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ORIGINAL ARTICLE

Effect of *Aloe vera* topical gel combined with tretinoin in treatment of mild and moderate acne vulgaris: a randomized, double-blind, prospective trial

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Background: **Topical retinoids are considered first-line therapy in the treatment of acne vulgaris, yet can be associated with cutaneous irritations. Combination therapy with natural preparations could be effective in treatment and decreasing adverse events.** ***Objective*****: The aim of this study was to compare the efficacy and safety of the combination of tretinoin (TR) cream (0.05%) and *Aloe vera* topical gel (50%) with TR and vehicle.** ***Material and methods:*** **The randomized, double-blind, prospective 8-week trial evaluated inflammatory and non-inflammatory lesion scores and tolerability in 60 subjects with mild to moderate acne vulgaris (global acne grading system scale).** ***Results*****:Several formulations of *A. vera* leaf gel were prepared and the most stable one was selected for clinical study based on physicochemical evaluations. The combination therapy showed superior efficacy to TR and placebo. TR/*Aloe vera* gel (AVG) was significantly more effective in reducing non-inflammatory ($p = 0.001$), inflammatory ($p = 0.011$) and total ($p = 0.003$) lesion scores than control group. The highest percentage of adverse cutaneous effect was reported for scaling. At the end of study, erythema in the TR/AVG-treated group was significantly less severe ($p = 0.046$).** ***Conclusion:*** **The combination TR/AVG was well tolerated and significantly more effective than TR and vehicle for the treatment of mild to moderate acne vulgaris.**

Key words: acne, Aloe vera, tretinoin, gel, adverse event, lesion

Introduction

Acne vulgaris is one of the most prevalent skin diseases, affecting up to 85% of teenagers and young adults (1). It is a multifactorial disease based on an alteration in the pattern of excess sebum production and keratinization within the pilosebaceous follicles (2–4). Acne characteristically presents in these sites with both non-inflammatory and inflammatory skin lesions. Non-inflammatory lesions consist of closed comedones (whiteheads) and open comedones (blackheads) and result from hypercornification of the pilosebaceous duct and consist of plugs of cornified cells in the dilated follicles. Inflammatory acne lesions take the form of erythematous macules, papules and pustules in the majority of cases. In more severe cases, deeper inflamed lesions present as acne nodules (5). Inflammatory lesion formation occurs most commonly when *Propionibacterium acnes* colonizes the pilosebaceous unit, triggering follicular rupture and a neutrophil cascade. Rarely, acne may have non-bacterial causes (6).

Most patients present with mild to moderate comedonal or papulopustular acne; in such patients, topical therapy is the first line of treatment (7,8). Retinoids play a crucial role in the treatment of acne because they inhibit the formation of microcomedones and reduce non-inflammatory and inflammatory lesions (9). Topical tretinoin (TR) 0.01–0.025% gel/cream is one of the common drugs for treatment of mild to moderate acne which is used alone or combined with other medicines (5). TR works by both comedolysis and by normalizing the maturation of follicular epithelium so that comedo formation ceases (10). Its low systemic absorption reduces the potential for the development of systemic adverse effects. Typically, adverse events (AEs) are limited to local cutaneous reactions, such as erythema, peeling, dryness, itching and burning (11,12).

The use of natural remedies is highly approached in human health, in particular drugs and cosmetics with an ongoing search for novel biologically active botanical agents (13,14). *Aloe vera* (synonym: *Aloe barbadensis* Miller, Liliaceae) has been used therapeutically in several cultures since many years ago. Cosmetics and some medicinal products are made from the mucilaginous tissue in the center of the *A. vera* leaf which is called *Aloe vera* gel (AVG) (15,16). Its pharmacological actions include anti-inflammatory, anti-irritant, healing of wounds and antibacterial effects (15–19). An Ayurvedic formulation containing *A. vera* and some other herbal extracts showed antibacterial activity against *P. acnes* (20). Another Ayurvedic formulation containing this gel and six herbal extracts showed clinical efficacy in the treatment of acne vulgaris (21). This study was designed to evaluate the clinical efficacy of AVG with that of placebo (P), combined with TR in patients with mild to moderate acne vulgaris.

Material and methods

The following chemicals were used as received from the suppliers: methyl and propyl paraben, glycerin, ethanol, triethanolamine (Merck, Germany), hydroxypropyl methylcellulose (HPMC) (Colorcon, UK) and Carbopol 934P (BF Goodrich Chemical Co., Cleveland, OH, USA).

