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COMPARISION OF CLINICAL EFFICACY OF TOPICAL CLINDAMYCIN WITH ADAPALENE AND ADAPALENE ALONE IN TREATMENT OF MILD TO MODERATE FACIAL ACNE VULGARIS

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ABSTRACT

Background: Antibiotics are often combined with other agents for topical acne treatments that are effective against inflammatory and non- inflammatory lesions and minimize the development of antibiotic resistance. Retinoids and associated treatments also have anti-inflammatory activity and decrease microcomedon formation. The study was a prospective study done from November 2008 to October 2009.
Objectives: To compare and evaluate the clinical efficacy of topical clindamycin with adapalene and adapalene gel in mild to moderate facial acne vulgaris.
Methods: Prospective, randomized, open label, comparative-efficacy study was carried out at a Tertiary Care Hospital after obtaining approval from the Institutional Ethics committee to investigate the efficacy and tolerability of adapalene gel 0.1% plus clindamycin phosphate lotion 1%, compared with adapalene 0.1% alone for the treatment of mild to moderate acne vulgaris. A total of 60 patients , divided into two groups, one receiving clindamycin 1% lotion and adapalene 0.1% twice daily (30 patients), while the other group received adapalene gel 0.1% (30 patients) once daily for 12 weeks.
Results: A significant reduction of total (P .001), inflammatory (P .004) and non-inflammatory lesions (P .001) was seen in the clindamycin 1% plus adapalene 0.1% group than in the adapalene 0.1% treated group. These significant treatment effects were observed as early as week 4 for both non inflammatory and total lesion counts. The mean percentage reductions were 46.45% versus 25.28% for total lesions, 55.1% versus 44.51% for inflammatory lesions, and 42.8% versus 17.06% for non-inflammatory lesions.
Conclusions: The study confirms that the use of adapalene gel 0.1% in combination therapy is beneficial at the initiation of treatment for those suffering from acne.

KEY WORDS- Inflammatory lesions, Non inflammatory lesions, Microcomedo, Clindamycin, Adapalene, Clinical efficacy, Total lesions.

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INTRODUCTION

Acne vulgaris is a common skin disorder affecting at least 85% of adolescents and young adults, a time of significant physical, emotional and social development. Selection of topical therapy is based on severity and type of acne. Topical retinoids, benzoyl peroxide, azelaic acid are effective for mild acne. Topical antibiotics like clindamycin and erythromycin which have bacteriostatic and anti- inflammatory properties are effective in mild to moderate acne.Adapalene has higher tolerance and efficacy than other concurrent acne medications, [(1)]which makes topical adapalene a key component in the treatment of both comedonal and inflammatory acne The preferred treatment for mild acne is topical medications with antibiotics and retinoids while for moderate acne, systemic antimicrobials with topical retinoids[(2)]As studies have shown that newer combination of 1% clindamycin with 0.1% adapalene gel has higher efficacy than 0.1% adapalene alone, this study is taken to evaluate the similar effect in our tertiary care hospital.

MATERIALS AND METHODS

Patients in the age group above 12 years attending the dermatology out-patient department at Tertiary care hospital were enrolled after obtaining approval from Institutional Ethics committee. Informed consent from the patient was obtained after explaining to them, the purpose of study.
Study group included patients having 5 to 40 inflammatory facial lesions (no more than 3 nodules or cysts) and 20 to 80 non inflammatory facial lesions.

Inclusion criteria

- Age above 12 years
- Gender-Male/Female.
- Patients with mild to moderate facial acne vulgaris: Comedonal, papular or pustular.

Exclusion criteria

- Females-pregnant/nursing mothers.
- Skin disease that may interfere with diagnosis / evaluation of acne vulgaris, like acne conglobata, acne fulminans, secondary acne, severe acne.
- Females on oral contraceptives
- History of hypersensitivity to clnidamycin and adapalene.
- Use of any topical anti acne drugs in past 14 days.

Materials

(a) Patients with acne after evaluating for above criteria.
(b) 1% Clindamycin with 0.1% Adapalene gel.
(c) 0.1% Adapalene gel.

