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Comparison of Salicylic Acid 40% vs. Salicylic Acid 30% with and without Oral Doxycycline in Treating Moderate Acne Vulgaris: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial

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Key words:
Acne vulgaris,
Doxycycline, Peel,
Salicylic acid

ABSTRACT

Aims Acne vulgaris is a cutaneous disorder that affects many individuals. Therapeutic modalities are various, with different outcomes. Chemical peels and antibiotics are effective and safe options for treating acne. This study aimed to compare the effects of 40% salicylic acid (SA) peel versus 30% SA peel, with and without doxycycline, in treating moderate acne vulgaris.

Materials & Methods In total, 78 subjects with moderate acne vulgaris were enrolled and divided into three groups. Group A received doxycycline plus SA peel 30%, Group B received SA peel 30% plus placebo, and Group C received SA peel 40% plus placebo. Outcomes were evaluated by a blinded dermatologist based on the number of lesions and the Michaelson Acne Score (MAS).

Finding The MAS, comedones, papules, and pustules decreased by the end of treatment in all groups. There was no difference among the three groups regarding the improvement of comedones, papules, and MAS. However, pustules significantly improved in Group A, compared to the other groups. Evaluation by a blinded dermatologist showed the best improvement in clinical manifestations in Group A.

Conclusion Doxycycline plus SA peel 30% had superiority to SA monotherapy (even with a higher concentration) in treating inflammatory lesions of acne vulgaris. Combining modalities with different mechanisms achieves better outcomes than monotherapy.

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طب داخلی روز
فصلنامه دانشگاه علوم پزشکی و خدمات درمانی گناباد

مقاله پژوهشی

مقایسه اسید سالیسیلیک ٤٠٪ در مقابل اسید سالیسیلیک ۳۰٪ با و بدون داکسی سایکلین خوراکی در درمان آکنه ولگاریس متوسط: یک کارآزمایی بالینی دوسوکور، تصادفی، کنترل شده با دارونما

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چکیده

هدف آکنه ولگاریس یک اختلال پوستی است که افراد زیادی را تحت تأثیر قرار می‌دهد. لایه‌برداری شیمیایی و آنتی‌بیوتیک‌ها گزینه‌های مؤثر و ایمنی برای درمان آکنه ولگاریس هستند. این مطالعه با هدف مقایسه اسید سالیسیلیک ۴۰٪ در مقابل اسید سالیسیلیک ۳۰٪ با و بدون داکسی سایکلین خوراکی در درمان آکنه ولگاریس متوسط انجام شد.

مواد و روش‌ها: در این مطالعه کارآزمایی بالینی هفتاد و هشت فرد مبتلا به آکنه ولگاریس متوسط ثبت‌نام و به سه گروه تقسیم شدند. گروه A، داکسی سایکلین به همراه لایه‌برداری SA 30%، گروه B، لایه‌برداری SA 30% به همراه دارونما و گروه C، لایه‌برداری SA 40% به همراه دارونما دریافت کردند. پیامدها توسط یک متخصص پوست که از گروه های مداخله اطلاع نداشت بر اساس تعداد ضایعات و امتیاز آکنه مایکلسون (MAS) ارزیابی شدند.

یافته‌ها: میزان MAS، کومدون‌ها، پاپول‌ها و پوستول‌ها در پایان درمان در همه گروه‌ها کاهش یافت. هیچ تفاوتی بین سه گروه از نظر بهبود کومدون‌ها، پاپول‌ها و MAS وجود نداشت. با این حال، پوستول‌ها در گروه A نسبت به سایر گروه‌ها به طور قابل توجهی بهبود یافتند. نتایج بهترین بهبود را در تظاهرات بالینی گروه A نشان داد.

نتیجه‌گیری: داکسی سایکلین به همراه لایه‌برداری SA 30% در درمان ضایعات التهابی آکنه ولگاریس نسبت به مونوتراپی SA (حتی با غلظت بالاتر) برتری بیشتری داشت. بنابراین این روش برای درمان آکنه ولگاریس متوسط پیشنهاد می شود.

کلیدواژه‌ها:
آکنه،
پیلینگ سالیسیلیک اسید،
داکسیسایکلین

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Introduction

Acne vulgaris is an inflammatory skin disorder affecting many adolescents. It presents with non-inflammatory comedones and/or inflammatory papules, pustules, and nodulocystic lesions that give rise to stress, depression, and social problems. Therapeutic options include antibiotics, retinoids, and chemical peels [1,2].

