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Comparative Clinical Study of Efficacy and Safety of Benzoyl Peroxide Gel Versus Adapalene Gel as Monotherapy for the Treatment of Mild to Moderate Acne Vulgaris

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Original Article

Summary

Background*: Acne vulgaris disease is a common dermatological public health problem affecting adolescents and young population. Many topical agents are used for treatment of mild to moderate acne vulgaris with different efficacy and adverse effects.*

Objective: To compare between Adapalene and Benzoyl peroxide for the treatment of mild to moderate acne and to assess the efficacy, sid effects and tolerability of both of them.

Methodology*: A randomized comparative study carried out in Erbil Dermatology Teaching center in Erbil city-Kurdistan region/Iraq during the period from 1st of April to 31st of August, 2021 included one hundred patients with mild to moderate acne vulgaris and randomized into two equal groups to be treated either with Adapalene or Benzoyl peroxide, all patients were followed up and the treatment outcomes were reported*

Results*: The mean number of inflammatory lesions, non-inflammatory lesions, total lesions and acne scores for patients of both groups were significantly reduced after 8 weeks treatment duration ($p<0.001$). However, a significant higher decline in number of non-inflammatory and total lesions in Adapalene group than benzoyl peroxide group. Similarly, skin oiliness decrease after 4 or 8 weeks treatment with Adapalene was significantly higher than oiliness decrease for patients treated with Bezoyl peroxide after 4 or 8 weeks. The adapalene application is related to moderate dryness and peeling, while benzoyl peroxide is related to itching or burning.*

Conclusions*: Topical Adapalene therapy is more efficacious and tolerable than Benzoyl peroxide in management of mild to moderate acne vulgaris*

Keywords: *Acne vulgaris, Adapalene, Benzoyl peroxide.*

1. INTRODUCTION

The acne vulgaris is a chronic inflammatory self-limiting disease affecting pilosebaceous unit located commonly in face, chest, back and upper arms. The etiology of acne vulgaris is related to hypersensitivity of sebaceous glands to androgens aggravated by Propionibacterium acnes and inflammatory effects. Many risk factors are related to pathogenesis of acne vulgaris such as genetic factors, medications, sunlight exposure, occlusive wears and endocrinal abnormalities (1-3). It is an adolescence disease that could continue to middle of age with predominance of male gender. In pubertal phase, the sebum secretion is increased leading to under effect of androgens leading to hyperproliferation of follicular epidermis and sebum retention that complicated by inflammation. This process is aggravated by high sugar content food, oily cosmetics, premenstrual hormonal effect and anxiety (4). These changes lead to dilating the follicle and plugging of keratin, however, some cases showed opened comedone. The acne lesion is combined by bacterial infection and inflammation. For severe cases, the large acne lesions were complicated by fibrosis and scarring 4. Acne vulgaris is an urban disease with racial differences as severe acne more prevalent in Asian and African population, while white population mostly appears with mild acne. Clinically, the acne is presented with comedones, papules, pustules, nodules in the skin of face, chest, back and upper limbs. Severe acne is developed in 20% of cases and may end with scarring (5, 6). The severity of acne vulgaris is assessed by many methods, the most applicable one is investigator global assessment of acne (IGA) which classified the disease into (clear, almost clear, mild, moderate and severe) (7).

The diagnosis of acne vulgaris is complemented by history, clinical examination and in some cases with hormonal assessment. Management of acne included lifestyle changes, diet modifications, avoidance of risk and aggravating factors, weight reduction and treatment with topical or systemic therapy or adjuvant therapy. The topical therapy is composed of antibiotics, retinoid, azelaic acid, dapsone and benzoyl peroxide which used either as monotherapy or in combination. The common adverse effect of topical therapy is skin irritation presented as dryness, erythema, scale, burning and itching 8. Systemic therapy of acne vulgaris involves the use of systemic antibiotics and hormonal therapy. Treatment of mild to moderate acne vulgaris is concentrated on application of topical therapy with use of systemic antibiotics in some moderate cases. Topical therapy for used is preferred to be a

combination of antibiotics and benzoyl peroxide or antibiotics with adapalene (8, 9).

