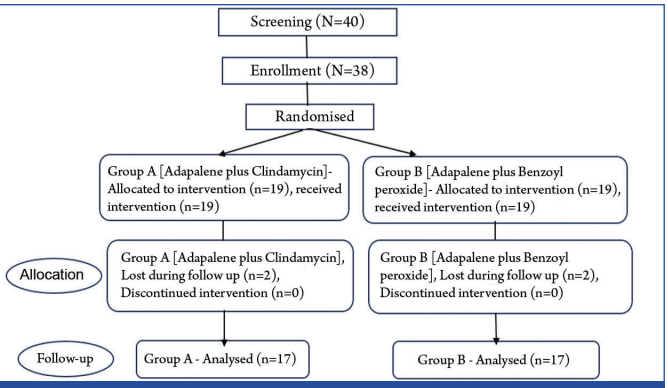
MATERIALS AND METHODS

This study was a prospective randomised, open-label, parallel group interventional trial, which was conducted in the Departments of Pharmacology and Dermatology at NRS Medical College and Hospital, Kolkata, West Bengal, India, from January 2023 to August 2023, after approval by the Institutional Ethics Committee (Memo no. NRMS/IEC/135/2022). It was registered under CTRI. (Reg no. CTRI/2024/02/062423).

Inclusion criteria: Patients aged 18 years and below 30 years of either gender with total lesions-inflammatory (papules and pustules) ≥2 but ≤30 in the face were included in the study.

Exclusion criteria: Age out of range, TLC- inflammatory (papules and pustules) (TLC) <2 or >30, very severe acne, patients regularly using any anti-acne medications in the last 30 days before study entry, pregnant mothers and women of childbearing age group using Oral Contraceptive Pill (OCP) and those who had received oral or topical antibiotics and steroid.

All adult patients (between 18 years to 30 years of age) diagnosed with inflammatory acne vulgaris (which correspond to a baseline investigator global assessment score of 2-3) in the Outpatient Department (OPD) of Dermatology, during the study period, were screened and had taken informed consent. A total of 40 patients were screened initially according to eligibility criteria [Table/Fig-1]. Only 40 patients were taken due to time constraints. Out of 40 patients, 38 were included in the study. A total of 19 patients were included in each group.



[Table/Fig-1]: Consolidated Standards of Reporting Trials (CONSORT) flowchart.

Study Procedure

Patients fulfilling the inclusion criteria were randomised to one of the two parallel arms of the study. Randomisation was done by the coin-toss method. Patients in group A had received topical FDC (fixed dose combination) of adapalene (0.1% w/w) and clindamycin (1% w/w) (Glenmark Pharmaceuticals, India). Patients in group B had received topical FDC of adapalene (0.1% w/w) and BPO (2.5%w/w) (Galderma India Pvt. Ltd., India). Among these 38 patients, four patients were lost to follow-up and hence were not included in this analysis. Those four patients were excluded on the basis of per protocol analysis. Attrition parameters were withdrawal of consent, ADR, etc., The sample size calculation was done prior to the intervention of the regimen. Considering the true mean difference between the two groups was zero, the expected Standard Deviation (SD) was set as 10%, 80% power; α=0.05, Considering of non response rate 10%, so the final sample size was approx. 17 in each group [6]. As this was an open-label study therefore; no blinding was done.

Patients in group A were advised to apply topical FDC of adapalene (0.1% w/w) and clindamycin (1% w/w) (Glenmark Pharmaceuticals, India) once daily at night time and patients in group B were advised to apply topical FDC of adapalene (0.1% w/w) and BPO (2.5%w/w) (Galderma India Pvt., Ltd., India) once daily at night. All patients were advised to wash their skin gently at least 10 minutes prior to administration of trial drug regimens (FDC of adapalene with clindamycin and adapalene with BPO). The patients were asked not to bathe, shower, wash or swim for at least 4-hours after the application of topical medications. Patients were advised not to undergo Ultraviolet (UV) treatment, to minimise exposure to direct sunlight. The following morning, all patients were advised to wash their skin with facewash at early morning.

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. Patients were informed to attend OPD for first, second and third follow up visits at 4 weeks interval. The primary efficacy parameters were changes in inflammatory lesion count, investigator global assessment score and CADI from baseline was assessed to determine the outcome at 4th, 8th and 12th week. Secondary efficacy parameters were severity of inflammatory acne vulgaris and the medication adherence score was assessed at baseline to determine the outcome at 4th , 8th and 12th weeks. Both secondary parameters were correlated with the efficacy of the therapy. Changes in the CADI [7] were also evaluated to assess the impact of the disease on their quality of life. The CADI included an assessment on a five-question scale.

