

Research Article



A Comparative Study to Evaluate the Efficacy and Safety of Topical Isotretinoin and Clindamycin Versus Adapalene and Clindamycin in The Treatment of Grade I – II Acne Vulgaris of Face

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Accepted on: 07-09-2014; Finalized on: 31-10-2014.

ABSTRACT

Topical retinoids in combination with topical or oral antimicrobials have been proven to reduce acne lesions faster and to a greater degree than antimicrobial therapy alone and it also prevents development of antimicrobial resistance. This prospective, open-labelled study was conducted to compare the efficacy of the combination of topical Isotretinoin and Clindamycin versus Adapalene and Clindamycin in the treatment of grade I – II acne vulgaris of face. A total of 200 patients were divided into 2 groups by using simple random sampling method: patients of the first group were prescribed to apply topical Isotretinoin gel 0.05 % and Clindamycin lotion 1 %; second group patients were prescribed to apply Adapalene 0.1 % gel and Clindamycin lotion 1 % for a period of 12 weeks. Out of the 200 patients participated, 191 patients completed the study. 9 patients withdrew from the study because of their skin intolerability issue. After 12 weeks of therapy, mean reduction in non inflammatory lesions, inflammatory lesions and total lesions of Adapalene plus Clindamycin group was found to be greater and statistically significant compared to that of Isotretinoin plus Clindamycin group (p value < 0.01). Again, Adapalene plus Clindamycin combination was found to be well tolerated compared to topical Isotretinoin plus Clindamycin combination. So overall this study proved the superior efficacy and better skin tolerability of Adapalene plus Clindamycin combination compared to topical Isotretinoin plus Clindamycin combination in the treatment of mild to moderate acne vulgaris of face.

Keywords: Acne vulgaris, Adapalene, Clindamycin, Inflammatory lesions, Isotretinoin, Non inflammatory lesions.

INTRODUCTION

Acne is a chronic inflammatory disease of the pilosebaceous units. It is characterized by seborrhea, the formation of open and closed comedones, erythematous papules and pustules and in more severe cases nodules, deep pustules and pseudocysts.¹ The condition usually starts in adolescence and frequently resolves by the mid-twenties. However, in 7–17% of individuals clinical acne persists beyond the age of 25 years.² Owing to its visible nature and the resulting scarring, acne is associated with a significant psychosocial impact on the patient's life. Patients suffering from acne are prone to embarrassment, social withdrawal, depression, anxiety and anger.^{3,4}

Topical retinoids like Adapalene or topical Isotretinoin are generally commonly prescribed along with combination of some antibiotics like Clindamycin in the treatment of mild to moderate acne vulgaris. Together they target three out of four pathogenetic factors, namely: ductal hyper cornification, P. acnes colonization, and inflammation. Further, topical retinoids, through a thinning effect on stratum corneum, facilitate percutaneous penetration of topical antibiotics, and help achieve higher concentrations of the antimicrobial agent in the pilosebaceous canal which P. acnes inhabits.⁵ So in this study we have decided to compare the efficacy and safety of combination of topical Isotretinoin gel 0.05 %

and Clindamycin lotion 1 % versus Adapalene gel 0.1 % and Clindamycin lotion 1 % in the treatment of mild to moderate acne vulgaris of face.

MATERIALS AND METHODS

It was a prospective, open-labeled single center, parallel group randomized comparative study at dermatology OPD of Raja Rajeshwari Medical College and Hospital, Bangalore. Study was conducted over a period of one year starting from May 2012 and was completed by April 2013. The patients attending Dermatology department with acne were evaluated for the grade of acne and for any other diseases.

In our study, we have included patients aged more than or equal to 10 years of both the genders suffering from grade I to grade II acne vulgaris of face as per grading mentioned by Indian authors⁶ (Grade I - Comedones, occasional papules; Grade II - Papules, comedones, few pustules; Grade III - Predominant pustules, nodules, abscesses; Grade IV - Mainly cysts, abscesses, widespread scarring).

Patients were excluded from the study if they were below 10 years of age and suffering from severe and very severe grade of acne; Patient who has allergy to any of the studied medication and photosensitivity; History of drug use for the treatment of acne within one month; Patients who has endocrinal problems like cushing syndrome,



polycystic ovarian syndrome; Women who was pregnant or planning for pregnancy; women who refused to apply topical Isotretinoin after proper counselling.

In our study, 200 consecutive patients were selected as per inclusion and exclusion criteria and divided into 2 groups by using simple random sampling method: first group - topical Isotretinoin plus Clindamycin group and second group - Adapalene plus Clindamycin group; each group contained 100 patients each. The study was conducted in accordance with ethical principles originating from the Declaration of Helsinki and Good Clinical Practices, and in compliance with regulatory requirements. The study protocol was reviewed and approved by the Institutional Ethics Committee of our institute.

