Original Article

A comparative study to evaluate the efficacy and safety of combination topical preparations in acne vulgaris

Jasleen Kaur, Vijay K Sehgal, Anita K Gupta, Surinder P Singh[1]

Department of Pharmacology, Government Medical College, [1]Department of Dermatology and Venereal Diseases, Rajindra Hospital, Government Medical College, Patiala, Punjab, India

Abstract

Background: The combinations of topical keratolytics with anti-microbials and topical retinoids with antimicrobials are commonly prescribed in the treatment of acne. **Aim:** The present study was undertaken with the aim of comparing the efficacy and safety of topical benzoyl peroxide and clindamycin versus topical benzoyl peroxide and nadifloxacin versus topical tretinoin and clindamycin in patients of acne vulgaris. **Materials and Methods:** 100 patients between 15 and 35 years having ≥2 and ≤30 inflammatory and/or noninflammatory lesions with Investigator's Global Assessment (IGA) score 2/3 were randomly divided into 3 groups. Group A was prescribed benzoyl peroxide 2.5% gel and clindamycin 1% gel, Group B was prescribed benzoyl peroxide 2.5% gel and nadifloxacin 1% cream and Group C was prescribed tretinoin 0.025% and clindamycin 1% gel. Total number of lesions and adverse effects during the treatment were assessed at 0, 4, 8, 12 weeks with IGA score. **Results:** There was statistically significant reduction in total number of lesions with better improvement in Group A. Adverse drug reactions during the study showed a better safety profile of Group B which is found to be statistically significant also. **Conclusion:** These findings confirm that Group A is more efficacious and Group B is safest among the other two groups.

Key words: Adverse drug reactions, anti-microbials, Investigator's Global Assessment score, keratolytics, retinoids

Submission: 10-12-2014 **Accepted:** 12-01-2015

Introduction

Acne vulgaris is a chronic, self-limiting, inflammatory disease of the pilosebaceous unit characterised by pleomorphic lesions like comedones, erythromatous papules, pustules, cysts and nodules.[1] Although the course of acne may be self-limiting, the sequelae can be lifelong, with pitted or hypertrophic scar formation.[2]

It is more common and more severe in males than in females, relating it to androgen activity. It starts at puberty or a few months earlier. The peak incidence is between 14-17 years in women and 16–19 years in men.[1] It seems to be famililial, but owing to the high prevalence of the disease this has been extremely difficult to assess. Nodulocystic acne has been reported to be more common in white males than in black males, and one group of investigators has found that acne is more severe in patients with the XYY genotype.[2]

It occurs due to alteration in the pattern of keratinization within the sebaceous follicles, level of circulating sex hormones, especially androgens, quantity and quality of sebum secretion, colonization by follicular microbial flora, immunological factors and environmental factors.[1]

Increased sebum secretion is associated with the development of acne lesions, since sebum serves as a nutrient source for the Gram-positive bacterium *Propionibacterium acnes* (*P. acnes*), a member of the normal skin flora. Microbiological colonization of the sebaceous gland has been identified as a major factor in disrupting the follicular epithelium, in which *P. acnes* produce enzymes such as lipases, proteases, and hyaluronidases leading to subsequent inflammatory reactions in the surrounding dermis.[3]

Address for correspondence: Dr. Jasleen Kaur,
Department of Pharmacology, Government Medical College,
Patiala, Punjab, India.
E-mail: docjasleen19@gmail.com

Access this article online

Quick Response Code:

Website: www.ijabmr.org

DOI: 10.4103/2229-516X.157155

It is one of the most common reason for visiting a physician.[4] Even though it is often perceived as a self-limited and not physically disabling disease of adolescence, its prevalence remains high into adulthood, and its psychological impact can be striking, contributing to lower self-esteem, anxiety, and depression. Consequently, there is significant patient-driven demand for effective acne therapies, including prescribed medications and over-the-counter products. In addition, taking into account the need for long-term treatment, there is increased need for topical medications that are popular with patients in order to achieve long-term compliance. As a result, agents are available in a variety of formulations. These include topical antibiotics, retinoids, and benzoyl peroxide in monotherapy or in combination products. Systemic medications also include antibiotics and retinoids, as well as hormonal agents.[5]

