

## A comparison study of the clinical efficacy and safety of topical adapalene gel (0.1%) and tretinoin cream (0.025%) in the treatment of acne vulgaris

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### ABSTRACT

**Background:** Adapalene a synthetic retinoid analogue, is an addition to the arsenal of topical retinoids developed for the topical treatment of acne vulgaris. The study was designed to compare the clinical efficacy and safety of topical adapalene gel 0.1% and tretinoin cream 0.025% in the treatment of acne vulgaris.

**Methods:** A total of 80 patients with grade I-III acne vulgaris seen in the outpatient department of a tertiary care center were randomized to 8 weeks of daily treatment with either adapalene gel 0.1% or tretinoin gel 0.025%. Counts of total lesions, inflammatory lesions and non-inflammatory lesions were made at baseline and again at treatment weeks 2, 4, 6 and 8. Global assessment ratings, based on percent lesion reduction from baseline were also made. Side-effects like erythema, burning, pruritus, scaling and dryness were rated on a 0-3 severity scale.

**Results:** Out of 80 patients there were 8 dropouts in the study; the 72 patients who completed the study were evaluated for efficacy and safety. Both adapalene and tretinoin produce dramatic reductions in total, inflammatory and non-inflammatory lesion counts, on an average. Cutaneous side-effects were limited to a mild retinoid dermatitis occurring in both treatment groups however patients treated with adapalene gel tolerated this therapy significantly better than those treated with tretinoin cream.

**Conclusions:** Adapalene gel 0.1% offers comparable efficacy to tretinoin cream 0.025 % cream, but is less irritating. Adapalene gel 0.1% is a safe and effective topical agent in the treatment of mild to moderate acne vulgaris in Indian patients.

**Keywords:** Adapalene, Tretinoin, Acne vulgaris, Treatment

### INTRODUCTION

Acne vulgaris an almost universal accompaniment of adolescence is a disease of the pilosebaceous unit with involving abnormalities in sebum production, microbial flora changes, abnormal keratinization, and inflammation. Acne usually appears at adolescence, a period of uncertainty in life when a person is making the mental and physical transition from child to adult and unless effectively managed the acne may ultimately scar the skin and, even the psyche.<sup>1</sup>

Retinoids ideally form the core of acne therapy. The situation as it stands today is that oral retinoids are teratogenic and are reserved for use in the severe forms of acne. Topical retinoids are preferred in the mild to moderated forms, however amongst the topical retinoids, tretinoin has been the only one available till recently and is in use since the past 20 years.

Adapalene is a novel mapthoic acid derivative, a new third generation retinoid and has a selective mode of action. It has a comedolytic, anti-proliferative and anti-inflammatory activity as well as is superior or

comparable to tretinoin, without the undesirable topical side-effects associated with tretinoin therapy, thus adapalene gel is a good choice in the treatment of acne vulgaris with less side-effects and high efficacy confirmed by numerous clinical studies.<sup>2,3</sup> The present study aims to compare the clinical efficacy and safety of topical adapalene gel and tretinoin cream in the treatment of acne vulgaris.

## METHODS

The study comprised of 80 patients clinically diagnosed as acne vulgaris attending the dermatology outpatient department of a teaching hospital in Central Mumbai with a primary objective to compare the clinical efficacy and safety of topical adapalene gel (0.1%) and Tretinoin cream (0.025%) in the treatment of acne vulgaris. The Institutional ethics committee approval was taken prior to the conduct of study.

Inclusion criteria included healthy adolescents above 12 years and adults with Grade I-III acne (non-inflammatory lesions-comedones, inflammatory lesions- papules, pustules <5, nodules <2) and not on any concomitant medications for other illness. Patients were excluded from the study if they had severe grade IV acne, known hypersensitivity to any of the ingredients present in the two study formulations or if they were pregnant or lactating.

Written informed consent was obtained from all patients prior to study enrollment and in cases of adolescent a verbal assent was taken. Patients in whom underlying diseases or other dermatological conditions that required the use of interfering topical therapy or systemic therapy, topical acne or anti-inflammatory treatment within the previous 1 week, systemic therapy for acne (other than oral retinoids) during the last 2 weeks and systemic retinoids taken during the last 3 months were not included in the study.

