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RESEARCH ARTICLE

COMPARISON OF THE EFFICACY AND SAFETY OF TOPICAL 1% CLINDAMYCIN WITH 0.1% ADAPALENE AND 2.5% BENZOYL PEROXIDE WITH 0.1% ADAPALENE IN THE TREATMENT OF MILD TO MODERATE FACIAL ACNE VULGARIS: A RANDOMIZED PROSPECTIVE STUDY

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ABSTRACT

Background: Acne vulgaris, a common skin disorder is treated by multitargeted approach. There is scarce data evaluating adapalene in combination with other drugs.
Objectives: We compared the efficacy and safety of efficacy of topical combination of 1% Clindamycin and 0.1% Adapalene with 2.5% Benzoyl peroxide and 0.1% Adapalene in mild to moderate acne.
Methods: 80 patients, attending outpatient department of dermatology with mild to moderate acne vulgaris as per Indian Acne Alliance grading were randomised into two groups with 40 patients in each group. Group A received topical 1% Clindamycin and 0.1% Adapalene and group B received 2.5% Benzoyl peroxide and 0.1% Adapalene. The efficacy of the drugs was evaluated at 4, 8 and at 12 weeks follow up by spot counting of acne lesions on face. The number of inflammatory lesions (pustules, papules) and non inflammatory lesions (open and closed comedones) were noted and compared between the two groups.
Results: The mean number of lesions namely comedones, papules, pustules and nodules were counted for each group during each visit and compared between the groups. There was no statistically significant difference in the reduction of lesions between both the groups ($p > 0.001$). There was slightly higher irritation with the adapalene benzoyl peroxide group but was statistically insignificant.
Conclusion: Hence both the combinations can be safely prescribed to the patients.

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INTRODUCTION

Acne vulgaris is one of the most common skin disorders prevalent among the adolescent age group. In this modern era, where cosmetics predominate the pharmaceutical market, acne affects the self esteem and causes emotional upset in the adolescents. Acne vulgaris is caused by Propionobacterium acnes and has a multifaceted pathogenesis (Pawin *et al*., 2004). Hence combination therapy provides multiple targets based on the pathogenesis and also produces synergistic effect (James 2003). Various topical applications and systemic therapy using adapalene (Waugh *et al*., 2004; Brogden *et al*., 1997), clindamycin, benzoyl peroxide (Tanghetti *et al*., 2009) and other agents have been tried in the treatment of acne. Topical application has the advantage of easy application and fewer side effects and is used to treat mild to moderate acne (Thiboutot *et al*., 2009; Gollnick *et al*., 2003; Berson *et al*.,1995). Adapalene is a third generation retinoid widely employed due to its faster onset of action and less irritating property (Thielitz *et al*., 2008; Caner *et al*., 2005). Adapalene in combination with benzoyl peroxide is found to have no superiority over benzoyl peroxide monotherapy (Wolf JE., 2001; Tan 2009). Adapalene in combination with clindamycin is proved to be more efficacious than adapalene monotherapy (Gans EH., 2002). There are numerous studies that evaluate the efficacy of clindamycin and benzoyl peroxide in combination therapy (Zouboulis *et al*., 2009). But there is scarce data evaluating adapalene in combination with other drugs. Hence the study was planned to compare the efficacy of topical 1% Clindamycin and 0.1% Adapalene with 2.5% Benzoyl peroxide and 0.1% Adapalene in mild to moderate acne and to compare

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the tolerability and safety of topical 1% Clindamycin and 0.1% Adapalene with 2.5% Benzoyl peroxide and 0.1% adapalene in mild to moderate acne.