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.[6]

One of the major limitations of topical therapies for acne vulgaris, 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. These reactions can result from direct effects of active ingredient (i.e., retinoid, benzoyl peroxide) and/or the characteristics of the vehicle, with patients in some cases electing to discontinue treatment or use therapy intermittently, which usually results in less than optimal therapeutic outcomes.[7]

Combination therapy is likely to have a more significant effect because it targets three major areas of acne pathophysiology: *P. acnes* proliferation, inflammation and hyperkeratinisation.[8]

Due to the multifactorial pathogenesis of acne vulgaris and the limitations of the conventional therapies, combination therapy utilizing agents with complementary mechanisms provides the opportunity to target multiple pathogenic causes of acne vulgaris.[9]

There is no published clinical study which compared three combinations of topical benzoyl peroxide 2.5% gel and clindamycin 1% gel versus benzoyl peroxide 2.5% gel and nadifloxacin 1% cream versus tretinoin 0.025% and clindamycin 1% gel in patients of acne vulgaris. Hence the present study was undertaken to compare the efficacy and safety of standard regimens with benzoyl peroxide and nadifloxacin.

Materials and Methods

Study design

This prospective, open labelled, randomized, comparative drug study was undertaken in the out-patient department. The study protocol was approved by the institutional review board. Patients attending the outpatient department were screened and assessed according to the specified inclusion and exclusion criteria. A total of 100 eligible patients of both sexes with inflammatory and/or noninflammatory lesions were taken who were willing to take medications as directed and can come for the follow-up were enrolled in the study. The written consent of patients was taken on informed consent form in the vernacular language.

Inclusion criteria

Patients of either sex in the age range of 15–35 years having ≥2 and ≤30 inflammatory and/or noninflammatory lesions with Investigator's Global Assessment score (IGA) 2 or 3.

Exclusion criteria

Patients whose age are out of range with total lesion count <2 or more than 30, regularly using any anti-acne medications in the last 30 days before study, having nodulocystic lesions, acne conglobata, acne fulminans, secondary acne (e.g., chloracne, drug-induced acne, or any other acne requiring systemic treatment), unwilling or unable to comply with the study proceedings to give informed written consent, with history of hypersensitivity to benzoyl peroxide or clindamycin or nadifloxacin or tretinoin and pregnant or lactating women were excluded from the study.

Treatment procedure

Demographic data and relevant medical history were obtained from all patients prior to initiation of therapy. Patients were randomly divided into three groups: Group A, Group B and Group C. Group A received benzoyl peroxide 2.5% gel once daily at bedtime and clindamycin 1% gel once daily topically. Group B received benzoyl peroxide 2.5% gel once daily at bedtime and nadifloxacin 1% cream once daily topically. Group C received with tretinoin 0.025% and clindamycin 1% gel once daily at bedtime topically. Commercial available preparations were used. Patients were evaluated after 4, 8, 12 weeks of starting the treatment. At each visit patients were asked to report any adverse effect if occurred during the treatment.

Criteria for evaluation

Primary efficacy measures

Assessment was done by calculating the change from baseline (visit 1), after 4 weeks (visit 2), after 8 weeks (visit 3) and after 12 weeks (visit 4) of the total lesion count-both inflammatory and noninflammatory lesions.