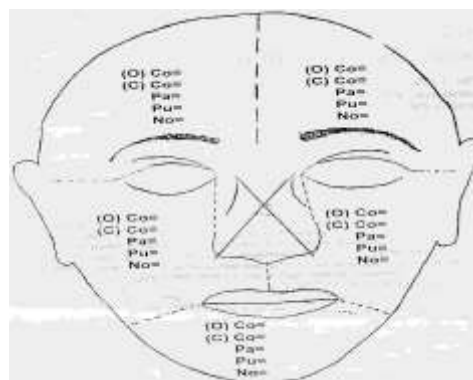
### Study method

A randomized double blind comparison study was done in patients fulfilling the inclusion criteria. A wash out period of one week for those using topical application and two weeks for those using systemic drugs for acne was given. The selected patients were randomly assigned to receive either of the two topical treatments according to their order of entry to the study. A detailed proforma was prepared and utilized to record history including age of onset of acne, duration of lesions, aggravating factors and previous therapy along with history of allergy to any product was included. In all these cases a general and cutaneous examination was carried out and the type and distribution of the acne lesions was recorded.

### Lesion counts

Lesions on the face were graded to estimate the overall severity and simultaneously, the individual types of

lesions were separately counted and total score obtained so as to quantify the improvement in each type of lesion. Acne lesions were counted by Leeds technique of Burke and Cunliffe which involved counting of all the individual lesions such as non-inflammatory lesions (comedones), inflammatory lesions (papules, pustules, nodules).<sup>4</sup> These were counted on the whole face i.e including forehead, right malar area, left malar area, chin and nose. A total count or score of the lesions on the face was obtained for individual lesions and as well as combining all individual areas (Figure 1).



**Figure 1: Facial template.**

Distribution of the acne lesions was recorded. The face is divided into five segments and counts were recorded of each lesion type within each template: Open comedones, closed comedones, papules, pustules and nodule.

### Grading of acne

Acne was graded according to a modification of Pillsbury's scale from grade I to IV.

*Modified Pillsbury's scale for grading of acne vulgaris.*<sup>5</sup>

Grade I: Open and closed comedones and inflamed open comedones. A few occasional papules may be seen.

Grade II: Comedones, papules and superficial pustules.

Grade III: Comedones, papules, superficial or deep pustules and cysts

Grade IV: Inflamed cysts in addition to those noted under Grade I to III, patients may have extensive interconnecting sinusoids and severe scarring.

### Treatment

Out of the 80 patients, 40 patients were randomly assigned to drug A (using tretinoin cream 0.025 % and the remaining 40 patients assigned to drug B (using adapalene gel 0.1%). Patients were asked to apply the study product to their face once daily at bed time for a period of 8 weeks (2 months).

**Study evaluations:**

Patients were scheduled for visits: a baseline visit followed by four visits at 2<sup>nd</sup>, 4<sup>th</sup>, 6<sup>th</sup> and 8<sup>th</sup> week after the start of the treatment, respectively.

Efficacy was determined by evaluating non-inflammatory lesions (comedones) and inflammatory lesions (papules, pustules, nodules) counts, at each visit for the assessment of improvement. A safety evaluation was carried at each scheduled visit with scoring of the following parameters i.e. burning, erythema, scaling and dryness on 0-3 scale as follows: 0-none, 1-mild, 2-moderate, 3-severe.

Global assessment of improvement in lesions was evaluated as percentage reduction utilizing four categories: 1) Excellent = >76%, Good = 51-75%, Fair = 26-50%, poor = <25%.

**Result Analysis**

*Efficacy*

To compare the effect of both the drugs i.e. drug A and drug B by evaluating the number of lesions (comedones and inflammatory lesions) that have decreased and which were calculated in percentages at different evaluation times against the number of lesions at baseline after starting application of both the drugs. Paired T-test was applied to compare the significance of difference between the observed percentage reduction in lesions between drug A and drug B which gives the efficacy of drug in comparisons at all-time intervals i.e. at 2 weeks, 4 weeks, 6 weeks and 8 weeks.