The benzoyl peroxide (BPO) is a topical therapy widely used in European and American countries for treatment of acne vulgaris (10). It has bactericidal effects against Cutibacterium acnes and changed to benzoic acid after absorption. It has mild sebostatic and keratolytic effects and its efficacy increased after combination with other topical therapy (11, 12). The benzoic acid is targeting with oxygen free radicals the bacterial protein and lowering Propionibacterium acnes, lipids and fatty acids (13). The main side effects of BPO are discoloration of skin, mild skin dryness, erythema and scaling (14).

Adapalene is a third generation of topical retinoid used in treatment of acne vulgaris. The adapalene retinoid topical therapy is used for multiple skin diseases like melasma, post-inflammatory hyperpigmentation, alopecia areata and others (15, 16). in addition to its role in management of infection, cancer and neurological disorders (16). The retinoids in general adjusted the epidermis development and differentiation, enhances the humoral and cellular immunity, reducing inflammatory reaction and lowering the proliferation of cells (17). The adapalene is active metabolite stimulates the genetic changes and destruction of keratinocytes leading to decrease of micro-comedone development, peeling mature comedone with anti-inflammatory role (16). Common side effects of topical adapalene are photosensitivity, skin irritation, dryness of skin, itching, redness and burning that are commonly mild (18). Acne vulgaris is the common dermatological disorder presenting to outpatients clinics in Iraq 19. It is accompanied with low quality of life among young population in Erbil city, especially among severe form of the disease (20). However, high proportion of acne vulgaris patients in Erbil city were presented with mild to moderate severity with predominance of female gender (21). Multiple treatment modalities are applied in management of acne vulgaris patients in Iraq and Kurdistan region including both topical and systemic therapies, however, little number of literatures searching the efficacy and safety of the topical treatments. This study aimed to compare between Adapalene and Benzoyl peroxide for the treatment of mild to moderate acne and to assess the efficacy, side effects and tolerability of both of them.

2. PATIENTS and METHODS

This study was a randomized comparative study carried out in Erbil Dermatology Teaching center in Erbil city-Kurdistan region/Iraq during the period of four months from 1st of April to 31st of August, 2021. All patients with acne vulgaris presented to outpatients' clinic of Dermatology center were the study population. Inclusion criteria were patients aging more than 12 years regardless of gender with mild to moderate acne vulgaris. Exclusion criteria were patients with younger age, severe acne vulgaris, truncal acne vulgaris lesions, pregnant females, patients on systemic retinoid, history of hypersensistivity to retinoid and patients refused to participate in the study. The study ethics were implemented in regard to Helsinki Declaration by documented agreement of patients, approved by ethical committee in Kurdistan Board for Medical Specialties, free to withdrawal from study and management of any adverse effect of both treatments. A sample of one hundred mild to moderate acne vulgaris patients was enrolled in present study and randomized into two groups (50 acne vulgaris patients were treated by Adapalene and other 50 patients were treated by Benzoyl peroxide).

Information of patients was collected directly by researchers through direct interview and subsequently by phone calling through a prepared questionnaire designed by the researchers. The questionnaire included patients sociodemographic characteristics (age, gender and occupation), acne vulgaris characteristics (Investigator Global Assessment acne score, skin type and family history of acne), outcome of treatment at baseline, after 4 weeks and after 8 weeks of treatment (number of inflammatory, non-inflammatory and total lesions, IGA acne score and skin oiliness), adverse effect of each treatment (itching or burning, erythema, dryness and peeling) and patients satisfaction (very satisfied, satisfied, don’t know and dissatisfied). The acne vulgaris diagnosis was done by the researchers according to presence of comedonal and inflammatory lesions of acne and used IGA score to detect the severity of acne just (mild and moderate acne). The researcher started the treatment applied for patients in each group after explaining the effect, outcome and expected adverse effects for them. The topical Adapalene used was ADOLIN gel 1% concentration by Avalon Pharma (Indian origin-30 gm) applied once daily after washing the skin with avoidance of eyes, lips and mucous membranes, while the topical Benzoyl peroxide used was Bonzyol gel 5% concentration by WAVE

Company (Indian origin-30 gm) applied once to two times daily. The outcome of each treatment was measured through following up the patients after 4 weeks and after 8 weeks of treatment by phone calling and sending clear pictures of skin lesions by phone to the researcher in addition to final second visit to evaluate the outcome and assessing the patients satisfaction.