Secondary efficacy measure

Global efficacy evaluation was evaluated based on the validated IGA, on a six point scale that is, (i) 0-indicating clearance of inflammatory lesions, some residual hyperpigmentation and erythema may be present; (ii) 1-almost clear, patients may have a few scattered comedones and fewer than five small papules; (iii) 2-mild severity, acne is easily recognizable, but less than half the face is involved and there are multiple comedones, papules, and pustules; (iv) 3-moderate severity, more than half the face is involved and there are numerous comedones, papules, and pustules; (v) 4-severe, the entire face is involved, covered with numerous comedones, papules, pustules, and a few nodules and cysts; (vi) 5-very severe, patients have high inflammatory acne covering the entire face, with nodules and cysts.[10]

Safety evaluation

At each visit, patients were inquired about any complaints that might have indicated an adverse drug reaction. Any such dermatological adverse reaction reported was recorded and analysed.

Statistical analysis

The results of observations of individual patients were pooled for each group. Statistical analysis was performed using SPSS software version 20.0 (IBM). All the analyses were performed on an intention to treat basis. For categorical variables, Friedman test and Chi-square test were used for analysis.

Results

A total of 100 patients were enrolled in the study. During the study period, three patients from Group A, four patients from Group B and three patients from Group C did not come for follow-up, so data of these ten patients were not included in the statistical analysis. This lead on to 30 patients in each group.

The effects of all three treatment groups on mean of the number of noninflammatory lesions were shown in Figure 1. Mean of the number of lesions decreased in Group A from 12.03 ± 5.53 to 3.93 ± 3.46 after 4 weeks, 0.60 ± 1.28 after 8 weeks and 0.00 ± 0.00 after 12 weeks. In Group B, reduction was from 12.90 ± 4.79 to 10.13 ± 4.19 after 4 weeks, 8.10 ± 3.59 after 8 weeks and 6.20 ± 3.26 after 12 weeks. In Group C, it was reduced from 13.70 ± 4.80 to 7.40 ± 3.69 after 4 weeks, 3.23 ± 3.04 after 8 weeks and 1.30 ± 2.95 after 12 weeks. There was statistically significant decrease in the number of noninflammatory lesions ($P < 0.001$).

Similar results were obtained in the evaluation of most efficacious group among three treatment groups on mean of the number of inflammatory lesions as shown in Figure 2. Mean of the number of lesions decreased in Group A from 3.57 ± 2.61 to 0.47 ± 0.86 after 4 weeks, 0.00 ± 0.00 after 8 weeks and 0.00 ± 0.00 after 12 weeks. In Group B, reduction was from 3.87 ± 2.67 to 2.43 ± 2.28 after 4 weeks, 1.30 ± 2.18 after 8 weeks and 0.70 ± 1.66 after 12 weeks. In Group C, it was reduced from 4.97 ± 3.03 to 1.60 ± 2.19 after 4 weeks, 0.40 ± 1.49 after 8 weeks and 0.27 ± 1.28 after 12 weeks. There was statistically significant decrease in the number of inflammatory lesions ($P < 0.001$).

Table 1 shows that mean of the IGA score at the baseline in Group A is 2.00 ± 0.00, after 4 weeks 0.37 ± 0.61, after 8 weeks 0.00 ± 0.00 and after 12 weeks 0.00 ± 0.00. At the baseline in

Table 1: Mean of the IGA score of all the three groups (Group A, Group B, Group C)

Follow-up	Group A		Group B		Group C	
	Mean of the IGA score	SD	Mean of the IGA score	SD	Mean of the IGA score	SD
Baseline	2.00	00	2.23	0.43	2.10	0.31
After 4 weeks	0.37	0.61	1.00	0.64	0.87	0.86
After 8 weeks	00	00	0.57	0.68	0.13	0.34
After 12 weeks	00	00	0.37	0.56	00	00
Mean rank	1.07		2.86		2.07	