*Safety*

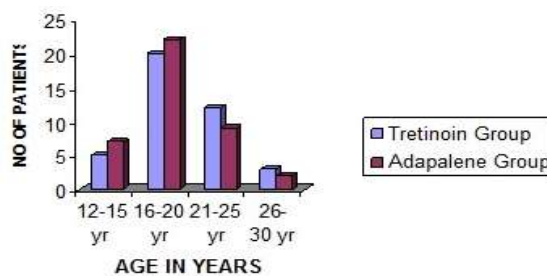
To compare statistically significant difference between the number of patients who experienced side effects (burning, erythema, scaling, dryness) and those who did not experience side effects after starting drug A and drug B. Chi-square test was applied at all time intervals separately i.e. at 2 weeks, 4 weeks, 6 weeks and 8 weeks to compare the relative safety of drugs.

**RESULTS**

The number of patients included in the study were 80 out of which 40 patients were on drug A (tretinoin cream 0.025%) and remaining 40 patients were on drug B (adapalene gel 0.1%). There were 8 patients who dropped out in the study number of patients included in the study of which 5 (3 in tretinoin group and 2 in adapalene group) dropped because of skin irritation and 3 were lost to follow up. There were no statistically significant differences at the baseline between the groups with regards to age and sex distribution of patients. The peak incidence of acne in 80 patients was in the age group 16-20years, i.e. 42 patients, which correlates with the observation of other workers.<sup>7</sup> This is attributed to the fact that acne is mainly the disease of adolescence, since this

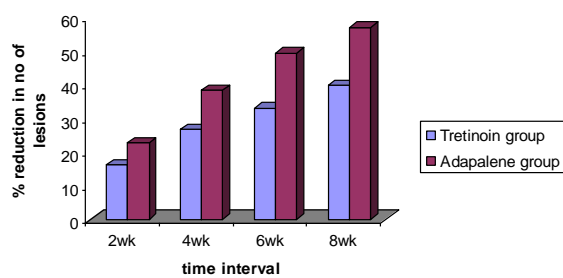
is the age of sexual maturity.<sup>8</sup> 15 patients out of a total of 37 (40.5%) gave history of premenstrual exacerbation signifying importance of the influence of hormones on the pilosebaceous unit.

3 patients had grade I acne lesions, 72 patients had grade 2 acne lesions and 5 patients had grade 3 acne lesions. The percentage of patients showing an improvement in their disease increased at each evaluation time-point. Starting at weeks 2 and 4, adapalene gel produced numerically greater lesion reductions than did tretinoin cream for all lesion types.

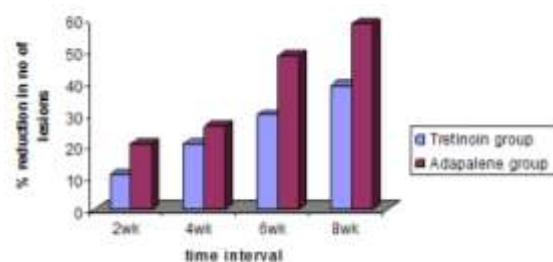


**Figure 2: Age distribution of patients.**

At week 8, the mean percent reduction in the total lesion counts compared with baseline was 58% versus 40% for mean total lesions (p <0.001) (Figure 2); 57% versus 40% for non-inflammatory lesions (p <0.001) (Figure 3); 58% versus 39% for inflammatory lesions (p <0.001) (Figure 4) in adapalene gel and tretinoin cream treatment groups, respectively.

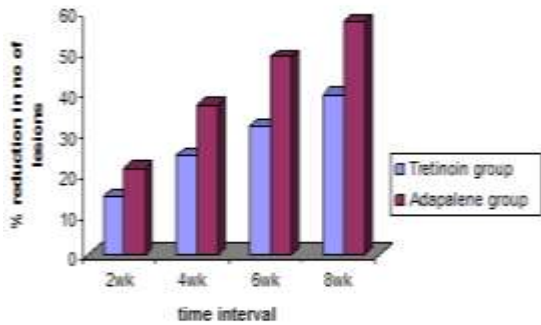


**Figure 3: % Reduction in comedones versus time interval.**



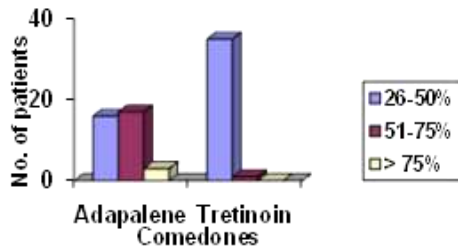
**Figure 4: % Reduction in number of inflammatory lesions.**

Cutaneous side effects were limited to a mild "retinoid dermatitis" occurring in both treatment groups; however, patients treated with adapalene gel tolerated this therapy statistically significantly better than those treated with tretinoin cream. Evaluation of facial skin tolerance parameters showed significant differences between the two treatments and was in favour of adapalene as compared to tretinoin. There were no systemic side-effects.