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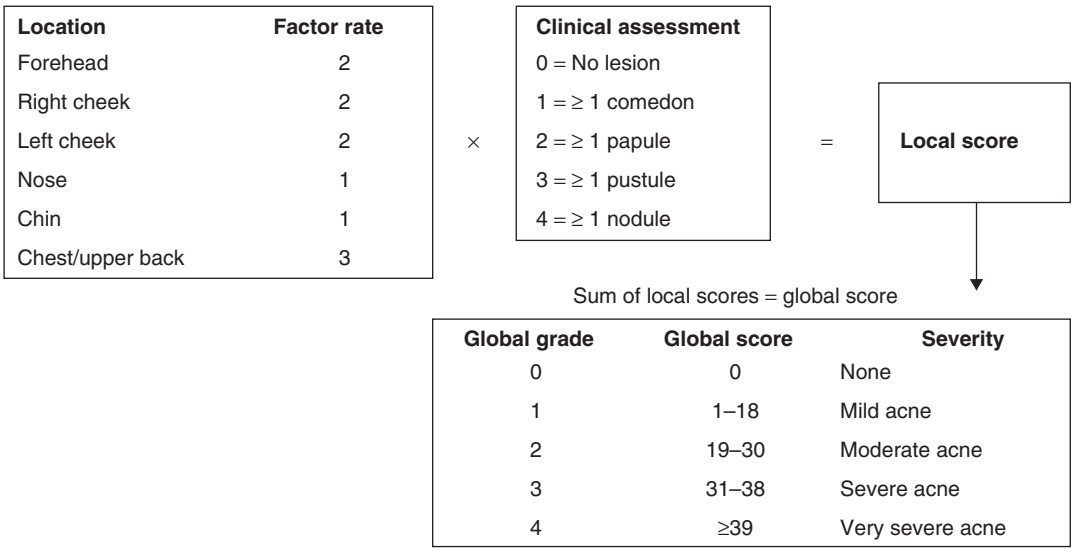

Figure 1. Determination of global acne grading system (GAGS) global grade (24).

Plant material

Fresh *A. vera* L. leaves were purchased from Sari township in Mazandaran province of Iran. The leaves were cleaned by 70% alcohol, then allowed to drain off the yellow sap from the rind and then cleaned with deionized water. The rind was removed with a sharp blade. The clear pulp was homogenized with a mixer.

Preparation of the formulations

Several concentrations of HPMC and carbopol were used as gelling agent. The homogenized *A. vera* leaf gel was dispersed in preserved solvent system (methyl paraben 0.18% and propyl paraben 0.02%) before addition of polymer and stirred with a double bladed mixer (Ika-Werk, Germany) 300 rpm for 30 min. The polymer was dispersed in this solution for overnight. The system was homogenized and neutralized by triethanolamine in formulations containing carbopol as gelling agent. The formulations were kept in 4, 25 and 40°C for physical stability evaluation (viscosity, syneresis, swelling, color change) during 2 weeks (22). The selected formulation for clinical trial was prepared freshly and controlled microbiologically based on USP 30 (United States Pharmacopoeia 30) (23).

Study design and population

The study was a randomized (simple-random sampling), double-blind, prospective trial. On the assumption of an overall mean difference of 0.5 units and a standard deviation of 0.5 units, 56 patients (28 in each group) were required to achieve a power of 90% to reject a null hypothesis of equality, applying a two-sided test at the 5% significance level. Seventy-five patients with mild to moderate acne, 11 years or older, defined as a score of 1–30 on the global acne grading system (GAGS) scale (Figure 1), who were not satisfied with their previous acne therapies participated in the study after giving written informed consent (24). The study was approved by the Research Ethics Committee of the council of Mazandaran University of Medical Sciences. Patients were excluded if they had an uncontrolled systemic disease; had received topical antiacne therapy 2 months before or during the study or any systemic therapy with antibiotics, oral contraceptive pill (OCP) and spironolactone 30 days before or during the study; were known to be allergic or sensitive to any of the study medications or their components; had previously been treated with systemic retinoids; had a skin disease that might interfere with the diagnosis or evaluation of their hyperpigmentation or were pregnant, or planning to become pregnant, and lactating.