Methods

Approval of Institutional Review Board at the medical college hospital was obtained. Prospective, randomized, open label, comparative-efficacy study. Place: Dermatology outpatient department at Tertiary Care Hospital. Duration:November 2008 to October 2009. Sample size: 60
In Group I: 30 received Clindamycin phosphate 1% lotion with Adapalene gel 0.1%, twice daily in the morning and evening for a period of 12-weeks
Group II: 30 received Adapalene gel 0.1% alone, once daily in the evening for a 12-week period

Study procedures

Patients attended the clinic for screening, including demographics, medical history and baseline assessments, by the lesion count. As the patients included were only the patients with facial acne vulgaris, the number of lesions that were distributed all over the face was counted and noted as inflammatory or non inflammatory lesions.. Patients treated their facial areas twice daily for 12 weeks. Patients in first group applied clindamycin topical lotion 1% in morning, after washing. In the evening they applied clindamycin topical lotion 1% after washing, followed 2 minutes later with study medication adapalene gel 0.1%.Second group patients applied adapalene gel 0.1% only in the evening after washing. Gentle Cleanser was prescribed to all patients for washing. Patients attended the

hospital at weeks 2, 4, 8, and 12 after the start of treatment. Once in 2 weeks, the lesions were evaluated; reduction or increase of number, also any adverse effects encountered during this time was noted.

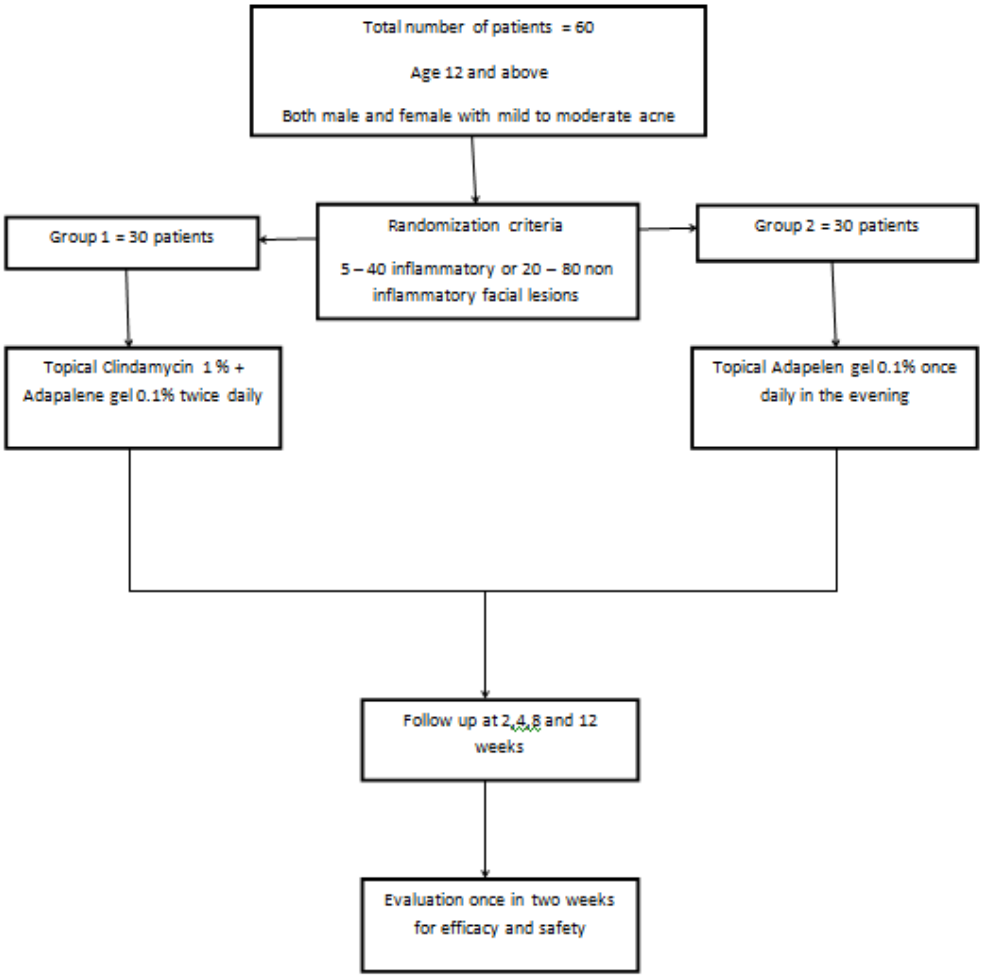
Efficacy assessment

The investigator assessed local facial tolerability at each visit by rating erythema, scaling, dryness and stinging /burning.