**Figure 5: % Reduction in number of total lesions.**

Improvement in non-inflammatory lesions was graded in the adapalene group as moderate (16 patients), good (17 patients) and excellent (3 patients), whereas that in the tretinoin group was graded as moderate (35 patients), good (1 patient) and excellent 0 patients (Figure 6).



**Figure 6: Improvement in comedones.**



**Figure 1a: 19 years old female patient on tretinoin cream having numerous inflammatory papules and few comedones at week 0.**



**Figure 1b: 19 years old female patient showing minimal reduction in acne lesions on tretinoin cream at week 8 (Side view).**



**Figure 1c: 19 years old female patient showing minimal reduction in acne lesions on tretinoin cream at week 8 (Front view).**



**Figure 2a: 24 years old female with numerous inflammatory lesions on adapalene gel at week 0 (Front view).**



**Figure 2b: 24 years old female on adapalene gel at week 0 (Side view).**



Figure 2c: 24 years female showing reduction in acne lesions at week 4.



Figure 2d: 24 years female patient showing more than 75% reduction in acne lesions at week 8.

Improvement in inflammatory lesions in adapalene group was graded as moderate = 13 patients, good = 20 patients and excellent-3 patients as compared to the tretinoin group with moderate = 32 patients, good = 3 patients and excellent = 1 patient (Figure 7) (Table 1). Difference in the two groups was statistically highly significant ( $p < 0.005$ , paired t-test). In our study the difference in reduction of inflammatory lesions between the two treatment groups was statistically highly significant in favour of adapalene gel ( $p < 0.01$ ) at week 4 and very highly significant ( $p < 0.001$ ) at 6 weeks and 8 weeks of follow-up in this study. No major adverse events were seen.

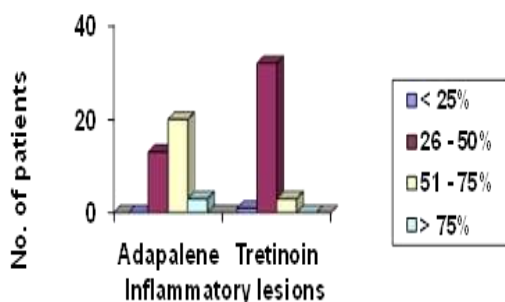


Figure 7: Improvement in inflammatory lesion.

Table 1: Global assessment of lesions between the two drug groups (tretinoin group and adapalene group).

Lesions	Improvement	Adapalene group	Tretinoin group
		No. of patients	No. of patients
Comedones	26-50%	16	35
	51-75%	17	1
	>75 %	3	0
Inflammatory lesions	≤ 25%	-	1
	26-50%	13	32
	51-75%	20	3
	>75 %	3	0

(0-25%=Poor; 26-50%=Fair; 51-75%=Good; >76%=Excellent)

### DISCUSSION

Finding the ideal acne product is a daily clinical challenge for the dermatologists and the use of effective and well-tolerated product is important for the patient compliance. The broad anti-acne activity and safety profile of topical retinoids justifies their use as a first-line treatment in most types of non-inflammatory and inflammatory acne. These agents target comedogenesis by normalizing desquamation of the follicular epithelium, preventing the formation of new microcomedo precursor lesions thus minimizing the formation of both inflammatory acne lesions and comedones. Several randomized controlled trials conducted by Cunliffe et al, Shalita et al, Dunlap et al, Grosshans et al clinical trials have compared adapalene with tretinoin, and a meta-analysis has been conducted of 5 trials involving a total of 900 patients (Table 2).<sup>9-11</sup> After 12 weeks of therapy, results showed that both agents were equally effective in reducing the total number of acne lesions, but adapalene had a faster onset of action, and was associated with significantly less skin irritation. As demonstrated in this study adapalene gel (0.1 %) produced statistically significant reduction in comedones, inflammatory lesions and total lesions count, and was also better tolerated than tretinoin cream (0.025%). These results confirmed the very good tolerance of adapalene that has already been reported in other studies done in the western literature.