MATERIALS AND METHODS

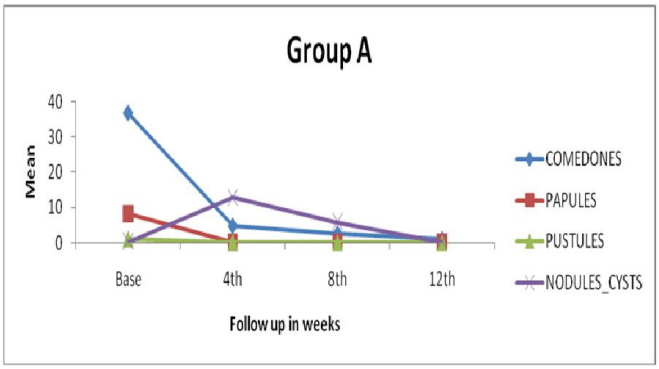
After getting approval from the Institutional Research and Human Ethics Committee, a Randomized, Prospective, Comparative Study was conducted on 80 patients with mild to moderate facial acne vulgaris attending the Outpatient department of Dermatology in a tertiary care teaching hospital, for a period of 12 weeks who were divided into two groups with 40 patients in each group. Patients aged 12-35 years of either sex, with mild to moderate acne as per Indian Acne Alliance Grading (Kubba *et al*., 2009) or Grade I, II, III acne as per Leed's grading, Women of reproductive age group with negative urine pregnancy test result and Patients who have given consent and willing for follow up were included in the study. Patients with other variants of acne like tropical acne, acne conglobata and drug induced acne, other skin lesions on the face, patients already on acne medications for past 2 week or with known hypersensitivity to any of the components of the drug, pregnant and lactating mothers, patients with Grade IV acne as per Leed's grading or Severe Acne as per Indian Acne Alliance grading, and patients not willing to give informed consent and follow up were excluded from the study. Detailed patient history regarding allergy, previous treatment history, demographic details were obtained using study proforma. Dermatologic evaluation of Acne Severity was done by the dermatologist as per Indian Acne Alliance Grading (Kubba *et al*., 2009). 80 patients suffering from mild to moderate acne on face were grouped in two groups of 40 each. They were randomly assigned to one of the two treatment schedules.

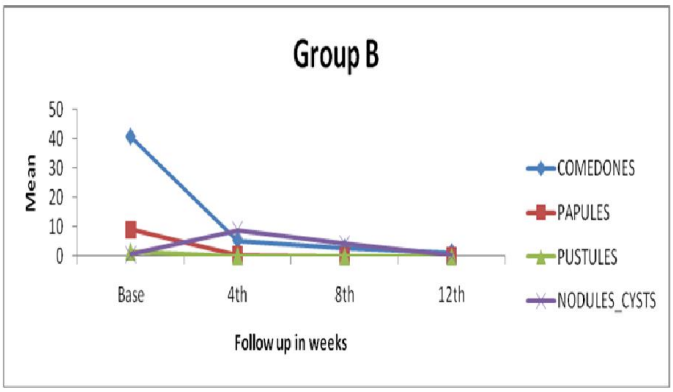
Group A received topical therapy with 1% Clindamycin and 0.1% Adapalene and **Group B** received topical therapy with 2.5% Benzoyl peroxide and 0.1% Adapalene.