Efficacy evaluation

The primary efficacy end point was the comparison of the counts of total, inflammatory, and non- inflammatory lesions at baseline and week 12 last observation carried forward (LOCF) end points. Secondary end points included a comparison of adverse events (dermatological) during the therapy.

Flowchart showing randomization of participants



PATHOPHYSIOLOGY OF ACNE VULGARIS

Acne is a chronic inflammatory disorder of the pilosebaceous follicles. Pathophysiology centres on interplay of retention hyperkeratosis, increased sebum production, propioni bacterium within the follicles, and inflammation. Following etiological factors are important:

a) Alteration in the pattern of keratinisation within the sebaceous follicle;
b) Circulating sex hormones;
c) Quality and quantity of sebum secretion;
d) Follicular microbial flora;
e) Environmental factors;
f) Genetic factors:

GRADING OF ACNE

Three level acne grading for primary acne vulgaris was developed by American academy of dermatology in 1990.

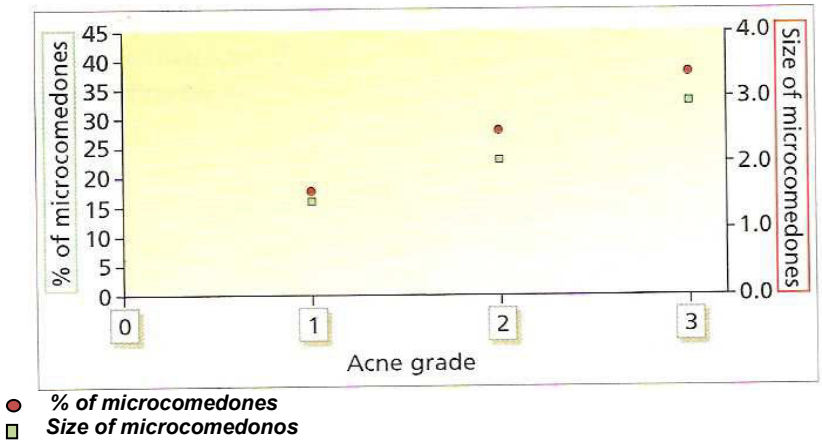
a) Mild acne: few to several papules but no nodules.

b) Moderate acne: several maculae and pustules nodules.

c) Severe acne: numerous papules and nodules

Figure1

Correlation between the number and size of microcomedones and acne severity.



Microcomedones are the earliest observable abnormality Colonization of the duct with P. acnes and the production of inflammation are late stages in the development of acne.

Clinical features

Classification systems for acne generally describe the following categories:[3]

Grade 1— mainly comedones with an occasional small inflamed papule or pustule; no scarring present

Grade 2 — comedones and more numerous papules and pustules (mainly facial); mild scarring

Grade 3 — numerous comedones, papules, and pustules, spreading to the back, chest, and shoulders, with an occasional cyst or nodule; moderate scarring

Grade 4 — numerous large cysts on the face, neck, and upper trunk; severe scarring

Acne is a polymorphic disease, which occurs predominantly on the face (99% of sufferers) and, to a lesser extent, occurs on the back (60%) and chest (15%).[4]

Non-inflamed lesions (comedones) develop earlier than inflamed lesions in younger patients. Comedones may be blackheads (open comedones), in which the black colour may be due to the presence of melanin , whiteheads (closed comedones. and the so-called intermediate non-inflamed lesions, which show features of both blackheads and whiteheads . Comedonal lesions called 'sandpaper comedones' consist of multiple very small whiteheads and are found most often on the forehead.