Any adverse drug reaction experienced by the patient was recorded and reported to AMC (ADR monitoring centre), uploaded in the Vigiflow System. Causality assessment of adverse events was done by using the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) scale and Severity was assessed by using the Modified Hartwig Seigel scale [8]. The Medication Adherence Rating Scale (MARS) was also assessed.

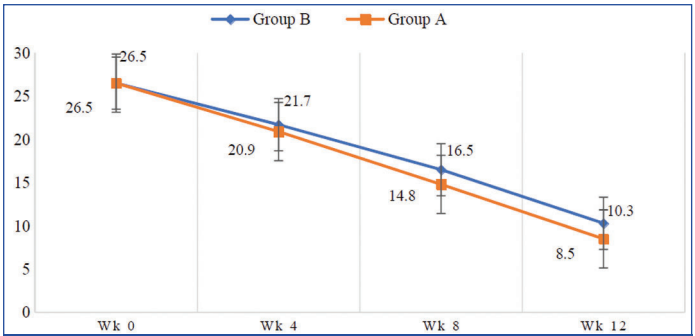
STATISTICAL ANALYSIS

Data was analysed according to intention to treat basis. Friedman's test (data in ordinal scale) and repeated measures ANOVA (data in numerical scale) were used for intragroup comparison for intergroup comparison, the Mann–Whitney U test was used for ordinal variables and the unpaired t-test was applied for numerical variables. Chi-square test was used for categorical data. A p-value <0.05 was considered statistically significant.

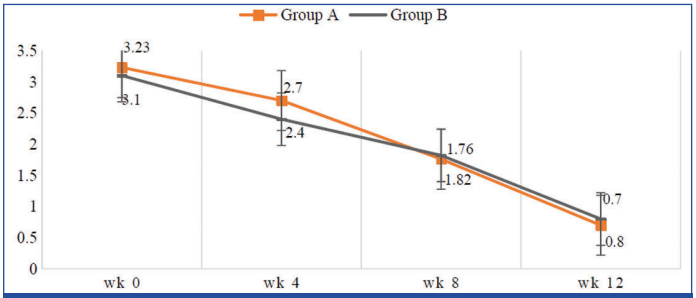
RESULTS

There was no statistically significant difference in baseline TLC [Table/Fig-2], IGA score [Table/Fig-3] and CADI score [Table/Fig-4]. TLC was decreased significantly in both groups at the 12th week from their respective baseline values (p-value <0.05). IGA and CADI scores also were decreased significantly at week 12 from their respective pretreatment values (p-value <0.05).

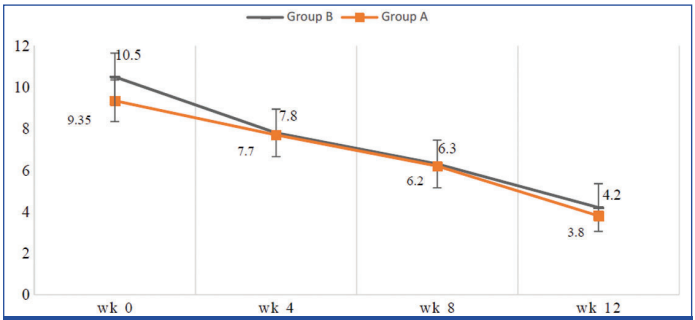
For intragroup comparison, a repeated measures ANOVA test was performed for both groups in response to the changes in the number of TLC and the p-value was <0.001 (p-value <0.05) for groups A and B. Therefore, the result was significant for both groups. Intergroup comparison, unpaired t-test was performed at baseline, 4th, 8th and 12th week intervals, respectively. The two-tailed p-value was 0.9934 at the 0th week, 0.5126 at the 4th week, 0.1565 at the 8th week and 0.1267 at the 12th week interval. Thus, the p-value was not statistically significant, where the confidence interval was 95% [Table/Fig-2].



[Table/Fig-2]: Changes in Total Lesion Count (TLC) in group A (adapalene plus clindamycin) and group B (adapalene plus BPO). TLC (Mean±SD) in group A were 26.53±3.6, 20.9±3.63, 14.8±3.3 and 8.5±3 at weeks 0, 4, 8 & 12, respectively; in group B were 26.52±3.4, 21.7±3.6, 16.6±3.7 and 10.3±3.7 at weeks 0, 4, 8, 12, respectively. p-value <0.05 weeks 4, 8, 12 versus 0 weeks in group A and B, respectively.