At first visit, patients were interviewed for their demographic profile, present and past history, medication history etc. Each patient were examined for baseline non - inflammatory, inflammatory and total lesions counting and documented in their respective case record forms. Then the patients of the first group (topical Isotretinoin plus Clindamycin group) were prescribed to apply topical Isotretinoin gel 0.05 % once daily at night and topical Clindamycin phosphate 1% lotion in the morning; second group patients (Adapalene plus Clindamycin group) were prescribed to apply Adapalene 0.1 % gel once daily at night and topical Clindamycin phosphate 1% lotion in the morning. The patients were advised to revisit at 2, 4, 8 and 12 weeks. At each visit, patients were examined for number of non - inflammatory, inflammatory and total lesions counting and documented in case record forms. They were also asked for skin tolerability of medications and other side effects observed during the course of the therapy.

The final efficacy of the medications were evaluated at the end of 12 week by comparing the mean reduction in non inflammatory lesions, inflammatory lesions and total lesions count between the two groups after 12 weeks of therapy. Safety was assessed in terms of skin irritation potentials (erythema, dryness, scaling, burning, itching) and other adverse effects of the study medications.

Statistical Test

Intra-group mean reduction for non inflammatory lesions, inflammatory lesions and total lesions was evaluated with

the help of one way ANOVA test. Whereas intergroup comparison of two groups for mean reduction in inflammatory lesions, non inflammatory lesions and total lesions counts was evaluated with the help of two sample Z- test. All the tests were done at 5 % level of significance. All the Statistical analysis were done using SPSS (Statistical Package for the Social Sciences) software package.

RESULTS

A total of 200 patients participated in our study, but out of 200, 191 patients completed the study. 6 patients from Isotretinoin plus Clindamycin group and 3 patients from Adapalene plus Clindamycin group withdrew from the study because of skin intolerability issues. In our study highest number of acne prevalence was found in the age group of 15 – 19 years of age (54.98 %).

The demographic profile and characteristics of both the groups were compared and depicted in table 1.

Table 1: Demographic characteristics of both the groups

	Isotretinoin Plus Clindamycin	Adapalene Plus Clindamycin
Number Of Patients	94	97
Gender : Male	23	27
Female	71	70
Grade Of Acne		
Grade I	30	31
Grade II	64	66
Mean Age (Yrs)	23.26±2.84	22.35± 3.25
Mean Duration Of Disease (Yrs)	3.3±0.6	3.6±0.7

In our study, both the group showed statistically significant intra group reduction in non- inflammatory lesions, inflammatory lesions and total lesions after 12 weeks of therapy (p value < 0.01) [Table 2, 3].

After comparison of percentage reduction in non inflammatory lesions of the two groups, it was found that there was no difference in percentage reduction up to 2 week of therapy between the two groups, but as study progressed, greater reduction was found in Adapalene plus Clindamycin group compared to topical Isotretinoin plus Clindamycin group. [Table 4]

Table 2: Reduction of Lesions in topical Isotretinoin Plus Clindamycin Treated Group

	Baseline	Week 2	Week 4	Week 8	Week 12	P Value
Non- Inflammatory Lesions	53.85 ± 8.12	50.17± 8.44	45.55 ± 9.12	40.0± 7.92	29.14 ± 11.37	<0.01
Inflammatory Lesions	28.42 ± 8.14	25.62± 7.9	21.91 ± 8.15	20.73 ± 9.05	18.08 ± 8.19	<0.01
Total Lesions	82.26 ± 15.56	75.67± 15.52	67.46 ± 16.40	60.73± 16.12	47.24 ± 18.2	<0.01



Table 3: Reduction of Lesions in Adapalene Plus Clindamycin Group

Duration	Baseline	Week 2	Week 4	Week 8	Week 12	P Value
Non- Inflammatory Lesions	54.4± 8.23	49.15± 7.9	38.5± 8.10	30.68± 8.7	24.9± 10.63	<0.01
Inflammatory Lesions	29.22± 7.44	25.96± 7.46	20.69± 8.04	17.74± 7.4	16.01 ± 8.2	<0.01
Total Lesions	83.12 ± 14.9	75.86± 14.79	59.5± 15.34	48.42± 15.1	40.50± 18.0	<0.01