Types of lesions

a) Non inflammatory

or

b) Inflammatory.

a) Non inflammatory lesions are comedones. Comedones are characteristic lesions of acne. A comedo (plural comedons) is a plug of sebaceous and deratinous material lodged in the opening of a hair follicle. Open comedones (Which are 1-2 mm in diameter on the skin surface) appears as a flat or slightly raised lesion with a central dark-coloured follicular impaction of keratin and lipid, represents follicles with widely dilated orifice. Closed comedones (which are 1-3 mm in diameter) may be difficult to visualize. They appear as pale, slightly elevated, small papules and do not have a clinically visible orifice. Stretching of the skin is an aid in detecting the lesions . They are macular or papular lesions without surrounding erythema.

b) The inflammatory lesions vary from small papules with an inflammatory areola to pustules to large, tender, fluctuant nodules. Some of the large nodules were previously called "cysts" and the term nodulocystic has been used to describe severe cases of inflammatory acne.

TREATMENT OF ACNE VULGARIS

Treatment of acne includes a number of topical and systemic therapies . It takes about 8 weeks for a microcomedo to mature, thus any therapy is to be continued beyond this duration in order to asses efficacy. [1]

(A)Sulphur preparations used to treat acne since the time of Hippocrates acts by keratolysis and irritative effect. [5].

(B) Salicylic acid in a concentration of 0.5 or 2 percent inhibits comedogenesis by promoting the desquamation of follicular epithelium.

(C) Benzoyl peroxide a has bactericidal and comedolytic properties (2.5 to 10 percent), with skin irritation as common adverse effect.

(D)Topical benzoyl peroxide and tretinoin[6])and combined use of

(E) benzoyl peroxide and adapalene is more effective than either agent used alone [7].

Patients with predominantly inflamed lesions should receive topical benzoyl peroxide, antibiotics or azaleic acid.

(F)Isotretinoin is a second-generation retinoid.

(G)A third-generation retinoid, adapalene, has a greater benefit/risk ratio than tretinoin.

(H) Fourth-generation retinoid tazarotene. Adapalenetopicalsynthetic naphthoic acid derivative has a significant anti inflammatory action in the first few days of therapy.

Adapalene is better tolerated than other formulations of tretinoin (cream and microsphere gel) [8]

Adapelene selectively binds to the nuclear retinoic acid receptor (RAR) subtypes β and γ [9]

)and inhibits keratinocyte differentiation more than tretinoin. Adapalene inhibits the inflammatory response to microcomedone formation and bacterial antigens [10,11]

Adapalene's anti-inflammatory effects result from inhibition of neutrophil chemotaxis and the lipoxygenase pathway than tretinoin. [9]

(I)Hormonal and corticosteroid therapy: Therapy with estrogen or an antiandrogen is an alternative to systemic isotretinoin in women with acne that is unresponsive to other methods of treatment... Hormonal regimens include: prednisolone plus oestrogen; oestrogens plus antiandrogens; and spironolactone. Low-dose glucocorticosteroids (i.e. 2.5 mg prednisolone on waking and 5 mg on retiring) to suppress adrenal androgens, with or without a contraceptive pill, will reduce sebum production by up to 50% with a concomitant improvement in acne. Cyclical oestrogen (30 µg) with medroxyprogesterone acetate (5 mg for 7 days) is also of benefit. Antiandrogens suppress sebum production.

(G)Clindamycin

Clindamycin is a lincosamide antibiotic with bacteriostatic effect. It is a bacterial protein synthesis inhibitor by inhibiting ribosomal translocation, [12] . It does so by binding preferentially to the 23SrRNA of the large bacterial ribosome subunit. [13]

(H) Combination Therapy

Since no one agent addresses all four key aspects of acne pathophysiology, most patients should be treated with more than one agent to control their disease. Fortunately, fixed-drug combinations provide a good option for simplifying regimens, improving both efficacy and tolerability, and addressing three of acne's key pathophysiological features (ie, hyperkeratinization, bacterial colonization and inflammation).