SD: Standard deviation; IGA: Investigator's global assessment

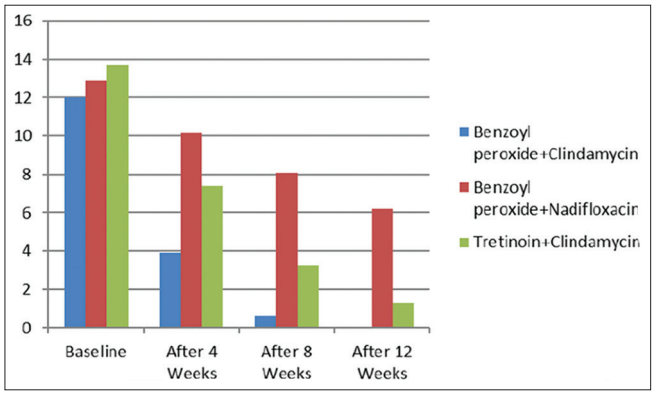

Figure 1: Comparison of all the three groups (benzoyl peroxide 2.5% gel and clindamycin 1% gel, benzoyl peroxide 2.5% gel and nadifloxacin 1% cream, tretinoin 0.025% and clindamycin 1% gel) on the mean of the number of noninflammatory lesions

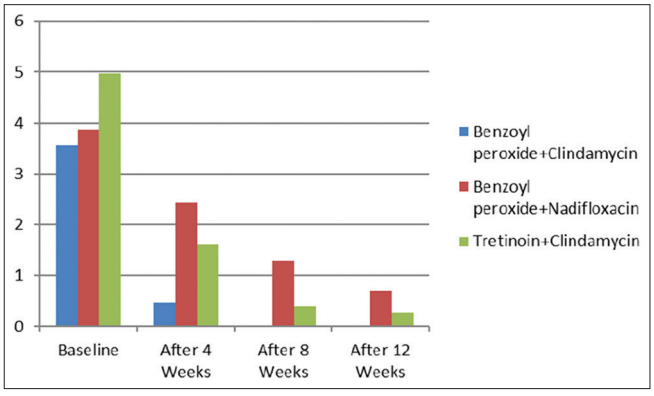

Figure 2: Comparison of all the three groups (benzoyl peroxide 2.5% gel and clindamycin 1% gel, benzoyl peroxide 2.5% gel and nadifloxacin 1% cream, tretinoin 0.025% and clindamycin 1% gel) on the mean of the number of inflammatory lesions

Group B mean of the IGA score is 2.23 ± 0.43, after 4 weeks 1.00 ± 0.64, after 8 weeks 0.57 ± 0.68 and after 12 weeks 0.37 ± 0.56. In Group C, mean of the IGA score is 2.10 ± 0.31, after 4 weeks 0.87 ± 0.86, after 8 weeks 0.13 ± 0.34 and after 12 weeks 0.00 ± 0.00. Mean ranks were calculated, among which least rank was of Group A (1.07), then Group C (2.07) and last is Group B (2.86). There was statistically significant difference ($P < 0.01$, $\chi^2 = 11.63$)

For safety assessment, about 94.4% patients do not show any adverse event during the treatment by all the three groups. Only two adverse events occurred during the study, that were, burning sensation and dryness. About 4% patients suffered with dryness and 1.1% patients had burning sensation

Table 2 shows that for burning sensation, mean rank of Group B and Group C was least (1.93). This shows that these groups are safer than Group A (2.14) for burning sensation. There was no statistically significant difference ($P > 0.05$, $\chi^2 = 2.00$).

Overall if we see, Group B was safest among all the groups, as no adverse event was reported in this group. Group A with just one incidence of adverse event can be quoted as safe but only next to Group B.

Discussion

Acne vulgaris is a very common skin disease worldwide. It is associated with the high probability of adverse cosmetic and psychosocial effects. Even with the presence of various effective treatments, there is always necessity for nearly harmless, accessible, and most effective treatment options for acne.[11]

Although the present study compares three groups of treatment, which was previously not done still we can evaluate other studies where one of the combination present in our study is compared with some other combination but of same class.