[Table/Fig-3]: Changes in IGA scores in group A (adapalene plus clindamycin) and group B (adapalene plus BPO). IGA score (Mean±SD) in group A were 3.23±0.6, 2.7±0.5, 1.76±0.4, 0.7±0.5, respectively and in group B were 3.1±0.6, 2.4±0.5, 1.8±0.5 and 0.8±0.5 respectively. The p-value <0.05 weeks 4, 8, 12 versus 0 week in group A and B, respectively.



[Table/Fig-4]: Changes in CADI scores in group A (adapalene plus clindamycin) and group B (Adapalene plus Benzoyl peroxide). CADI scores (Mean±SD) in Group-A were 9.35±1.8, 7.7±1.7, 6.2±1.7 and 3.8±1.3 respectively and in group B were 10.5±1.3, 7.8±1, 6.3±1 and 4.2±1, respectively. p-value <0.05 weeks 4, 8, 12 versus 0 week in group A and B, respectively.

For intragroup comparison, Friedman's test was performed in groups A and B due to the changes in the CADI score [Table/Fig-4] and IGA scores [Table/Fig-3]. Both scores were gradually declined by 4, 8 and 12 weeks intervals. The p-value was <0.00001 in both groups in terms of intragroup comparison, thus the result was significant at (p-value <0.05). So, both topical treatment regimens were equally effective in reducing the severity of acne vulgaris. In case of intergroup comparison, the Mann-Whitney U test was performed at 0^{th}, 4^{th}, 8^{th} and 12^{th} week intervals for both CADI and IGA scores. The p-value was not significantly different from baseline to every follow-up interval; thus, there was no significant difference in reducing the severity of inflammatory acne vulgaris in both groups.

Safety Analysis

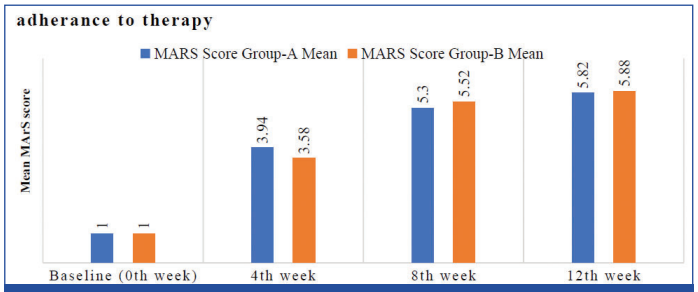
All patients who were randomised were considered for safety analysis. Four participants from group A (Adapalene with clindamycin) and five participants from group B (Adapalene with BPO) reported adverse effects. Adverse effects were skin irritation, itching and burning sensation. Two cases of skin irritation, one case of itching and two cases of burning sensation over skin had been reported from group B and two cases of skin irritation, one case of itching and one case of burning sensation over skin had been reported from group A. All reports were submitted to the Vigiflow portal. Adverse effects resolved spontaneously and none of the patients required any modification of treatment. Causality analysis of adverse events was done as per the WHO UMC criteria [9]. Analysis showed that they were in the "possible" category.

Severity Assessment

Modified Hartwig Seigel scale was performed to assess severity. An adverse drug reaction occurred after administration of both topical regimens. ADR has been resolved without modification of the treating regimens. According to the Modified Hartwig Seigel scale, all ADRs were categorised as mild, Level-1.

Medication Adherence

According to the MARS scoring system, a higher number denotes superior Adherence. Scores of 5 and above were classified as high, indicating a satisfactory level of treatment adherence, while scores below 5 were classified as low, indicating a poor level of treatment adherence. So, it was clearly reflected that a significant improvement in adherence to treatment was shown in group A (Adapalene plus clindamycin) with comparison to group B (Adapalene plus BPO) [Table/Fig-5].



[Table/Fig-5]: Mean MARS score distribution among Group-A and Group-B.