RESULTS

A total of 60 patients took part in the study, 30 receiving clindamycin plus adapalene and 30 receiving adapalene plus vehicle There were more females (75%) than males (25%)). The peak prevalence age was 19.5 years. Mean total facial lesion count at baseline was about 70, non inflammatory lesions were 49 and mean inflammatory lesional count was about 20. The number of total, inflammatory and non inflammatory lesions was similar in the 2 treatment groups (*P* 0.765, 0.984, and 0.724, respectively).

Statistical Analysis

For the primary efficacy variables of total, inflammatory and non inflammatory lesion counts, descriptive statistics (means and standard deviations) were calculated for each treatment group at each post-baseline time point. After transformation to square roots, these primary variable changes in lesion counts were analyzed by analysis of covariance with the transformed baseline

count as a covariate and treatment as main effect in the model. Adverse event data were summarized in frequency tables by treatment group, but no statistical analysis was performed.

All statistical tests were 2-sided and had the significance probability level set at .05.

Efficacy evaluation

Mean percentage changes in total, non-inflammatory and inflammatory lesion counts from baseline at weeks 2, 4, 8, and 12 are shown in Table 1, 2 and 3 respectively.

TABLE 1
PERCENTAGE OF REDUCTION IN TOTAL LESIONS

Duration	Baseline	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Clindamycin with adapalene	0	-11.69	-18.8	-30.54	-31.3	-37.57	-46.45
Adapalene	0	-7.02	-13.8	-18.78	-22.13	-23.83	-25.28

TABLE 2
PERCENTAGE OF REDUCTION IN NON INFLAMMATORY LESIONS

Duration	Baseline	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Clindamycin with adapalene	0	-11.27	-17.84	-25.54	-29.66	-36.81	-42.8
Adapalene	0	-4.74	-9.6	-12.15	-13.95	-15.41	-17.06

TABLE 3
PERCENTAGE OF REDUCTION IN INFLAMMATORY LESIONS

Duration	Baseline	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Clindamycin with adapalene	0	-12.62	-21.12	-42.39	-44.79	-53.77	-55.1
Adapalene	0	-12.28	-23.64	-34.32	-41.26	-43.54	-44.51

For the primary end point, there was a significantly greater reduction of total lesions (*P* 0.001), inflammatory lesions (*P* 0.004) and non- inflammatory lesions (*P* 0.001) in the clindamycin 1% plus adapalene 0.1% group(Fig.2) than in the adapalene 0.1% group(Fig.3) at week 12.The mean percentage reductions were 46.45% versus 25.28% for total lesions, 55.1% versus 44.51% for inflammatory lesions(Fig.7), and 42.8% versus 17.06% for non-inflammatory lesions(Fig.6). Statistically significant reductions of lesions were reported for the clindamycin plus adapalene group from weeks 4 to 12 for total lesions, week 12 for inflammatory lesions(Fig.5) and weeks 4 to 12 for non-inflammatory lesions(Fig.4)

Safety evaluation

Both treatment regimens were well tolerated during the study. More patients reported adverse events in the clindamycin 1% plus adapalene 0.1% group than in the adapalene 0.1% group (30.4% vs. 21.8%). However, dermatologic events were reported by similar proportions of patients in both groups (10.4% vs. 9.7%, respectively.