Table 2: Adverse events among all the three groups (Group A, Group B, Group C)

Follow-up	Burning sensation			Dryness		
	Group A	Group B	Group C	Group A	Group B	Group C
Baseline	00	00	00	00	00	00
After 4 weeks	01	00	00	00	00	01
After 8 weeks	00	00	00	00	00	02
After 12 weeks	00	00	00	00	00	01
Mean ranks	2.14	1.93	1.93	1.79	1.79	2.43
χ^2	2.00 (P>0.05)			6.00 (P>0.05)		

A study was conducted by Webster *et al*.[12] where it was found that benzoyl peroxide-clindamycin has high efficacy and good overall tolerability in the topical treatment of patients with mild to moderately severe acne vulgaris. This is in accordance with our present study.

A study was conducted by Jain *et al*.[13] where on comparing the efficacy of two combinations benzoyl peroxide-clindamycin and benzoyl peroxide-metronidazole therapy regimes with each other, no statistically significant difference was found. Hence, both of these groups have same efficacy. This finding is might be due to difference of drug (metronidazole) present in combination, which is being compared with combination benzoyl peroxide-clindamycin than our present study.

Another study conducted by Choudhury *et al*.[14] where comparison of efficacy of two combinations benzoyl peroxide-nadifloxacin and benzoyl peroxide-clindamycin was done. No differences in total lesion counts was observed among these two groups. Improvements in the IGA scores were more in benzoyl peroxide-nadifloxacin than benzoyl peroxide-clindamycin, but the difference did not reach to statistically significant values. This is not in accordance to the present study due to variations in sample size and compliance of the patients.

A study was conducted by Shwetha *et al*.[15] where comparison of efficacy of combination of topical 1% clindamycin and 2.5% benzoyl peroxide was done with 1% clindamycin and 0.1% - adaplene in mild to moderate acne. Here, combination of topical 1% clindamycin and 0.1%-adaplene was found to be more efficacious than the other group. There is dissimilarity in the combinations although clindamycin-retinoid combination is used in both the studies. Clindamycin 1%-adaplene 0.1% is used in the above study and in present study clindamycin 1%-tretinoin 0.025% was used. We cannot correlate this study with this present study as two different retinoids with two different concentrations were used (adaplene 1% in this study and tretinoin 0.025% in present study).

The present study confirms the efficacy of all the three treatment groups in acne vulgaris. The present study reported a statistically significant total clearance of noninflammatory lesions ($P < 0.001$) and inflammatory lesions ($P < 0.001$) by Group A when compared to Group B and Group C, at the end of the study.

In present study, none of the patient reported any adverse event in Group B and is found to be safest when compared to Group A and Group C. It is in contrary to a previous study where during the safety and tolerability assessment, Group A (Group A) and Group B (Group B), they both were found to be equally well-tolerated.[14]

The limitations of our study could be overcome by a multi-centric, double-blind study of longer duration with simultaneous microbial susceptibility testing.This could further reinforce the scientific evidence.

Conclusion

The incidence of acne vulgaris is very common. Innumerable remedies have been tried, to treat acne, ranging from topical therapies with topical antibiotics, retinoids (retinoic acid), keratolytics (benzoyl peroxide, sulfur) etc., and systemic therapies with oral antibiotics (tetracyclines, doxycycline, erythromycin, minocyclines etc.) or systemic hormonal therapy with corticosteroids. It is previously reported that acne responds well to oral therapies but the main problem is relapse after cessation of therapy. Until now, various regimens have been evolved, still it requires more research to search out the fully proved and most effective therapy.

In this randomized trial, Group A containing topical benzoyl peroxide and clindamycin, which is a standard regimen was found to be more efficacious than other groups. It produces decrease in the total number of lesions (inflammatory and/or noninflammatory). IGA score reaches to 0 (clear) earlier than the other groups. Group B containing benzoyl peroxide and nadifloxacin was found to be the most safest among all the groups as no treatment emergent dermatological adverse event occurred throughout the study.