At the first visit, the score of acne was determined based on GAGS scale, and a urinary pregnancy test was performed (for women). Each patient's medical history was recorded. The baseline examination included a lesion count, assessment of disease severity and the recording of signs (scaling, erythema, edema) and symptoms (burning, itching). Every morning and evening, patients washed their face with non-medicated soap, then thoroughly rinsed and dried it. Over the 8-week course, patients applied AVG 50% and P gel in the morning and evening in case and control groups, respectively, and TR 0.025% cream in the evening (in two groups). In both treatment groups, the second evening medication was applied approximately 10–15 min after the first medication. Non-medicated cosmetics were permitted during the study provided the regimen was consistently followed.

Clinical assessments

The clinical efficacy assessment was facial lesion counts (total, inflammatory and comedones) at each clinic visit (baseline and weeks 2, 4 and 8). The % of reduction of lesions score (based on GAGS scale) from baseline was calculated as efficacy of treatment. At the final visit, each patient assessed AVG acceptability. Tolerability was assessed at each visit using direct questioning and assessment of clinical AEs by the investigator. The signs and symptoms evaluated were scaling, edema, erythema, burning and itching, and were rated on a scale of 0 = none to 3 = severe. For the final assessment and to determine the efficacy of the treatment, total lesion count (TLC) and acne severity index (ASI) were used based on following formula (25):

$$\mathrm{TLC} = \mathrm{comedones} + \mathrm{papules} + \mathrm{pustules}$$

$$\mathrm{ASI} = \mathrm{papules} + (2 \times \mathrm{pustules}) + (\mathrm{comedones}/4)$$

This trial was registered at "Iranian Registry of Clinical trials (www.irct.ir)" with the registration number IRCT 2012070810203N2.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 15; SPSS Inc., Chicago, IL, USA). Student's *t*-test was

Table I. Demographic and baseline characteristics of patients.

Characteristic	TR/AVG (treatment)	TR/P	*p*-Value
Mean age, y (±SD)	22.33 ± 4.82	24.70 ± 5.56	NS ($p = 0.084$)
Sex, No. (%)			NS
Female	30 (100)	30 (100)	
Male	-	-	
Mean acne duration, m (±SD)	3.53 ± 1.25	3.23 ± 1.17	NS ($p = 0.341$)
Patients who used medication, No.	37	38	
Patients who completed study, No.	30	30	
Reason for discontinuation			
Allergy to medication	-	3	
Personal reason	7	5	
Mean baseline lesion scores (±SD)			
Total	12.17 ± 4.53	10.63 ± 3.23	NS ($p = 0.137$)
Comedones	6.23 ± 1.92	5.36 ± 2.06	NS ($p = 0.098$)
Inflammatory	6.08 ± 4.13	5.07 ± 3.13	NS ($p = 0.289$)
Mean baseline TLC (±SD)	9.23 ± 2.75	8.10 ± 2.52	NS ($p = 0.103$)
Mean baseline ASI (±SD)	4.36 ± 2.17	4.94 ± 1.59	NS ($p = 0.242$)

ASI = acne severity index; AVG = *Aloe vera* gel; P = placebo; SD = standard deviation; TLC = total lesion count; TR = tretinoin.

used to determine significant differences between the groups. In all cases, $p < 0.05$ was taken as statistically significant.

Results

Baseline characteristics

Table I shows the demographic and baseline characteristics of patients who were randomized to treatment. A total of 75 patients were recruited in the present study by a single investigator, 15 patients were excluded from the efficacy analyses. Three patients suffered from severe allergic reactions in control group and 12 men patients (7 persons in case group and 5 persons in control group) discontinued treatment due to personal reasons. All of the 60 evaluable women subjects (30 patients in each group) completed 8 weeks treatment (Figure 2). The minimum and maximum ages in the case group were 11 and 32 years, respectively; and in the control group were 14 and 37 years, respectively. There were no significant differences between patients' age in two groups ($p = 0.084$).

At baseline (Table I), no significant differences were noted between groups in terms of mean total lesion score ($p = 0.137$). This similarity was observed between groups in the mean inflammatory lesion score ($p = 0.289$) and mean comedone score ($p = 0.098$) too.

Efficacy

The effect of topical AVG in combination therapy with TR cream (case), on mean changes (%) of total lesion, comedones and inflammatory lesions from baseline, are summarized in Figures 3,4,5, compared with P (control).

Total lesion scores.

At baseline, the mean scores of total (inflammatory and non-inflammatory) lesions in case and control groups were 12.17 ± 4.53 and 10.63 ± 3.23, respectively (Table I). Patients in both groups experienced increased total lesion score in comparison with baseline at 2nd week (Figure 3), but the percentage increase in P group was higher than patients who received TR and AVG ($p = 0.017$). From baseline to week 4 and 8 (end of treatment), the percentage reduction of total lesion scores in the case group was significantly higher than control group ($p < 0.000$ and $p = 0.003$, respectively).