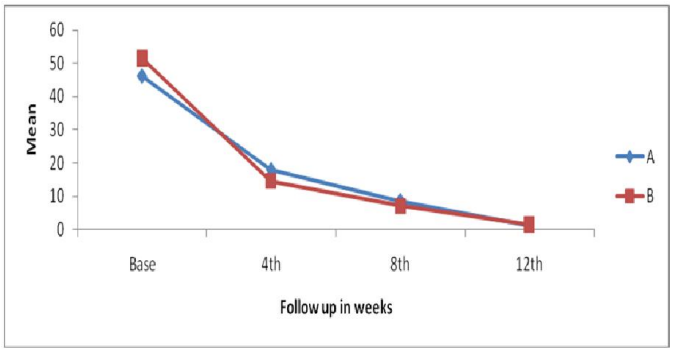
Patients were advised to wash the face, dry it well at bedtime and then apply one fingertip unit (approximately 0.5 gram) of each study drug by dotting it over forehead, cheeks, chin and nose and spread a thin film evenly over entire face avoiding periorbital, paranasal and perioral areas. Group A was advised to apply 1% clindamycin and Group B 2.5% Benzoyl peroxide first. After half an hour both groups were advised to apply 0.1% adapalene over it without washing the face. The medication was left over night. Initially if there is irritation with the drugs within short contact time of 15 – 30 minutes, it was left overnight. If there was intolerable irritation, patients were asked to wash it off with plenty of water and they were excluded from the study. The importance of adherence to treatment was explained and schedule for follow up visits was issued to the patient. Missed applications were evaluated during each visit by checking the usage of ointment tubes. If the disease progresses to severe acne in a patient during treatment, then systemic therapy was given. Such patients would be treated as drop outs and included in intention to treat analysis.

Efficacy assessment

The efficacy of the drugs were evaluated at 4, 8 and at 12 weeks follow up by spot counting of acne lesions on face by the investigator with the guidance of the dermatologist. The number of inflammatory lesions (pustules, papules) and non-inflammatory lesions (open and closed comedones) were noted during each visit in a separate chart maintained for each patient. At baseline total number of lesions on face were taken as 100%. Any reduction in number of acne lesions at follow ups is compared with baseline and expressed as percentage of improvement.







Safety and Tolerability parameters

Dryness, Erythema, Burning, Peeling and Irritation – Each parameter was assessed and graded by the dermatologist at 4, 8 and 12 weeks follow up using a 5 point scale (Lawrence *et al*., 2012) and any adverse event was noted.

RESULTS

The data was collected and analyzed statistically using descriptive statistics namely mean, standard deviation, percentage wherever applicable. T- test and Chi-Square test were used for analysis. All the patients completed the study.

None withdrew from the study.

Demographic details

The demographic details regarding age and gender were compared between the two groups and found to be statistically insignificant.

Reduction in the number of lesions

The mean number of lesions namely comedones, papules, pustules and nodules were counted for each group during each visit and compared between the groups. There was no statistically significant difference in the reduction of lesions between both the groups ($p > 0.001$) and is depicted in Table 1.

(Zouboulis *et al*., 2009) performed a similar study and demonstrated that clindamycin/benzoyl peroxide combination (C/BPO) and adapalene/benzoyl peroxide (A/BPO) have comparable efficacy in the topical treatment of acne. He reported a greater incidence of local reactions with A/BPO than with C/BPO and C/BPO was significantly better tolerated than A/BPO. In our study, though there was not statistically significant difference in the efficacy and safety of topical 1% Clindamycin and 0.1% Adapalene with 2.5% Benzoyl peroxide and 0.1% Adapalene, there was slightly higher irritation with benzoyl peroxide with adapalene and faster onset with higher reduction of lesions in this group. Our study comply with the results reported by Leyden (Leyden *et al*., 2011) who evaluated the fixed-dose combination gel containing adapalene 0.1% and benzoyl peroxide 2.5% and reported that it effectively inhibited

Table 1. Comparison of lesion count between the two groups

Group	Visit number	Comedones	Papules	Pustules	Nodules_CYSTS	TOTAL LESION
A	1	36.75 (10.82)	8.2 (4.5)	1 (0.99)	0.28 (0.68)	46.23 (14.29)
	4	1.1 (1.63)	0 (0)	0 (0)	0.23 (0.8)	1.33 (1.8)
	t-test	0.0000	0.0000	0.0000	0.7435	0.0000
B	1	40.65 (18.83)	8.9 (5.45)	1.65 (2.38)	0.45 (0.85)	51.65 (20.98)
	4	1.28 (1.54)	0.05 (0.32)	0 (0)	0.13 (0.56)	1.45 (1.85)
	t-test	0.0000	0.0000	0.0001	0.0307	0.0000
Mean Diff	A1-A4	0.38 (0.93)	0.28 (0.85)	0.53 (1.13)	0.13 (0.46)	1.3 (1.9)
	B1-B4	0.35 (0.95)	0.15 (0.66)	0.4 (0.98)	0.03 (0.16)	0.93 (1.73)
t-test		0.9053	0.4643	0.5993	0.2003	0.3585