References

1. Tutakne MA, Vaishampayan SS. Acne, rosacea and perioral dermatitis. In: Valia RG, Valia AR, editors. IAVDL Textbook of Dermatology. 3rd ed. Mumbai: Bhalani Publication House; 2008. p. 839-43.
2. Zaenglein AL, Graber EM, Thiboutot DM, Strauss JS. Acne vulgaris and acneiform eruption. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Lefell DJ, editors. Fitzpatrick's Dermatology in General Medicine. 7th ed. New York: McGraw Hill Companies; 2007. p. 687-703.
3. Pretsch A, Nagl M, Schwendinger K, Kreiseder B, Wiederstein M, Pretsch D, *et al.* Antimicrobial and anti-inflammatory activities of endophytic fungi *Talaromyces* wortmannii extracts against acne-inducing bacteria. PLoS One 2014;9:e97929.
4. Gollnick HP, Zouboulis CC. Not all acne is acne vulgaris. Dtsch Arztebl Int 2014;111:301-12.
5. Gregoriou S, Kritsotaki E, Katoulis A, Rigopoulos D. Use of tazarotene foam for the treatment of acne vulgaris. Clin Cosmet Investig Dermatol 2014;7:165-70.
6. Kraft J, Freiman A. Management of acne. CMAJ 2011;183:E430-5.
7. Del Rosso JQ, Brandt S. The role of skin care as an integral component in the management of acne vulgaris: Part 2: Tolerability and performance of a designated skin care regimen using a foam wash and moisturizer SPF 30 in patients with acne vulgaris undergoing active treatment. J Clin Aesthet Dermatol 2013;6:28-36.
8. Lai KW, Mercurio MG. Update on the treatment of acne vulgaris. J Clin Outcomes Manag 2009;16:115-26.
9. Zhou R, Jiang X. Effects of adapalene-benzoyl peroxide combination gel in treatment or maintenance therapy of moderate or severe acne vulgaris: A meta-analysis. Ann Dermatol 2014;26:43-52.
10. Del Rosso JQ. Defining criteria used to evaluate response to treatment of acne vulgaris. Cutis 2006;78:117-21.
11. Faghihi G, Isfahani AK, Hosseini SM, Radan MR. Efficacy of intense pulsed light combined with topical erythromycin solution 2% versus topical erythromycin solution 2% alone in the treatment of persistent facial erythematous acne macules. Adv Biomed Res 2012;1:70.
12. Webster G, Rich P, Gold MH, Mraz S, Calvarese B, Chen D. Efficacy and tolerability of a fixed combination of clindamycin phosphate (1.2%) and low concentration benzoyl peroxide (2.5%) aqueous gel in moderate or severe acne subpopulations. J Drugs Dermatol 2009;8:736-43.
13. Jain VK, Chopra KL, Dayal S. Comparative evaluation of topical benzoyl peroxide, metronidazole and benzoyl peroxide – Clindamycin combination in treatment of acne vulgaris. Indian J Dermatol Venereol Leprol 1998;64:71-4.
14. Choudhury S, Chatterjee S, Sarkar DK, Dutta RN. Efficacy and safety of topical nadifloxacin and benzoyl peroxide versus clindamycin and benzoyl peroxide in acne vulgaris: A randomized controlled trial. Indian J Pharmacol 2011;43:628-31.
15. Shwetha H, Geetha A, Revathi TN. A comparative study of efficacy and safety of combination of topical 1% clindamycin and 0.1% adaplene with 1% clindamycin and 2.5% benzoyl peroxide in mild to moderate acne at a tertiary care hospital. J Chem Pharm Res 2014;6:736-41.

How to cite this article: Kaur J, Sehgal VK, Gupta AK, Singh SP. A comparative study to evaluate the efficacy and safety of combination topical preparations in acne vulgaris. Int J App Basic Med Res 2015;5:106-10.

Source of Support: Nil. **Conflict of Interest:** None declared.