Non-inflammatory lesion (comedone) scores.

At baseline, the mean scores of non-inflammatory lesions in case and control groups were 6.23 ± 1.92 and 5.36 ± 2.06, respectively (Table I). Patients in both groups experienced increased comedone score in comparison with baseline at 2nd week (Figure 4), like together ($p = 0.578$). From baseline to week 4 and 8 (end of treatment), the percentage reduction of non-inflammatory lesion scores in the case group was significantly higher than control group ($p = 0.041$ and $p = 0.001$, respectively).

Inflammatory lesion scores.

At baseline, the mean scores of inflammatory lesions in case and control groups were 6.08 ± 4.13 and 5.07 ± 3.13, respectively

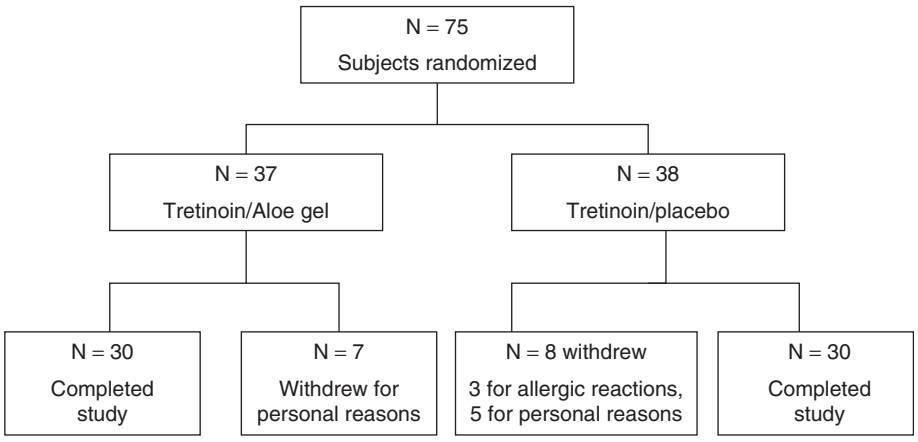

Figure 2. Profile of randomized controlled trial.

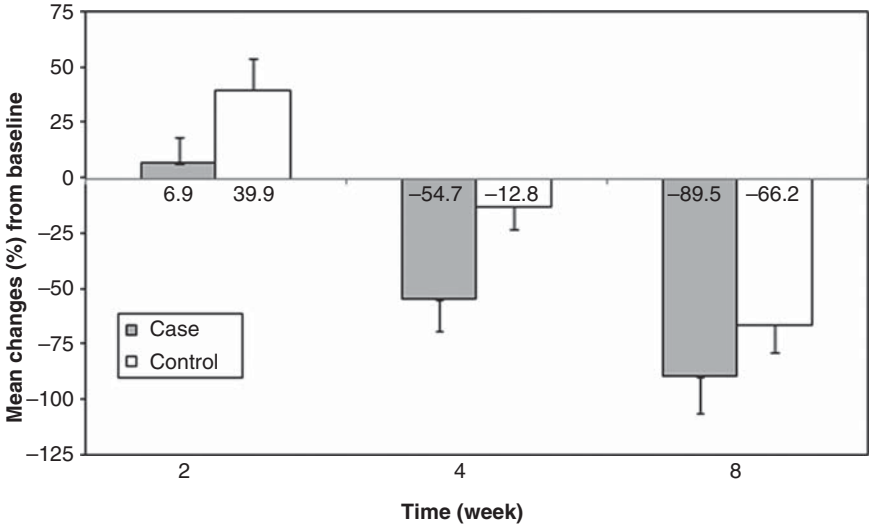

Figure 3. Acne vulgaris: mean percent changes in total lesion scores from baseline to weeks 2, 4 and 8.

(Table I). Patients in both groups experienced increased inflammatory lesion score in comparison with baseline at 2nd week (Figure 4), but the percentage increase in P group was higher than patients who received TR and AVG ($p = 0.047$). When compared with baseline, the scores of inflammatory lesions with TR/AVG was significantly lower than TR/P after 4 weeks ($p < 0.000$), and was maintained until end of study ($p = 0.011$).

Efficacy on TLC.