Table 4: Reduction in Non Inflammatory Lesions

Reduction From Baseline	Baseline	Week 2	Week 4	Week 8	Week 12
Isotretinoin Plus Clindamycin	0	-3.79± 1.4 (-7.03 %)	-8.28± 2.56 (-15.3 %)	-13.85± 2.48 (-25.71%)	-24.70 ± 5.04 (-45.86%)
Adapalene Plus Clindamycin	0	- 4.25± 1.8 (-7.81%)	-15.06± 1.11 (-27.68 %)	-23.21± 2.41 (-42.66%)	-29.0± 5.05 (-53.3%)

[Data depicted as: Mean Reduction ± Standard Deviation (Percentage Reduction)]

Table 5: Reduction in Inflammatory Lesions

Reduction From Baseline	Baseline	Week 2	Week 4	Week 8	Week 12
Isotretinoin Plus Clindamycin	0	-2.81± 1.4 (-9.88 %)	-6.5± 0.51 (-22.8 %)	-7.71± 2.5 (-27.1 %)	-10.30± 5.0 (-36.2%)
Adapalene Plus Clindamycin	0	-3.01± 1.09 (-10.3%)	-8.7± 2.28 (-29.77 %)	- 11.5± 0.5 (-39.35)	-13.64 ± 5.27 (-46.66%)

[Data depicted as: Mean Reduction ± Standard Deviation (Percentage Reduction)]

Table 6: Reduction in Total Lesions

Reduction From Baseline	baseline	2 week	4 week	8week	12 week
Isotretinoin Plus Clindamycin	0	-6.6± 2.28 (-8.023 %)	-14.79± 2.72 (-17.9 %)	-21.53± 3.13 (-26.17 %)	-35.03± 7.72 (-42.58 %)
Adapalene Plus Clindamycin	0	-7.27± 2.30 (-8.74 %)	-23.61± 2.2 (- 28.4 %)	-34.7± 2.14 (-41.74 %)	-42.61± 9.20 (-51.26 %)

[Data depicted as: Mean Reduction ± Standard Deviation (Percentage Reduction)]

By comparing the percentage reduction in inflammatory lesions of the two groups, it was found that there was no difference in percentage reduction up to 2 week of therapy between the two groups, but as study progressed, greater reduction was found in Adapalene plus Clindamycin group compared to topical Isotretinoin plus Clindamycin group.[table 5]

Again after comparison of percentage reduction in total lesions of the two groups, it was found that there was no difference in percentage reduction up to 2 week of therapy between the two groups, but as study progressed, greater reduction was found in Adapalene plus Clindamycin group compared to topical Isotretinoin plus Clindamycin group. [Table 6]

Mean reduction in non inflammatory lesion was -29.0± 5.05 in Adapalene plus Clindamycin group and -24.70 ± 5.04 in Isotretinoin plus Clindamycin group and statistically significant reduction was found in Adapalene plus Clindamycin group compared to Isotretinoin plus Clindamycin group (p value < 0.01). [Table -7]

Table 7: Comparative Reduction in Non Inflammatory, Inflammatory and Total Lesions between the Two Groups after 12 Weeks of Therapy

Reduction from baseline after 12 weeks of therapy	Isotretinoin Plus Clindamycin	Adapalene Plus Clindamycin	P Value
Non Inflammatory Lesions	-24.70 ± 5.04	- 29.0 ± 5.05	< 0.01
Inflammatory Lesions	-10.30± 5.0	-13.64 ± 5.27	< 0.01
Total Lesions	-35.03± 7.72	-42.61± 9.20	< 0.01

[Data depicted as: Mean Reduction ± Standard Deviation]

Mean reduction in inflammatory lesion was -13.64 ± 5.27 in In Adapalene plus Clindamycin group and -10.30± 5.0 in Isotretinoin plus Clindamycin group, and statistically significant reduction was found in Adapalene plus

Clindamycin group compared to Isotretinoin plus Clindamycin group (p value < 0.01). [Table-7]

Again Mean reduction in total lesion was -42.61 ± 9.20 in Adapalene plus Clindamycin group and -35.03 ± 7.72 in Isotretinoin plus Clindamycin group, and statistically significant reduction was found in Adapalene plus Clindamycin group compared to Isotretinoin plus Clindamycin group (p value < 0.01). [Table-7]

Safety analysis

In our study, no serious adverse effects were reported. Adapalene 0.1% in combination therapy with Clindamycin 1% was well tolerated compared to topical Isotretinoin 0.05 % plus Clindamycin 1 %. Reports of erythema, dryness, scaling, burning and pruritus were statistically significantly more in patients receiving topical Isotretinoin plus Clindamycin group compared to Adapalene plus Clindamycin group. [Table-8]