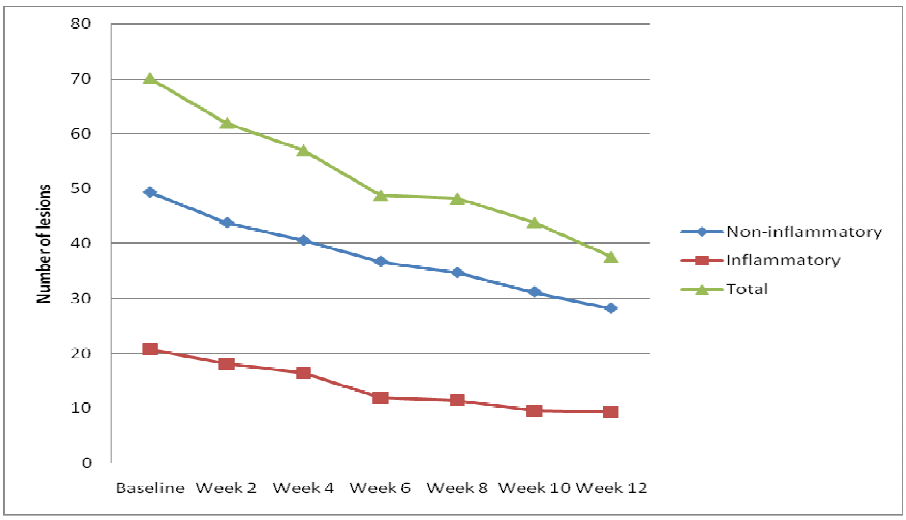


FIGURE 2
REDUCTION OF LESIONS IN CLINDAMYCIN WITH ADAPALENE TREATED GROUP

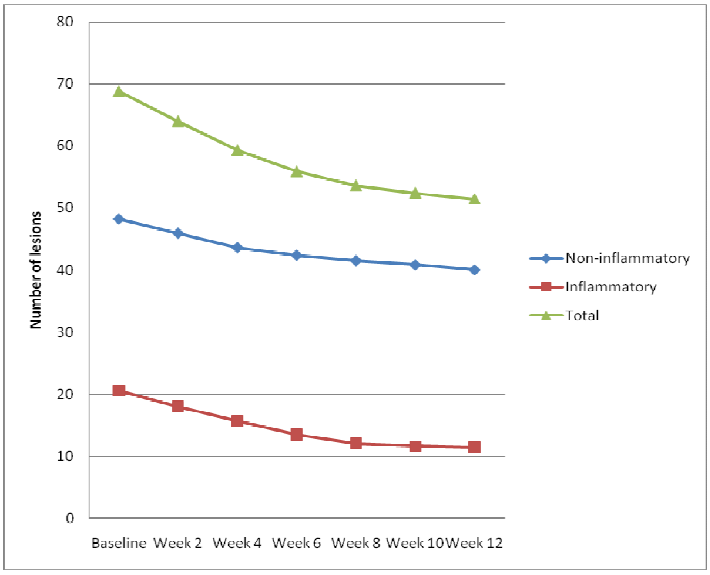


FIGURE 3
REDUCTION OF LESIONS IN ADAPALENE TREATED GROUP

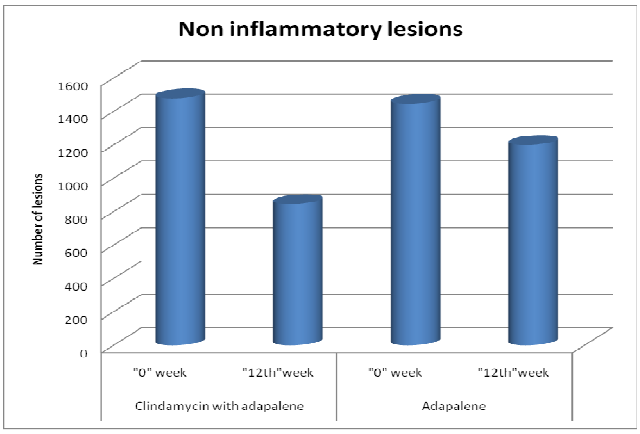


FIGURE 4
COMPARISION OF NON INFLAMMATORY LESIONS BEFORE AND AFTER THE

TREATMENT

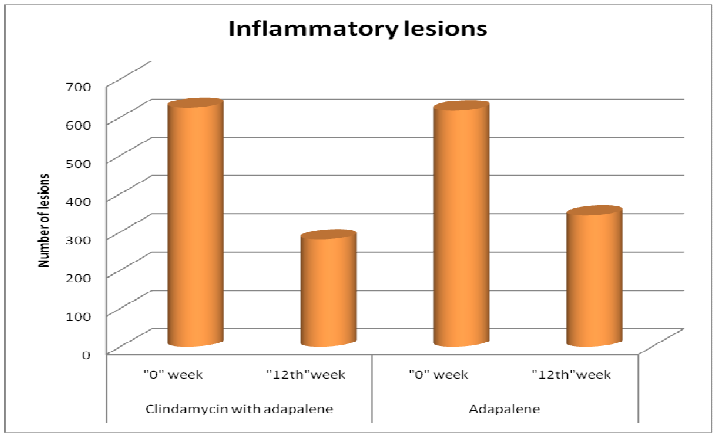


FIGURE 5
COMPARISION OF INFLAMMATORY LESIONS BEFORE AND AFTER THE TREATMENT

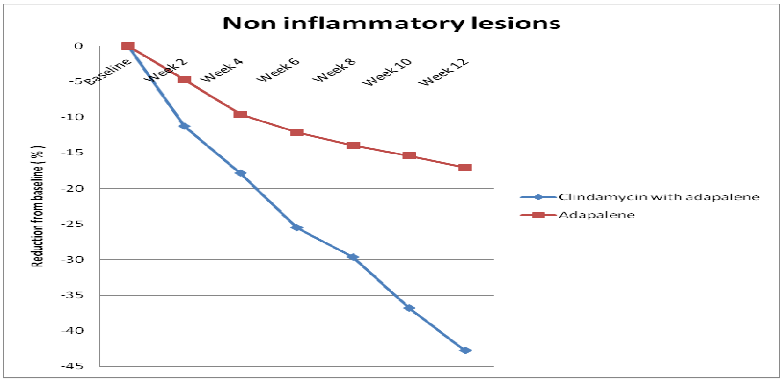


FIGURE 6
PERCENTAGE OF REDUCTION IN NON INFLAMMATORY LESIONS

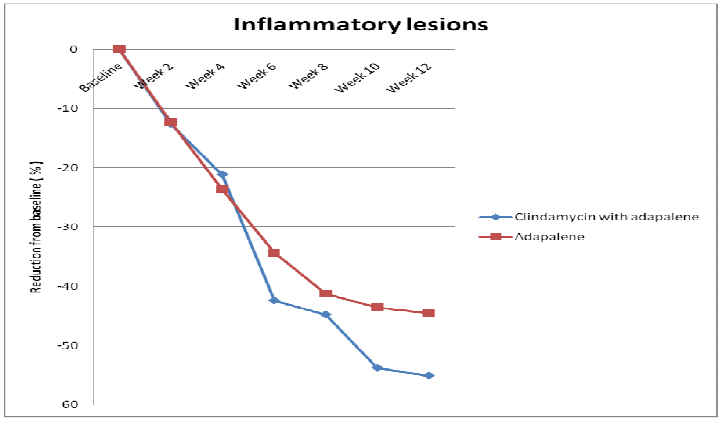


FIGURE 7
PERCENTAGE OF REDUCTION IN INFLAMMATORY LESIONS

DISCUSSION

This study was designed to investigate whether the combination of clindamycin topical lotion 1% plus adapalene gel 0.1% provides a significantly greater and faster efficacy than adapalene 0.1% for the treatment of mild to moderate acne vulgaris.

Results showed that the addition of adapalene gel 0.1% produced a faster and a clinically significant enhancement of the efficacy of clindamycin topical lotion 1% therapy for acne vulgaris. There were significantly greater reductions in total, inflammatory, and non-inflammatory lesions in the adapalene plus clindamycin group than in the adapalene 0.1% treated group. After 12 weeks of treatment, there was an almost 2-fold greater decrease in total lesion counts for the adapalene group than for the vehicle group (46.7% vs. 25.5%). The combination of adapalene and clindamycin significantly reduced the number of both inflammatory and non-inflammatory lesions, with an approximately 25% greater reduction in inflammatory lesions (55.0% vs. 44.2%) and a 2- to 3-fold greater reduction in non-inflammatory lesions (42.5% vs. 16.3%) than in the adapalene group at week 12. Patients also demonstrated a faster response to the combination therapy, with a statistically significantly greater improvement in the reduction of total and non-inflammatory lesions seen as early as week 4. The significantly greater and faster effect on acne lesions obtained by adding adapalene to clindamycin indicates that this combination can be used at the onset of therapy to obtain a better clinical response than that obtained by use of the antibiotic alone,Adapalene has a significant anti-inflammatory effect that enhances the therapeutic action of clindamycin on inflammatory acne lesions. Adapalene has selective affinity for retinoid receptors, including retinoic acid receptor β (RAR-β) and retinoic acid receptor α (RAR-α), it also acts indirectly on cellular function through anti-AP-1 mechanism. [(14)]In conclusion, the combination regimen of clindamycin topical lotion 1% plus adapalene gel 0.1% was significantly more effective than adapalene 0.1% alone for the treatment of mild to moderate acne vulgaris in reducing inflammatory and non- inflammatory lesions.