Poor patient compliance is one of the main reasons for treatment failures in acne. The main drawback to topical retinoids in the treatment of acne has been the typical irritation that accompanies their use. In this study due to irritation 5 patients dropped out of study (3 in tretinoin group and 2 in adapalene group) however signs and symptoms of skin irritation were mostly mild to moderate in severity and transient in nature. Several comparative studies have shown adapalene to have a superior cutaneous safety profile as compared to different formulations (gel, cream and micro-sphere gel) of tretinoin as well as isotretinoin gel.<sup>12,14-17</sup> Although mild irritation was reported for both treatment groups specific irritancy tests have confirmed that adapalene has a low potential for causing skin irritation and causes significantly less irritation than tretinoin. This may be because adapalene has intrinsic anti-inflammatory activity that may lessen the irritant effect and enhance tolerability.

**Table 2: Summary of individual studies comparing adapalene gel 0.1% and tretinoin gel 0.025%.<sup>9-11</sup>**

Study	Study design	Patient Population	Results
Alirezai et al	Investigator blind randomized parallel- group, multicenter 12 week treatment period	89 patients mild to moderated acne (Grade 1-5, Burke-Cunliffe's scale); 59 (adapalene 0.1% gel, and 0.3% gel) 30 (tretinoin gel 0.025 %)	Comparable efficacy; adapalene demonstrates superior tolerability.
Shalita et al	Investigator blind randomized parallel- group, multicenter 12 week treatment period	323 patients with mild to moderate acne (grade 2 and 3 ); 149 (adapalene gel 0.1 %), 139 (tretinoin 0.025% gel), 35 discontinued	Adapalene demonstrates more rapid and superior efficacy (weeks 2, 4, 12); and superior tolerability.
Berger et al	Investigator blind randomized parallel- group, multicenter 12 week treatment period	180 patients with mild to moderate acne (grades 1-5); 72 (adapalene gel 0.1 %), 72 tretinoin gel (0.025%) 36 vehicle	Adapalene demonstrates significant better improvement in non-inflammatory lesions (week 12), inflammatory lesions (week 2); tretinoin demonstrates significantly worse burning at week 12
Cunliffe et al	Investigator blind randomized parallel- group, multicenter 12 week treatment period	268 patients with mild to moderate acne( grade 1-5) 134 adapalene (0.1 % gel )134 tretinoin (0.025 % gel)	Comparable efficacy : adapalene demonstrates superior tolerability
Grosshans et al	Investigator blind randomized parallel- group, multicenter 12 week treatment period	105 patients with mild to moderate acne (grade 1-5) 52 adapalene (0.1 % gel) 53 tretinoin (0.025 % gel)	More rapid response with adapalene gel on inflammatory lesions (week 1): comparable effects at week 12: adapalene gel demonstrates superior tolerability

The development of adapalene signifies the onset of a new era in topical retinoid therapy-an era of "low-irritancy retinoids."<sup>18</sup>

There are several possible explanations for the lower degree of skin irritation produced by adapalene:

- Different retinoic acid receptor (RAR) subtype binding pattern. Adapalene is relatively selective for the RAR $\beta$  and somewhat for the RAR $\gamma$  receptors, whereas tretinoin binds all three subtypes. Also, adapalene does not bind to (CRABP).
- Different molecular structure. Different retinoids can produce cytotoxic effects in keratinocytes to a degree that does not necessarily correlate with receptor binding activity.<sup>7</sup> In the case of tretinoin, a long-chain organic acid, there could be nonspecific interference with cell membrane function, whereas adapalene is a more neutral molecule.
- Adapalene is more chemically stable than tretinoin and does not break down in the presence of light, as does tretinoin. It is possible that some break-down products of tretinoin (which have not been completely identified) may be irritant.

- Adapalene has intrinsic anti-inflammatory properties that are superior to tretinoin in several experimental models.

## CONCLUSION

Adapalene gel is a cosmetically acceptable gel formulation, novel retinoid with anti-inflammatory activity and has superior efficacy in reducing non-inflammatory and inflammatory lesions as compared to 0.025% tretinoin cream and superior tolerability versus tretinoin leading possibly to better compliance.<sup>19</sup>

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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