The means of the TLC in treatment and P group at baseline (Table I) were similar (8.10 ± 2.52 and 9.23 ± 2.75, respectively, $p = 0.103$). TLC (Figure 6) showed no changes after 2 and 4 weeks in P groups. The decrease in TLC was observed after 8 weeks ($p < 0.001$) in P group. TLC showed significant decrease after 4 and 8 weeks in treatment group ($p < 0.001$). TLC was similar in two groups after 2 weeks ($p = 0.0738$), but after 4 and 8 weeks the TLC was decreased in treatment group significantly ($p < 0.0001$, $p = 0.0015$, respectively).

Efficacy on ASI.

The means of the ASI in two groups at baseline (Table I) were similar (4.94 ± 1.59 and 4.36 ± 2.17, respectively, $p = 0.242$). The decrease in ASI (Figure 7) was observed only after 8 weeks in P groups ($p < 0.001$). ASI showed significant decrease after 4 and 8 weeks in treatment group ($p < 0.001$). ASI was similar in treatment and P groups after 2 weeks ($p = 0.876$), but after 4 and 8 weeks the ASI was decreased in treatment group significantly ($p = 0.0001$, $p = 0.0010$, respectively).

Adverse reactions (AE)

Twenty-four (76.7%) patients receiving TR cream and AVG, and 23 (70.0%) receiving TR cream and P reported at least one AE after 2 weeks. These AE decreased to 60% and 30% in case group, and 66.7% and 33.3% in control group, at weeks 4 and 8, respectively. The number of severe AE was relatively small: only 5.6% in case group at week 2 was observed. This incidence in control group was 4.8% and 10.8% at weeks 4 and 8, respectively. Three patients, receiving TR/P, withdrew from the study due to severe allergic reaction. The incidence of moderate AE were 38.9%, 33.3% and 0.0% in case group, and 23.8%, 21.6% and 9.5% in control group, at weeks 2, 4 and 8, respectively. The most AE were of mild intensity, 55.5%, 66.7% and 100% of adverse reactions in case group, and 71.4%, 67.6% and 90.5% of AE in control group were mild at weeks 2, 4 and 8, respectively.

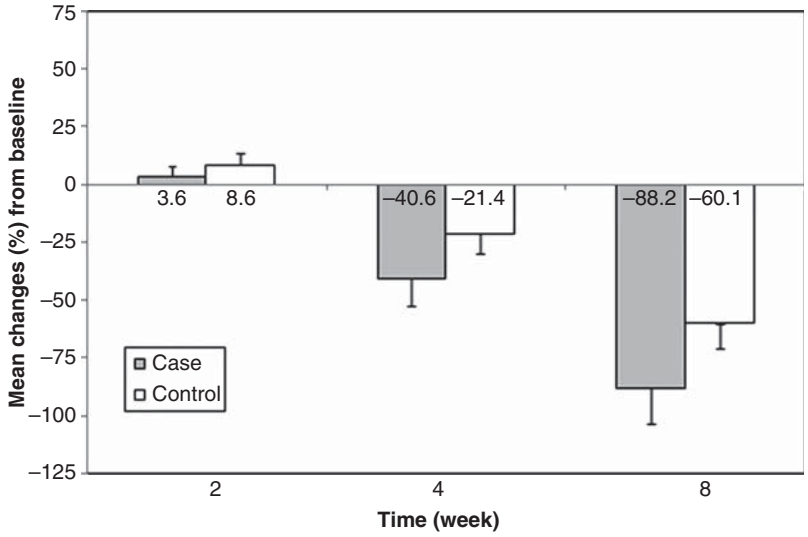

Figure 4. Acne vulgaris: mean percent changes in non-inflammatory lesion scores from baseline to weeks 2, 4 and 8.