SUMMARY

1. Patients belonging to various age groups (between 12-32 years) were studied. The peak prevalence age was 19.5 years. The number of cases reduced after age 26 year's age group.
2. In the study group of patients with mild to moderate facial acne cases, about 75% were females, hence the disease was more common in females attending the hospital. Males constituted for about 25% of cases.
3. Various parameters like inflammatory lesions, non inflammatory lesions, and total lesions were studied. Mild facial acne vulgaris was seen in 43% of patients where as 57% patients were with moderate acne.

OBJECTIVE

To compare and evaluate the clinical efficacy of topical clindamycin 1% with adapalene 0.1% and adapalene gel 0.1% in mild to moderate facial acne vulgaris.

CONCLUSION

Overall, this study shows that the combination of adapalene 0.1% plus clindamycin 1% is more effective than adapalene 0.1% alone for the treatment of acne vulgaris. The results support the existing published data showing the efficacy of combination therapy for the treatment of acne vulgarisThe complementary as well as discrete mechanisms of action of adapalene and tibiotics produce a significantly superior and faster reduction of acne lesions, indicating that this therapeutic regimen may be useful at the onset of therapy to obtain an enhanced clinical response. The quick response afforded by the combination regimen may also reduce the duration of antibiotic therapy and thereby reduce the potential for developing resistance. The study confirms that the use of adapalene gel 0.1% in combination therapy is beneficial at the initiation of treatment for those suffering from acne.

REFERENCES

1. Goulden, V, Clark, SM, Cunliff, WJ. Post-adolescent acne: a review of clinical features. Br. J. Dermatol 1997; 136:66.
2. Gollinick H et al. Management of acne: A report from global alliance to improve outcomes in acne.J.AmAcadDermatol 2003;49-1
3. Harrison-Atlas, R, Bernhard, JD, O'Connor, RC, Weinreb, LF. What to do when typical teenage acne strikes. JCOM 1996; 3:9.
4. Dreno B, Poli F. Epidemiology of acne, Dermatology 2003; 206:7-1.
5. KligmanAM.Acne vulgaris: tricks and treatments. Part II: the benzoyl peroxide saga.cutis 1995;56:260-1.
6. Hurwitz, S. Acne vulgaris: pathogenesis and management. Pediatr Rev 1994; 15:47.
7. Thiboutot, DM, Weiss, J, Bucko, A, et al. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized double-blind, controlled study. J Am AcadDermatol 2007; 57:791.
8. Galvin SA, Gilbert R, Baker M, et al. Comparative tolerance of adapalene 0.1% gel and six different tretinoin formulations. Br J Dermatol 1998;139(Suppl 52):34–40.
9. Galvin SA, Gilbert R, Baker M, et al. Comparative tolerance of adapalene 0.1% gel and six different tretinoin formulations. Br J Dermatol 1998;139(Suppl 52):34–40.
10. Webster GF. The pathophysiology of acne. Cutis 2005;76(2 Suppl):4 –7.
11. Shalita A. The integral role of topical and oral retinoids in the early treatment of acne. J EurAcadDermatolVenereol 2001;15(Suppl 3):43–9.
12. Meyers BR, Kaplan K, Weinstein L. "Microbiological and pharmacological behavior of 7-chlorolincomycin". ApplMicrobiol 1969; 17 (5): 653–7.
13. Lell B, Kremsner PG. “Clindamycin as an antimalarial drug: review of clinical trials”. Antimicrob Agents Chemother 2002; 46 (8): 2315–20.
14. Shroot B, Michel S. Pharmacology and chemistry of adapalene. J Am AcadDermatol 1997; 36:596-603.