Variable	Time	Group A	Group B	Group C
Comedones	Baseline	27.84 ± 22.40	32.80 ± 23.69	34.53 ± 26.06
	Session 1	27.26 ± 20.18	27.42 ± 21.20	37.88 ± 30.57
	Session 2	23.69 ± 21.81	21.69 ± 17.75	27.80 ± 19.38
	Session 3	24.16 ± 21.82	18.30 ± 17.83	23.23 ± 13.93
	Session 4	17.45 ± 14.72	19.34 ± 17.59	23.57 ± 20.32
	Session 5	19.90 ± 15.16	18.09 ± 16.33	24.64 ± 21.39
	Session 6	18.73 ± 14.60	18.73 ± 16.04	27.37 ± 24.71
Papules	Baseline	28.38 ± 19.41	23.84 ± 14.16	24.65 ± 14.15
	Session 1	17.96 ± 12.76	18.42 ± 14.28	20.42 ± 10.90
	Session 2	17.96 ± 14.50	14.65 ± 13.63	15.96 ± 12.86
	Session 3	14.62 ± 10.74	11.34 ± 8.86	13.85 ± 9.59
	Session 4	13.08 ± 12.88	12.43 ± 9.99	10.15 ± 6.75
	Session 5	11.13 ± 8.01	10.95 ± 8.31	11.11 ± 5.84
	Session 6	12.60 ± 11.31	8.52 ± 7.11	13.50 ± 12.87
Michaelson Acne Score	Baseline	47.46 ± 25.0	45.78 ± 26.68	51.30 ± 30.40
	Session 1	36.21 ± 19.86	37.90 ± 21.02	45.51 ± 31.20
	Session 2	32.34 ± 19.36	28.03 ± 16.15	36.18 ± 22.78
	Session 3	30.62 ± 19.50	23.26 ± 15.44	30.04 ± 15.55
	Session 4	23.56 ± 16.97	24.54 ± 15.97	24.15 ± 16.38
	Session 5	24.54 ± 14.54	21.90 ± 13.35	29.08 ± 18.27
	Session 6	24.50 ± 13.98	18.75 ± 11.79	31.06 ± 18.73
Pustules	Baseline	2.0 (3.0)	2.0 (3.25)	3.0 (5.50)
	Session 1	1.0 (4.25)	2.0 (2.0)	1.50 (3.50)
	Session 2	1.0 (2.0)	0 (2.0)	2.0 (3.0)
	Session 3	1.50 (2.75)	1.0 (2.0)	2.0 (2.50)
	Session 4	0.50 (1.75)	1.0 (2.0)	0 (2.0)
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Chemical peeling is a safe and relatively inexpensive method for treating acne vulgaris [3]. It destroys the outer layers of damaged skin, speeding up the healing process using superficial, medium, or deep peels. The extent of injury varies depending on acid concentration, vehicle type, contact time, and buffering [4].

Salicylic acid (SA) is a beta-hydroxy acid with lipophilic,

keratolytic, and comedolytic properties. It aggravates desquamation by decreasing adhesion between corneocytes, mainly in the lipophilic upper layers of the stratum corneum [5]. In addition, SA is miscible with epidermal lipids and sebaceous gland lipids in hair follicles and possesses anti-inflammatory properties. Various SA concentrations have been used for unique dermatological conditions and cosmetics; concentrations of 20 to 30% are usually used for superficial chemical peeling of the face and as a therapeutic modality for acne vulgaris [6]. The efficacy and safety of higher concentrations have not been studied, making it unclear whether they improve outcomes or lead to more adverse effects.

Combination therapies often yield better outcomes in treating acne vulgaris than monotherapy. Doxycycline is a tetracycline derivative that is well-accepted in the treatment of acne vulgaris. It suppresses the growth of *Cutibacterium acnes*, thereby reducing bacteria-mediated inflammation [7]. Treating acne vulgaris with SA peel plus oral doxycycline has not previously been investigated. This study aimed to evaluate whether combining 30% SA with doxycycline provides better therapeutic outcomes for acne compared to simply increasing the concentration of SA alone. The objective was to determine which approach offers superior efficacy in managing acne.

Materials and Methods

Study Design

This study was a double-blind, randomized, placebo-controlled trial conducted from September 2021 to December 2022. The Institutional Ethics Committee approved the study protocol. The study protocol and objectives were explained to all participants. All patients filled out and signed the informed consent form, and the guardians of those under 18 also completed it.

Patients

We enrolled all patients aged ≥ 12 years, who attended our outpatient dermatology clinic and suffered from moderate acne based on a classification system by Vaishampayan et al. [8] (Table 1). Participants who were pregnant, breastfeeding, using anti-acne medications (within the past 30 days, isotretinoin, azithromycin, erythromycin, clindamycin, minocycline, benzol peroxide, adapalene, tretinoin, and dapsone), or had active or recurrent orolabial Herpes Simplex Virus infection, active dermatitis on the face, renal or liver dysfunction, or hypersensitivity to the study formulations were excluded.

Table 1. System of acne grading[8] by Vaishampayan et al.

Category	Description
Grade I (Mild)	Comedones and occasionally papules
Grade II (Moderate)	Comedones, many papules, and few pustules
Grade III (Severe)	Predominantly pustules, nodules, and abscesses
Grade IV (Cystic)	Mainly cysts or abscesses; widespread scarring

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Sample Size Determination

The sample size was determined using G*Power software (version 3.1.9.2) and the formula for comparing means between the two groups. Considering a type I error of 0.05, a test power of 0.80, and an effect size of 0.90 based on the pilot study, the required sample size was calculated to be 26 participants per group.