The patients' information were entered and interpreted statistically by SPSS program-26. Suitable statistical tests for data (Chi square test, Fishers exact test, independent sample t-test and repeated measures ANOVA test) were implemented accordingly and p value of ≤0.05 was significant.

3. RESULTS

A total of 100 patients were enrolled in this study and were assigned equally into two groups, the mean age of patients was (23.9 years). Both studied groups were almost matched for their baseline characteristics, (P>0.05), (**Table 1**). The acne vulgaris characteristics such as Investigator Global Assessment (IGA) acne score, skin type and family history of acne were not significantly different between acne patients treated with different treatment types. (**Table 2**) . As shown in (**Table 3**), the means of inflammatory lesions count, non-inflammatory lesions count, total lesions count and IGA acne score of acne vulgaris patients treated by Adapalene were significantly reduced after 8 weeks of treatment (p<0.001). Means of inflammatory lesions count, non-inflammatory lesions count, total lesions count and IGA acne score of acne vulgaris patients were significantly decreased after 8 weeks treatment by Benzoyl peroxide (p<0.001). The mean difference in inflammatory lesions after 8 weeks of treatment by Adapalene was significantly not different than that for treatment by Benzoyl peroxide (p=0.2). Mean difference in non-inflammatory lesions count was significantly higher for patients treated by Adapalene (p<0.001). The mean difference in total lesions count was significantly higher for patients treated by Adapalene than patients treated by Benzoyl peroxide (p=0.006). Mean difference in IGA acne score after 8 weeks treatment was significantly higher for patients treated by Adapalene (p<0.001). (**Table 4)**.

Baseline skin oiliness was equal for both treatment groups. Skin oiliness decrease after 4 weeks treatment with Adapalene was significantly higher than oiliness decrease for

patients treated with Bezoyl peroxide after 4 weeks (p<0.001). Similarly, the skin oiliness decrease after 8 weeks treatment with Adapalene was significantly higher than oiliness decrease for patients treated with Bezoyl peroxide after 4 weeks (p<0.001). (**Table 5**)

The mild to moderate itching or burning was significantly related to patients treated by Benzoyl peroxide (p<0.001). The erythema adverse effect is not significantly different between patients treated by Adapalene or Benzoyl peroxide (p=0.5). The moderate dryness and peeling was significantly more among acne patients treated by Adapalene (p<0.001). The patients' satisfaction was not significantly different between patients treated by Adapalene or Benzoyl peroxide (p=0.06), although the dissatisfaction was present among 8% of patients treated by Adapalene and dissatisfaction was present in 20% of patients treated by Benzoyl peroxide. (**Table 6**)

Table 1. Socio-demographic characteristics of patients according to treatment types.

Variable		**Treatment types**				**P**
		Adapalene		**Benzoyl**		
		No.	**%**	**No.**	**%**	
Age	12 - 24	46	92.0	41	82.0	0.130
	24 - 35	4	8.0	9	18.0	
Gender	Male	29	58.0	33	66.0	0.410
	Female	21	42.0	17	34.0	
Occupation	Student	30	60.0	26	52.0	0.380
	Housewife	4	8.0	7	14.0	
	Governmental employee	1	2.0	4	8.0	
	Private employee	15	30.0	13	26.0	

Table 2. Distribution of acne vulgaris characteristics according to treatment types.

Variable		Treatment types				P
		Adapalene		Benzoyl		
		No.	%	No.	%	
IGA acne score	Grade 1	10	20.0	12	24.0	0.710
	Grade 2	16	32.0	18	36.0	
	Grade 3	24	48.0	20	40.0	
Skin type	Oily	28	56.0	25	50.0	0.740
	Dry	4	8.0	6	12.0	
	Combination	18	36.0	19	38.0	
Family history of acne	Yes	17	34.0	21	42.0	0.410
	No	33	66.0	29	58.0	

Table 3. Outcome measures of each treatment type after eight weeks treatment.