Table 8: Side Effects of the Medications

Side Effects	Isotretinoin Plus Clindamycin n (%)	Adapalene Plus Clindamycin n (%)	P Value
Erythema	25 (26.6 %)	11 (11.3 %)	< 0.05
Dryness	43 (45.7 %)	22 (22.7 %)	< 0.05
Scaling	16 (17.0%)	6 (6.1 %)	<0.05
Burning	44 (46.8 %)	25 (25.7 %)	< 0.05
Pruritus	56 (59.6 %)	32 (32.9 %)	< 0.05

DISCUSSION

Topical retinoids play a vital role in the treatment of mild to moderate acne through multiple actions. They act on the primary lesion - the microcomedo. By regulating the rate of differentiation and proliferation of the follicular keratinocytes, they inhibit the formation of and reduce the number of microcomedones. Topical retinoids promote normal follicular keratinocyte desquamation and thus help against the development of a propitious microenvironment for *P. acnes*.⁷

The main objective of our study was to evaluate the comparative efficacy and tolerability of topical Isotretinoin plus Clindamycin versus Adapalene plus Clindamycin in the treatment of mild to moderate acne vulgaris of face. In our study, both the group showed statistically significant mean reduction in both inflammatory lesions, non-inflammatory lesions along with total lesion (p value < 0.01). Again when we compared between the two groups, mean reduction in non inflammatory lesions, inflammatory lesions and total lesions of Adapalene plus Clindamycin group was found to be greater and statistically significant compared to that of Isotretinoin plus Clindamycin group (p value < 0.01). Our study support the result of a randomized open-label clinical trial conducted to evaluate the efficacy of topical Adapalene gel 0.1% vs. Isotretinoin gel 0.05% in the treatment of acne vulgaris, where it was found that

Adapalene gel produced greater reductions in non inflammatory and inflammatory lesion counts than Isotretinoin gel.⁸

Despite proven efficacy in the treatment of mild to moderate acne vulgaris, topical retinoids are not well accepted by patients because of its inherent irritation property to skin and so results in lack of compliance; but skin tolerability is found to be better in newer synthetic retinoids like Adapalene compared to older retinoids like Tretinoin and Isotretinoin. Several comparative studies have shown Adapalene to have a superior cutaneous safety profile as compared to different formulations of Tretinoin^{9,10} as well as Isotretinoin gel.⁸

In our study, Adapalene 0.1% in combination therapy with Clindamycin 1% was well tolerated compared to topical Isotretinoin 0.05 % plus Clindamycin 1 %. Reports of erythema, dryness, scaling, burning and pruritus were statistically significantly more in patients receiving topical Isotretinoin 0.05 % plus Clindamycin 1 % compared to Adapalene 0.1% in plus Clindamycin 1% (p value < 0.05). Our study also supports the findings of another study where it was found that Adapalene have better tolerability profile than that of topical Isotretinoin.¹¹

Adapalene was the first synthetic retinoid used in the treatment of acne vulgaris. It is a highly lipophilic compound, derived from naphthoic acid, which is easily taken up by the pilosebaceous unit and no evidence of teratogenicity has been reported till date.^{12, 13} Another advantage of Adapalene is its chemical structure which is more stable to light and oxidation compared with Tretinoin and Isotretinoin.¹⁴

A proposed mechanism for Adapalene's greater tolerability is its selective binding affinity. Unlike Tretinoin and Isotretinoin, Adapalene selectively binds to the nuclear retinoic acid receptor (RAR) subtypes beta and gamma and does not bind to the cytosolic retinoic acid binding proteins.^{15,16} This selective binding affinity may play a role in Adapalene's greater inhibition of keratinocyte differentiation than Tretinoin.

Another important factor in acne pathogenesis is the inflammation that occurs after microcomedone formation. Adapalene inhibits the inflammatory response to microcomedone formation and bacterial antigens.^{17, 18} Adapalene's anti-inflammatory effects result from inhibition of neutrophil chemotaxis and the lipoxygenase pathway, both of which are associated with cutaneous inflammatory reactions. Adapalene is more effective at inhibiting neutrophil lipoxygenase than is Tretinoin. Adapalene also has other unique anti-inflammatory mechanisms that may contribute to its efficacy.¹⁶

The main limitations of our study were single centered and open labelled study. So in future we expect a large multicenter study to prove the efficacy of this novel combination of Adapalene and Clindamycin in the treatment of acne vulgaris.



CONCLUSION

Newer generation topical retinoids like Adapalene have better skin tolerability, efficacy compared to older generation topical retinoids because of its unique selective retinoic acid receptor binding property. So we can conclude that Adapalene plus clindamycin combination will be great addition to the antiacne medications of dermatologist with relatively high safety and tolerability profile.

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Source of Support: Nil, Conflict of Interest: None.