Treatment protocol

The patients were recruited by the convenience sampling method and then divided based on permuted block randomization into three groups: Group A was treated with oral doxycycline 100 mg daily (12 weeks) with SA peel 30% (six sessions across two-week intervals), Group B received SA peel 30% (six sessions across two-week intervals) and oral placebo daily, and Group C received SA peel 40% (six sessions across two-week intervals) and oral placebo daily.

A dermatologist performed salicylic acid peeling according to standard guidelines. Alcohol as an antiseptic was applied first, then SA 30% or 40% was used by an applicator onto the skin from the center to the periphery. The skin was rinsed with water after five minutes. The endpoint was pseudofrost formation (immediate whitening) within 30 seconds.

Clinical assessment of efficacy

Demographic characteristics (age, gender, skin type) were registered. Using documented photographs, a blinded dermatologist evaluated outcomes based on the Michaelson Acne Score (MAS) (Table 2). Clinical photographs of each patient were taken from the right, left, and front. The MAS and the number of comedones, papules, and pustules were recorded for each session. The dermatologist assessed the percentage of acne improvement from baseline to the end of treatment. Patient satisfaction was registered at the end of the study. Patients were followed for three months after the final treatment session to evaluate any side effects or recurrence.

Table 2. Acne severity as per the Michaelson Acne Score (MAS)

Lesion Type	Severity Index	Definition
Comedones	0.5	Horny follicular plug and pinhead-sized follicular papules
Papules	1	Infiltrated papules (2–8 mm)

Pustules	2	Pustules (42 mm) with surrounding inflammation
Infiltrates	3	Nodules and infiltrates (48 mm) and coalescent papules, where individual papules cannot be distinguished
Cysts	4	Lesions where infiltrate has broken down to form a discharging cyst

Data analysis

Statistical analysis was performed with Statistical Package for the Social Sciences (version 22). The standard deviation and mean of quantitative variables, and the number and percent of qualitative variables, were registered. The Kolmogorov-Smirnov test was applied to test normality. Categorical data were analyzed using the Chi-squared test, whereas continuous data were analyzed using one-way ANOVA. Linear regression was used to compare the response variable over time. A P-value of less than 0.05 was considered statistically significant.

Results

A total of 78 participants were recruited (26 patients in each group). The groups were comparable regarding age, sex, skin type, and disease duration. Demographic data and baseline characteristics are shown in Table 3.

Table 3. Baseline characteristics and demographic data of the participants, n (%) or Mean ± SD

Variable		Group A	Group B	Group C	*P*-value
Sex	Male	5(19.2)	6 (23.1)	4 (15.4)	0.78
	Female	21 (80.8)	20 (76.9)	22 (84.6)	
Skin type	III	5 (19.2)	8 (30.8)	9 (34.6)	0.43
	IV	21 (80.8)	18 (69.2)	17 (65.4)	
Age, years		19.69 ± 5.22	20.15 ± 2.41	19.26 ± 3.59	0.79
Acne duration, months		4.13 ± 4.01	5.73 ± 3.40	4.34 ± 2.67	0.19

Group A: doxycycline plus salicylic acid 30%; Group B: placebo with salicylic acid 30%; Group C: placebo with salicylic acid 40%. SD: standard deviation; n: number

Comedones

The mean number of comedones decreased across all groups following treatment (Fig. 1). It was 27.84 ± 22.40, 32.80 ± 23.69, and 34.53 ± 26.06 in groups A, B, and C, respectively, at baseline, falling to 18.73 ± 14.60, 18.73 ± 16.04, and 24.64 ± 21.39 at the end of the treatment (Table 4). There was no significant difference between the three groups at the end of the treatment (P>0.05). The linear regression test showed that the effect of time was significant, with the number of comedones falling over time in all treatment groups (P<0.001). However, the interaction effect of time and group was not significant, indicating no significant difference in comedone counts among the three groups (P>0.05; Table 5).

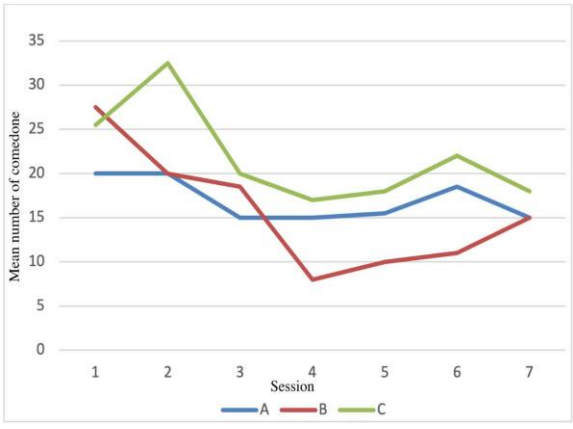

Figure 1. Trend of change in the mean number of comedones across treatment sessions

Papules

The mean number of papules also decreased in all three groups (Fig. 2), with no significant difference between them after the treatment (P>0.05; Table 4). Similarly, time had a substantial effect according to linear regression (P<0.001). However, the interaction effect of time and group was not significant (P>0.05; Table 5).