Group	Measures	Baseline	After 4 weeks	After 8 weeks	P
		Mean ±SD	Mean ±SD	Mean ±SD	
Adapalene	Inflammatory lesions	28.7 ± 10.9	31 ± 13	17.5 ± 8	<0.001
	Non-inflammatory lesions	38.1 ± 20.3	31.2 ± 17.6	18.9 ± 13.1	<0.001
	Total lesions	66.6 ± 27.4	62.3 ± 27.1	36.2 ± 19.3	<0.001
	IGA acne score	2.2 ± 0.7	2.2 ± 0.8	1.4 ± 0.67	<0.001
Benzoyl peroxide	Inflammatory lesions	27.6 ± 13	21.2 ± 10.5	14.7 ± 8.3	<0.001
	Non-inflammatory lesions	36 ± 20.4	30.9 ± 17.8	26 ± 14.9	<0.001
	Total lesions	63.7 ± 30.5	51.9 ± 25.4	40.6 ± 20.7	<0.001
	IGA acne score	2.1 ± 0.79	2 ± 0.8	1.7 ± 0.9	<0.001

Table 4. Distribution of outcome measures difference after treatment according to treatment types.

Measures	Treatment types		P
	Adapalene	Benzoyl peroxide	
	Mean ± SD	Mean ± SD	
Inflammatory lesions	11.18 ± 7.6	12.49 ± 6.5	0.200
Non-inflammatory lesions	19.24 ± 10.7	10 ± 7.2	<0.001
Total lesions	30.4 ± 14.1	23 ± 12	0.006
IGA acne score	0.84 ± 0.54	0.42 ± 0.3	<0.001

Table 5. Changes in skin oiliness change after treatment in both studied groups

Time of assessment	Reduction in skin oiliness	Treatment types				P
		Adapalene		Benzoyl peroxide		
		No.	%	No.	%	
Baseline	No change	50	100.0	50	100.0	1.00
After 4 weeks	25%	26	52.0	45	90.0	<0.001
	50-70%	22	44.0	5	10.0	
	>70%	2	4.0	0	-	
After 8 weeks	25%	14	28.0	29	58.0	0.002
	50-70%	20	40.0	17	34.0	
	>70%	16	32.0	4	8.0	

Table 6. Distribution of drugs adverse effects and patients satisfaction according to treatment types.

Variable		Treatment types				P
		Adapalene		Benzoyl peroxide		
		No.	%	No.	%	
Itching or burning	None	26	52.0	6	12.0	<0.001
	Mild	16	32.0	22	44.0	
	Moderate	8	16.0	22	44.0	
Erythema	None	12	24.0	8	16.0	0.500
	Mild	25	50.0	25	50.0	
	Moderate	13	26.0	17	34.0	
Dryness and peeling	None	8	16.0	23	46.0	<0.001
	Mild	19	38.0	20	40.0	
	Moderate	23	46.0	7	14.0	
Patients satisfaction	Very satisfied	15	30.0	7	14.0	0.060
	Satisfied	25	50.0	22	44.0	
	Don't know	6	12.0	11	22.0	
	Dissatisfied	4	8.0	10	20.0	

4. DISCUSSION

The acne vulgaris affected about 80% adolescents globally. Generally, the topical treatment of acne vulgaris needs longer duration therapy and adherence of patients to achieve higher outcomes in addition to satisfaction of patients (22).

The present study showed higher efficacy and safety of Adapalene as compared to benzoyl peroxide in treatment of mild to moderate acne vulgaris. This finding is consistent with results of Dubey and Amane randomized, open-labelled, prospective study in India which reported that adapalene had better efficiency and safety than benzoyl peroxide in management of mild to moderate acne vulgaris (23). Our study findings are close to results of Wali and Almosuly comparative study in Iraq (Erbil city) on 89 patients with mild to moderate acne vulgaris which reported that combination of topical clindamycin and