DISCUSSION

Acne vulgaris is a common skin disease encountered by dermatologists. Non inflammatory acne is characterised by the presence of open or closed comedones, which begin as invisible microcomedones that precede all other acne lesions. Microcomedo formation is caused by the abnormal keratinisation of the infundibular epithelium of hair follicles. Further retention of a dense material composed of sebum and keratinous debris dilates the follicles of microcomedones, which leads to the formation of comedones. Two types of comedones can be distinguished morphologically, one being a closed comedone, or whitehead, and the other being an open comedone, or blackhead. In contrast, inflammatory lesions consist of papules, which are raised erythematous lesions measuring less than 0.5 cm, and pustules, which are papules with a visible collection of white pus at the surface. These lesions often enlarge, becoming firm or indurated, and are termed nodules. Scarring may be associated with any form of severe inflammatory acne. Clinical manifestations of acne vulgaris range from non inflammatory comedones to inflammatory papules, pustules, and cysts. In most patients with acne, these lesions are usually intermingled to a varying extent [10]. The choice of acne treatment depends on multiple factors such as the severity of acne, duration of disease, previous treatments, and presence of scarring and post-inflammatory pigmentation. Therapy, therefore, given to the individual patient depends on the nature and severity of the acne. Many topical and systemic treatments are available, covering all the variants of acne.

Common topical agents include retinoids, antibiotics (clindamycin and erythromycin), and BPO with other agents like salicylic acid, azelaic acid, and alpha-hydroxy acids. Topical retinoids in combination with clindamycin or BPO serve as the first-line therapy recommended for mild-to-moderate acne. Adapalene targets abnormal follicular

epithelial hyperproliferation, decreases microcomedones, follicular plugging, non inflammatory and inflammatory lesions [11].

Combination therapy targets three different aspects of the pathophysiology of acne vulgaris - 1) proliferation of P. acnes; 2) inflammation; and 3) hyperkeratinisation [12]. Various studies have compared the efficacy and tolerability of adapalene-clindamycin or adapalene-BPO with other topical and systemic agents. Few studies have evaluated different two-drug combinations in the treatment of acne vulgaris. Inbamini APD et al., found a higher incidence of complete clearance with the clindamycin group than the BPO group, but the intergroup difference was not significant (p-value=0.9250) [13]. A randomised double-blind controlled trial of 517 patients reported a success rate of 149/517 (27.5%) after 12 weeks of combination treatment with adapalene and BPO, with adapalene and BPO achieving significantly better TLC reductions than control treatments as early as week one (19.7%) [14].

In a study by Wolf JE et al., the combination of topical adapalene plus clindamycin was more effective than topical clindamycin alone in reducing total lesions (p-value <0.001), inflammatory lesions (p-value=0.004) and non inflammatory lesions (p-value <0.001) [15]. The addition of adapalene gel (0.1%) produced a faster and clinically significant enhancement of the efficacy of clindamycin topical lotion for acne vulgaris.

The present study suggested that TLC was significantly reduced in both groups (groups A and B). In the adapalene and clindamycin group (group A), TLC was 26.5±3.6 and 8.5±3, respectively, at baseline and 12th week interval. In the adapalene and BPO group (group B), TLC was 26.5±3.4 and 10.3±3.7, respectively, at baseline and 12th week interval. IGA score was 3.23±0.6 and 3.1±0.6 (for clindamycin and BPO group, respectively at the 0th week. The score was 0.7±0.5 and 0.8±0.5 (for both groups, respectively at the 12th week interval. Therefore, severity was significantly declined with both treatment modalities and intergroup difference was not significant (p-value=0.63). CADI score was 9.35±1.8 and 10.5±1.3 for clindamycin and BPO group, respectively, at the 0th week. The score was 3.8±1.3 and 4.2±1.9 for both groups at the 12th week interval.

Limitation(s)

The present study had some obvious limitations. For some logistical reasons, the study was to be completed in a short time frame and thus was done with a small sample size. It was a single-centred and open-level randomised trial. The findings were mainly based on the investigators' and educators' judgements, but the authors also tried to coordinate the observations, which have a subjective-basis. Further studies with a large sample size and a longer follow-up period were required for better outcomes. Variations in the number of adverse effects could be explored in future studies.

CONCLUSION(S)

It was observed that different primary and secondary parameters were observed to assess efficacy, severity, safety and medication adherence of both treatment groups. Due to the time constraints, the authors have conducted the study within three months. Both efficacy and severity were significantly improved in the clindamycin group as well as in the BPO group. Treatment adherence was also significantly improved in the clindamycin group. Adverse effects were resolved spontaneously without modification of the treating agent. At the end of the study, it was concluded that topical adapalene plus clindamycin was significantly more effective than topical adapalene plus BPO treatment.

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