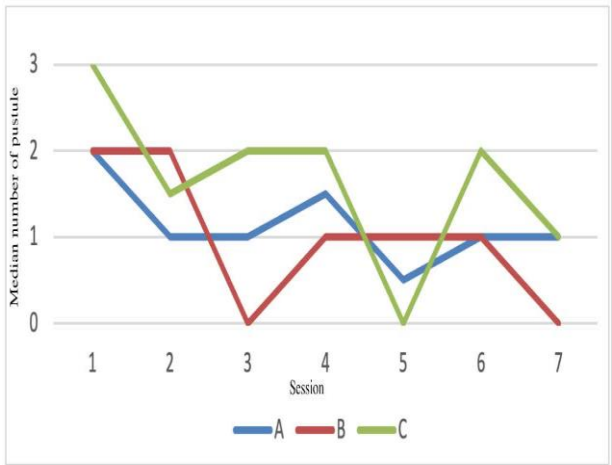

Figure 2. Trend of change in the mean number of papules across treatment sessions

Pustules

Similar to comedones and papules, a decrease in the median number of pustules was seen following treatment in all three groups (Fig. 3), with no significant

difference between the groups (P>0.05; Table 4). Again, linear regression confirmed the considerable effect of time on the pustule count (P<0.001). However, a unique finding was the significant interaction effect of time and group, where the pustule improvement was significantly greater in Group A relative to the other two groups (P<0.001; Table 5).

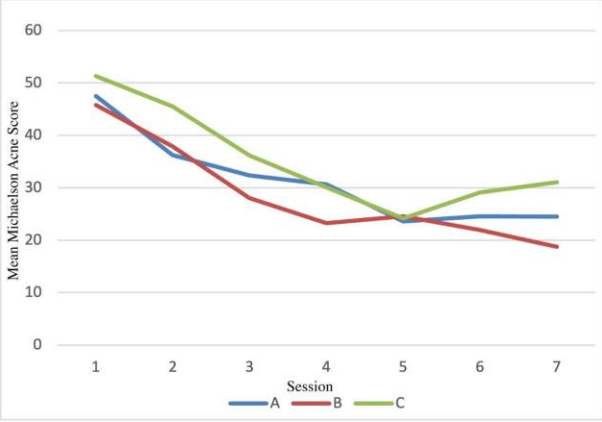

Figure 3. Trend of change in the mean number of pustules across treatment sessions
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Michaelson Acne Score (MAS)

The mean MAS decreased in all groups (Fig. 4), with no significant difference between the groups at the end of the treatment (P>0.05; Table 4). Linear regression analysis revealed a significant effect of time (P < 0.001), while no interaction effect was observed between time and group regarding the MAS (P > 0.05; Table 5). Figures 6-8 exhibit the results of the therapeutic interventions.

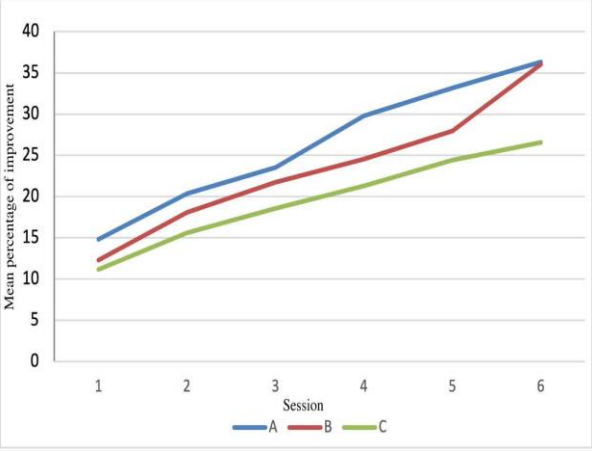

Figure 4. Trend of change in the mean Michaelson Acne Score (MAS) across treatment sessions
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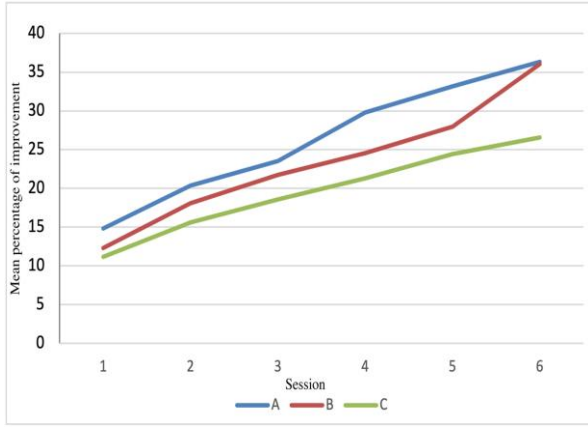