Table 2. Comparison of tolerability profile between the two groups

DRYNESS	4th week	8th week	12th week
A	0.175	0	0
B	0.225	0	0.125
ERYTHEMA	4th week	8th week	12th week
A	0.125	0	0.075
B	0	0	0.1
BURNING	4th week	8th week	12th week
A	0.175	0	0
B	0.125	0	0
PEELING	4th week	8th week	12th week
A	0.025	0.325	0.175
B	0	0.55	0.55
IRRITATION	4th week	8th week	12th week
A	0.025	0.225	0.05
B	0	0.525	0.275

Tolerability profile

The results of our study revealed both the treatment combinations were well tolerated. There was slightly higher irritation with the adapalene benzoyl peroxide group but was statistically insignificant and is depicted in Table 2.

DISCUSSION

Our study compared the efficacy and safety of the topical of 1% Clindamycin and 0.1% Adapalene with 2.5% Benzoyl peroxide and 0.1% Adapalene in mild to moderate acne. And the results revealed that there was no significant difference in the mean lesion count between the two groups. Zouboulis

both antibiotic-susceptible and antibiotic-resistant *Propionibacterium acnes* and reduced skin colonization by antibiotic-sensitive and antibiotic-resistant *Propionibacterium acnes*.

Higher irritation with benzoyl peroxide was not statistically significant in our study. Thiboutot *et al.* reported that fixed-dose combination gel of adapalene and BPO was significantly more effective than corresponding monotherapies, with significant differences in total lesion counts observed as early as 1 week. Adverse event frequency and cutaneous tolerability profile for adapalene-BPO were similar to adapalene monotherapy.

Similar study was done by Brand *et al* (Brand *et al*., 2003) who evaluated the level of skin tolerance to adapalene gel 0.1%, tretinoin cream 0.025%, or tretinoin microsphere gel 0.1% when applied in combination with clindamycin phosphate lotion 1%, erythromycin gel 2%, benzoyl peroxide gel 5%, or erythromycin-benzoyl peroxide gel. Adapalene gel 0.1% demonstrated statistically significantly (P <.001) less irritation after repeated application under occlusive conditions than tretinoin cream 0.025% or tretinoin microsphere gel 0.1%. Moreover, the application of adapalene gel 0.1% under these conditions, concomitantly with various antimicrobial agents, was safe and well tolerated in this subject population. In view of its low irritation potential and its efficacy, he recommended that adapalene gel 0.1%, in combination with antimicrobial agents should be considered for the treatment of acne vulgaris.

Langner *et al*. (Langner *et al*., 2008) studied the effectiveness of two treatments for facial acne: a ready-mixed once-daily gel containing clindamycin phosphate 10 mg mL(-1) + benzoyl peroxide 50 mg mL(-1) and a once-daily gel containing adapalene 0.1%. CDP + BPO showed an earlier onset of action with a faster significant reduction in inflammatory and total lesion counts than ADA.

Hence both the treatment regimens can be safely prescribed to the patients. The limitation of our study was that we did not include severe acne and other variants of acne. Also the evaluation of tolerability profile was a subjective one which may vary.

Conclusion

Our study reveals no statistical difference in the efficacy and safety of topical 1% Clindamycin and 0.1% Adapalene with 2.5% Benzoyl peroxide and 0.1% Adapalene though quick onset of action with mild irritation was seen in the benzoyl peroxide group. Hence, both the topical combinations can be safely prescribed in mild to moderate acne vulgaris.

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Conflict of interest: None

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