adapalene was more effective than clindamycin solution alone 24. Although these findings, Gold et al. (25) multicenter, randomized, double blind, parallel-group, active- and vehicle-controlled study in USA on 1668 patients with different severity grades of acne vulgaris (415 treated by adapalene-BPO combination gel, 420 treated by adapalene alone, 415 treated by BPO alone and 418 treated by vehicle) found that combination topical therapy included adapalene-BPO is highly effective than using each of adapalene or benzoyl peroxide alone in management of acne vulgaris. On other hand, previous open-labeled prospective Turkish study by Korkut and Piskin revealed that adapalene or benzoyl peroxide monotherapy are effective and tolerated agents in management of acne vulgaris without superiority of combination of both of them on their efficacy alone (26). In our study, the means of inflammatory lesions, non-inflammatory lesions, total lesions numbers and IGA acne scores for patients treated with adapalene and benzoyl peroxide were significantly reduced after 8 weeks treatment duration ($p<0.001$). These findings are in agreement with results of Gold et al 27 randomized double blind controlled study in USA and Yang et al (28) meta-analysis study in China which all revealed the effectiveness each of adapalene and benzoyl peroxide alone in reducing the inflammatory, non-inflammatory and total lesions with effect on reducing the IGA acne score. Our study showed a significant higher decline in number of non-inflammatory and total lesions among acne patients treated with adapalene as compared to benzoyl peroxide ($p<0.001$, $p=0.006$, respectively). These findings are similar to results of Babaeinejad and Fouladi single-center, randomized, double-blind, clinical trial on 60 patients with mild acne vulgaris (30 patients treated by adapalene and 30 patients treated by benzoyl peroxide) which showed that although the adapalene or benzoyl peroxide could reduce the number of inflammatory, non-inflammatory and total lesions alone, but the effect of adaplalene in reducing the non-inflammatory and total lesions was more than benzoyl peroxide (29). Inconsistent to our findings, Nascimento et al. (30) in their single-blind comparative study on 178 patients with acne vulgaris , 89 patients treated by adapalene and 89 patients treated by benzoyl peroxide) for 11 weeks reported higher efficacy of benzoyl peroxide-4% in reduction of inflammatory and non-inflammatory lesions at 2-5 weeks of treatment than adapalene. This finding was also reported by Dubey and Amane study in India imp1 and explained this quick action of benzoyl peroxide to its potential cutaneous bactericidal effects that make it faster than adapalene (23). This inconsistency might be due

to differences in benzoyl peroxide concentration and duration of treatment (23).

In present study, skin oiliness decrease after 4 or 8 weeks treatment with Adapalene was significantly higher than oiliness decrease for patients treated with Bezoyl peroxide after 4 or 8 weeks ($p<0.001$, $p=0.002$, respectively). Consistently, Endly and Miller study in USA 31 reported that retinoid topical treatments specifically adapalene is effective in reducing skin oiliness of acne vulgaris patients. In general, the adverse effects of both topical treatments are minor, however, our study showed mild to moderate itching or burning was significantly related to patients treated by Benzoyl peroxide ($p<0.001$). This finding coincides with results of Eichenfield et al. (32) study. Our study found that moderate dryness and peeling was significantly more among acne patients treated by Adapalene ($p<0.001$). This finding is similar to results of Percy study in India (33). The patients' satisfaction for both monotherapies was not significantly different, although the dissatisfaction was present among 8% of patients treated by Adapalene and dissatisfaction was present in 20% of patients treated by Benzoyl peroxide. This finding is parallel to results of Cook-Bolden study in USA (34) which reported higher satisfaction of patients with acne vulgaris to adapalene treatment. However, the satisfaction of patients is related to their adherence to treatment (34).

5. CONCLUSIONS

Topical adapalene therapy is more efficacious and tolerable than benzoyl peroxide in management of mild to moderate acne vulgaris. The adapalene treatment has higher efficacy in lowering number of non-inflammatory and total lesions, IGA acne score and skin oiliness than benzoyl peroxide. The adapalene application is related to moderate dryness and peeling, while benzoyl peroxide is related to itching or burning. This study recommended the Dermatologists to apply topical adapalene monotherapy in treatment of mild to moderate acne vulgaris.

Ethical Clearance: Ethical clearance and approval of the study are ascertained by the authors. All ethical issues and data collection were in accordance with the World Medical Association Declaration of Helsinki 2013 for ethical principles for medical research involving human subjects. Data and privacy of patients were kept confidentially.

Conflict of interest: Authors declared none

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