Figure 5. Improvement of acne according to the blinded dermatologist evaluation across treatment sessions
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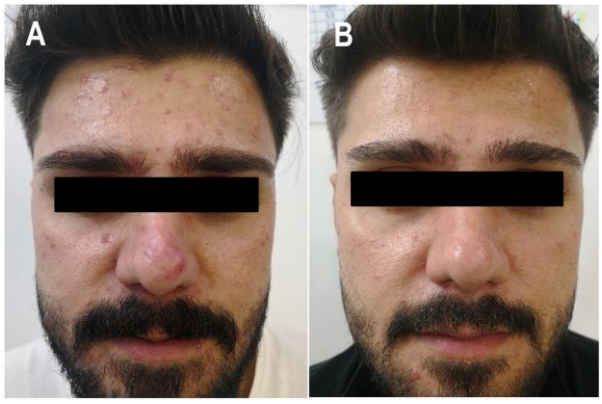

Figure 6. A patient who received salicylic acid 30% plus oral doxycycline: A, baseline; B, after treatment
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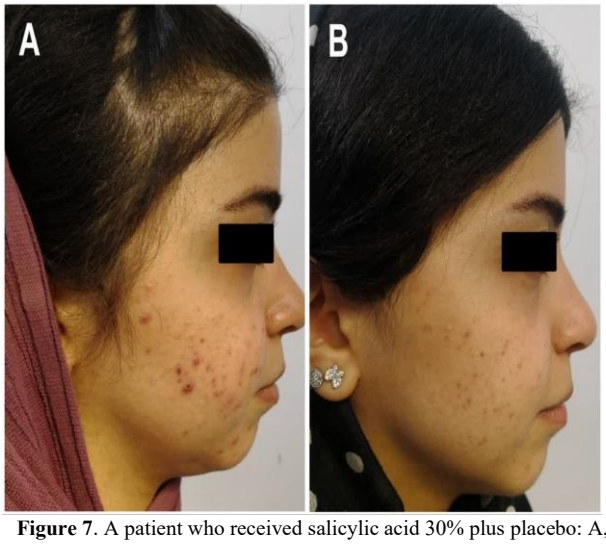

Figure 7. A patient who received salicylic acid 30% plus placebo: A, baseline; B, after treatment
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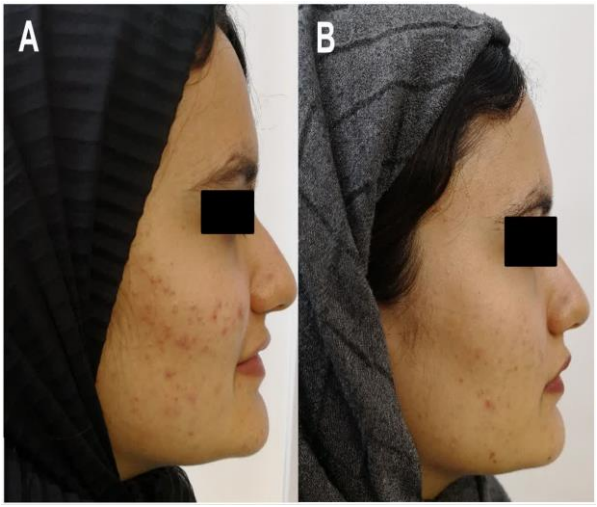

Figure 8. A patient who received salicylic acid 40% plus placebo: A, baseline; B, after treatment
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Evaluation by a blinded dermatologist

According to the evaluation by a blinded dermatologist, the mean percentage of improvement in acne increased across each session in all three groups, reaching 36.33 ± 16.41%, 36.05 ± 16.03%, and 26.56 ± 8.70% in groups A, B, and C at the end of the treatment, respectively (Fig. 5). The three groups showed no significant difference (P>0.05). Linear regression analysis reported that the mean percentage of improvement increased over time. The interaction effect of time and group was significant, with Group A achieving the best results (P<0.001; Table 6).

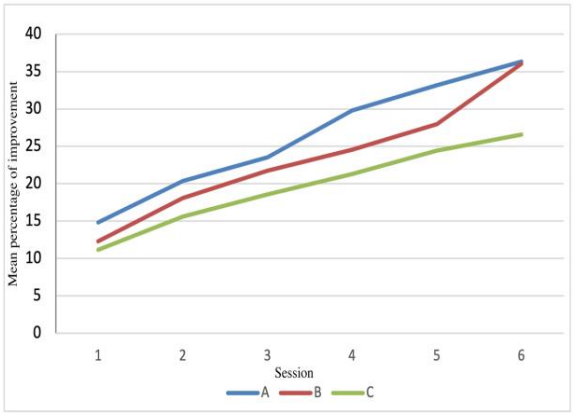

Figure 5. Improvement of acne according to the blinded dermatologist evaluation across treatment sessions
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Patient satisfaction

Most patients reported good improvement, including 75% in Group A, 78.9% in Group B, and 68.8% in Group C. The remaining participants noted partial improvement. The groups were statistically similar regarding patient satisfaction at the end of the treatment (Table 6).

Side effects

Seven participants reported transient mild erythema, and 14 noted temporary scaling; these findings were similar between the groups (P=0.332 and 0.323, respectively). Edema, scarring, post-inflammatory hyperpigmentation, or other serious side effects were not observed.

Table 4. Total acne score and number of comedones, papules, and pustules at baseline and after each treatment session, Mean ± SD or median (IQR)

Variable	Time	Group A	Group B	Group C
Comedones	Baseline	27.84 ± 22.40	32.80 ± 23.69	34.53 ± 26.06
	Session 1	27.26 ± 20.18	27.42 ± 21.20	37.88 ± 30.57
	Session 2	23.69 ± 21.81	21.69 ± 17.75	27.80 ± 19.38
	Session 3	24.16 ± 21.82	18.30 ± 17.83	23.23 ± 13.93
	Session 4	17.45 ± 14.72	19.34 ± 17.59	23.57 ± 20.32
	Session 5	19.90 ± 15.16	18.09 ± 16.33	24.64 ± 21.39
	Session 6	18.73 ± 14.60	18.73 ± 16.04	27.37 ± 24.71
Papules	Baseline	28.38 ± 19.41	23.84 ± 14.16	24.65 ± 14.15
	Session 1	17.96 ± 12.76	18.42 ± 14.28	20.42 ± 10.90
	Session 2	17.96 ± 14.50	14.65 ± 13.63	15.96 ± 12.86
	Session 3	14.62 ± 10.74	11.34 ± 8.86	13.85 ± 9.59
	Session 4	13.08 ± 12.88	12.43 ± 9.99	10.15 ± 6.75
	Session 5	11.13 ± 8.01	10.95 ± 8.31	11.11 ± 5.84
	Session 6	12.60 ± 11.31	8.52 ± 7.11	13.50 ± 12.87
Michaelson Acne Score	Baseline	47.46 ± 25.0	45.78 ± 26.68	51.30 ± 30.40
	Session 1	36.21 ± 19.86	37.90 ± 21.02	45.51 ± 31.20
	Session 2	32.34 ± 19.36	28.03 ± 16.15	36.18 ± 22.78
	Session 3	30.62 ± 19.50	23.26 ± 15.44	30.04 ± 15.55
	Session 4	23.56 ± 16.97	24.54 ± 15.97	24.15 ± 16.38
	Session 5	24.54 ± 14.54	21.90 ± 13.35	29.08 ± 18.27
	Session 6	24.50 ± 13.98	18.75 ± 11.79	31.06 ± 18.73
Pustules	Baseline	2.0 (3.0)	2.0 (3.25)	3.0 (5.50)
	Session 1	1.0 (4.25)	2.0 (2.0)	1.50 (3.50)
	Session 2	1.0 (2.0)	0 (2.0)	2.0 (3.0)
	Session 3	1.50 (2.75)	1.0 (2.0)	2.0 (2.50)
	Session 4	0.50 (1.75)	1.0 (2.0)	0 (2.0)

Session 5	1.0 (3.0)	1.0 (1.25)	2.0 (3.50)
Session 6	1.0 (2.0)	0 (1.0)	1.0 (2.0)

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Group A: doxycycline plus salicylic acid 30%; Group B: placebo with salicylic acid 30%; Group C: placebo with salicylic acid 40%. SD: standard deviation; IQR: interquartile range

Table 5. Comparing the changes in total acne score and number of comedones, papules, and pustules based on mixed linear regression

Variable			Regression coefficient	Standard error	Test statistic	*P*-value
Comedones	Time		-1.859	0.520	-3.572	<0.001
	Group*	A	-6.057	5.484	-1.104	0.272
		B	-4.854	5.480	-0.886	0.378
		C	1	-	-	-
	Time and group	A	-0.204	0.717	-0.286	0.775
		B	-0.811	0.705	-1.151	0.250
		C	1	-	-	-
Papules	Time		-2.026	0.341	-5.932	<0.001
	Group*	A	1.781	3.088	0.577	0.565
		B	-0.756	3.084	-0.245	0.807
		C	1	-	-	-
	Time and group	A	-0.272	0.470	-0.579	0.563
		B	-0.474	0.463	-1.024	0.306
		C	1	-	-	-
Pustules	Time		-0.386	0.112	-3.427	<0.001
	Group*	A	-1.635	0.723	-2.260	0.025
		B	-1.238	0.722	-1.714	0.088
		C	1	-	-	-
	Time and group	A	0.193	0.156	1.240	0.215
		B	0	0.154	-0.001	0.999
		C	1	-	-	-
Michaelson Acne Score	Time		-3.688	0.514	-7.171	<0.001
	Group*	A	-4.493	5.482	-0.820	0.414
		B	-5.571	5.478	-1.017	0.312
		C	1	-	-	-
	Time and group	A	0.003	0.708	0.005	0.996
		B	-0.961	0.699	-1.374	0.170
		C	1	-	-	-

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*Group A: doxycycline plus salicylic acid 30%; Group B: placebo with salicylic acid 30%; Group C: placebo with salicylic acid 40%.

Table 6. Comparison of the improvement rate (evaluated by a blinded dermatologist) and patient satisfaction based on mixed linear regression

Variable			Regression coefficient	Standard error	Test statistic	P-value
Improvement rate	Time		2.988	0.369	8.081	<0.001
	Group*	A	3.50	2.793	1.253	0.213
		B	1.288	2.789	0.462	0.645
		C	1	-	-	-
	Time and group	A	1.402	0.510	2.747	0.006
		B	0.906	0.501	1.809	0.071
		C	1	-	-	-
Patient satisfaction	Time		0.292	0.161	1.815	0.069
	Group*	A	0.760	1.107	0.687	0.492
		B	0.736	1.096	0.672	0.501
		C	1	-	-	-
	Time and group	A	0	0.237	0.002	0.998
		B	0.045	0.236	0.194	0.846
		C	1	-	-	-

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*Group A: doxycycline plus salicylic acid 30%; Group B: placebo with salicylic acid 30%; Group C: placebo with salicylic acid 40%.

Discussion

Salicylic acid peels are a good option for treating acne vulgaris, especially the comedonal type, and can be a suitable adjunctive modality for treating post-acne erythema and hyperpigmentation. In various studies, SA at concentrations of 20%-30% has been reported as safe and effective for treating acne vulgaris, acne scars, melasma, and similar conditions as a superficial peel. However, the efficacy and safety of higher

concentrations of SA have not been investigated. We compared SA peel 40% vs. SA peel 30%, both with and without doxycycline, in treating moderate acne vulgaris, examining the safety and efficacy of each treatment. We found that SA 30% and 40% reduced the MAS and the inflammatory and non-inflammatory lesions over time. At the end of the treatment, no significant difference was observed between the two groups in the MAS and the number of comedones, papules, or pustules. Our study revealed that although increasing the SA concentration to 40% was safe, it had no superiority over 30% SA in treating moderate acne vulgaris. In addition, the improvement in the severity of acne vulgaris, as evaluated by a blinded dermatologist, was similar between the two groups. However, adding doxycycline as an antibiotic and anti-inflammatory drug caused a greater improvement in inflammatory lesions compared with SA monotherapy.

In line with our findings, Dayal et al. reported that SA 30% improved both inflammatory and non-inflammatory lesions of mild to moderate acne vulgaris [5]. Similarly, Kong et al. showed significant reductions in inflammatory and non-inflammatory lesions, MAS, and PAHPI scores with 30% SA by the end of the treatment [4]. Moreover, Lee et al. obtained similar results [9]. Abdel Meguid et al. found that 30% SA peels are superior to 25% Trichloroacetic Acid (TCA) peels in treating inflammatory lesions in dark-skinned patients. Therefore, the results of our study regarding the improvement in inflammatory acne lesions agree with the findings of that study. The superior effects of improving papules and pustules (inflammatory lesions) with the SA peel than the TCA peel may be due to the anti-inflammatory action of SA through inhibition of the arachidonic acid cascade [10]. All the mentioned studies showed that a 30% SA peel was effective in treating both inflammatory and non-inflammatory lesions of acne vulgaris, which agrees with our study.

Antibiotics possess anti-inflammatory effects and can safely treat acne. Doxycycline, a tetracycline derivative, is commonly used because it has greater penetrative ability than its parent due to its more lipophilic nature. Its properties facilitate accumulation in the sebaceous glands, where it can counter the growth of C. acnes [7]. Our study is the first to investigate the efficacy and safety of combining the SA peel with oral doxycycline in treating acne vulgaris. While the MAS and counts of papules and comedones were similar between the SA 30%, SA 40%, and SA 30% + doxycycline groups, combination therapy caused the most significant improvement in pustules. Therefore, combining SA with an anti-inflammatory systemic medication was superior to monotherapy with different concentrations of SA only in treating pustules. A blinded dermatologist also confirmed the improvement in acne in all groups, with the combination therapy group achieving the best results.

Gurung et al. showed that both azithromycin and doxycycline effectively reduced the severity of acne vulgaris, with azithromycin being a little superior in reducing the number of inflammatory lesions [11]. Sadati et al. reported a significant reduction in the total number of lesions with either doxycycline or metformin, noting that the decrease in inflammatory lesions was significantly greater in the doxycycline group [12]. We also observed that doxycycline was more effective in reducing inflammatory lesions. Findings by Dreno et al. support our conclusion that combining a topical retinoid with oral doxycycline is an appropriate regimen for severe acne, showing that combination therapy is more effective than monotherapy in treating acne vulgaris [13].

Conclusions

Combination therapy targeting multiple pathophysiologic mechanisms should yield better results than monotherapy. Our study shows that SA peel plus doxycycline is superior to SA peel monotherapy, even at a higher concentration. Furthermore, increasing the concentration of the SA peel from 30 to 40% did not alter the outcome.

Ethical Considerations

Compliant with ethical guidelines

This study has been approved in accordance with the ethical code IR.GMU.REC.1399.114.

Funding/Support

This study received no financial support.

Authors' contributions

Mohammadzadeh H and Amani M designed the study. Mohammadzadeh H, Amani M, and Mokhtari A performed the clinical trial. Mohammadzadeh F analyzed the collected data. Mohammadzadeh H, Amani M, Mokhtari A, and Mohammadzadeh F wrote and approved the manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

Acknowledgments

The authors of this article acknowledge the contributions of the study participants.

References

1. Arshdeep DD. What's new in the management of acne? Indian J Dermatol Venereol Leprol. 2013;79:279. [DOI:10.4103/0378-6323.110748] [PMID]
2. Dayal S, Singh S, Sahu P. Efficacy and safety of 25% trichloroacetic acid peel versus 30% salicylic acid peel in mild-to-moderate acne vulgaris: a comparative study. Dermatol Pract Concept. 2021;20;11(3):e2021063.[DOI:10.5826/dpc.1103a63] [PMID] [PMCID]
3. Wiegmann D, Haddad L. Two is better than one: The combined effects of glycolic acid and salicylic acid on acne-related disorders. J Cosmet Dermatol. 2020;19(9):2349-51.

[DOI:10.1111/jocd.13387] [PMID]
4. How KN, Lim PY, Wan Ahmad Kammal WS, Shamsudin N. Efficacy and safety of Jessner's solution peel in comparison with salicylic acid 30% peel in the management of patients with acne vulgaris and postacne hyperpigmentation with skin of color: a randomized, double-blinded, split-face, controlled trial. Int J Dermatol. 2020;59(7):804-12. [DOI:10.1111/ijd.14948] [PMID]
5. Dayal S, Kalra KD, Sahu P. Comparative study of efficacy and safety of 45% mandelic acid versus 30% salicylic acid peels in mild-to-moderate acne vulgaris. J Cosmet Dermatol. 2020;19(2):393-9. [DOI:10.1111/jocd.13168] [PMID]
6. Arif T. Salicylic acid as a peeling agent: a comprehensive review. Clin Cosmet Investig Dermatol. 2015;26:455-61. [DOI:10.2147/CCID.S84765] [PMCID] [PMID]
7. Baldwin H. Oral antibiotic treatment options for acne vulgaris. J Clin Aesthet Dermatol. 2020;13(9):26.[PMCID] [PMID]
8. Vaishampayan S, Baveja S, Garg S. Acne, rosacea and perioral dermatitis. In: IADVL Textbook of Dermatology. 4th ed. Mumbai: Bhalani Publishing House; 2016. p. 1400–1447. [PMCID] [PMID]
9. Lee HS, Kim IH. Salicylic acid peels for the treatment of acne vulgaris in Asian patients. Dermatol Surg. 2003;29(12):1196-9. [DOI:10.1111/j.1524-4725.2003.29384.x] [PMID]
10. Meguid AM, Attallah DA, Omar H. Trichloroacetic acid versus salicylic acid in the treatment of acne vulgaris in dark-skinned patients. Dermatol Surg. 2015;41(12):1398-404. [DOI: 10.1097/DSS.0000000000000522] [PMID]
11. Gurung S, Patil N, Rao K, Chaudhary G, Nazeer M, Varghese GM, Bhutani R, Parida A. A comparative study on efficacy of azithromycin and doxycycline in the treatment of acne vulgaris at a tertiary care centre. Biomed Pharmacol J. 2020;13(3):1451-5. [DOI :10.13005/bpj/2016]
12. Sadati MS, Yazdanpanah N, Shahriarirad R, Javaheri R, Parvizi MM. Efficacy of metformin vs. doxycycline in treating acne vulgaris: an assessor-blinded, add-on, randomized, controlled clinical trial. J Cosmet Dermatol. 2023;22(10):2816-23. [DOI:10.1111/jocd.15785] [PMID]
13. Dréno B, Kaufmann R, Talarico S, Torres Lozada V, Rodríguez-Castellanos MA, Gómez-Flores M, De Maubeuge J, Berg M, Foley P, Sysa-Jedrzejowska A, Kerrouche N. Combination therapy with adapalene–benzoyl peroxide and oral lymecycline in the treatment of moderate to severe acne vulgaris: a multicentre, randomized, double-blind controlled study. Br J Dermatol. 2011;165(2):383-90. [DOI:10.1111/j.1365-2133.2011.10374.x] [PMID]
14. Bolognia JL, Schaffer JV, Cerroni L, editors. Dermatología. Elsevier Health Sciences; 2018;23. [Link]