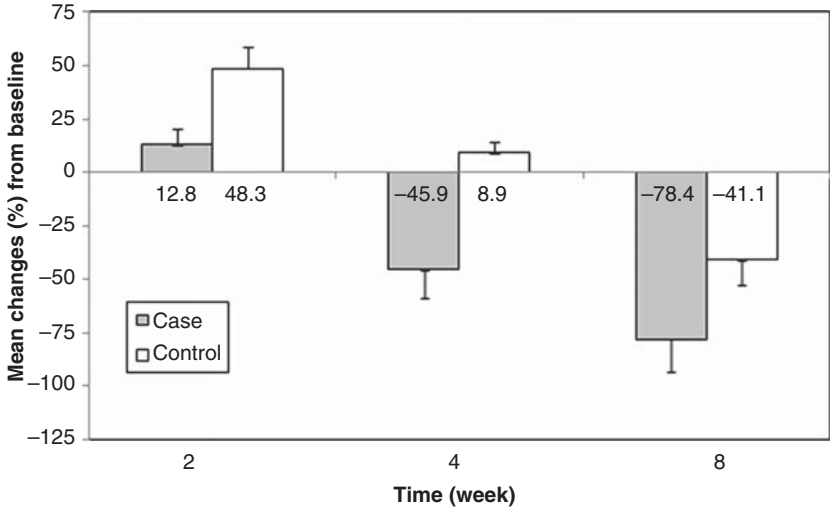

Figure 5. Acne vulgaris: mean percent changes in inflammatory lesion scores from baseline to weeks 2, 4 and 8.

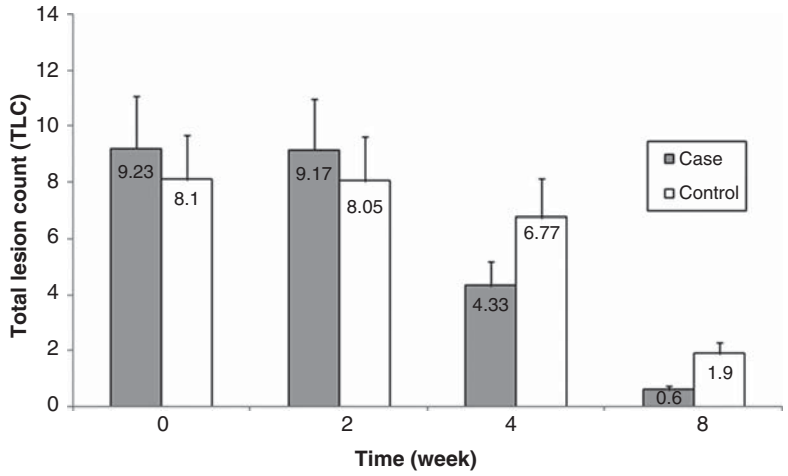

Figure 6. Total lesion score (TLC) in treatment and placebo groups at baseline and after 2, 4 and 8 weeks.

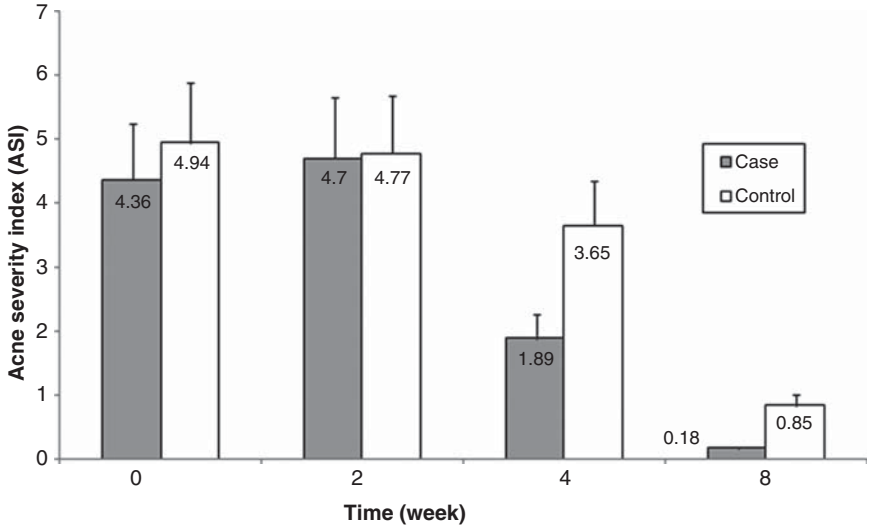

Figure 7. Acne severity index (ASI) in treatment and placebo groups at baseline and after 2, 4 and 8 weeks.

Table II. Overall summary of AEs based on no. of patients and mean scale.

Adverse effect		TR/AVG (case)			TR/P (control)		
		Week 2	Week 4	Week 8	Week 2	Week 4	Week 8
Scaling	No. (%)	21 (70%)	15 (50%)	9 (30%)	18 (60%)	18 (60%)	9 (30%)
	Mean scale ± SD	1.03 ± 0.85	0.67 ± 0.76	0.3 ± 0.47	0.87 ± 0.82	0.87 ± 0.82	0.3 ± 0.47
Edema	No. (%)	0 (0%)	0 (0%)	0 (0%)	2 (6.6%)	2 (6.6%)	2 (6.6%)
	Mean scale ± SD	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.06 ± 0.25	0.13 ± 0.57	0.06 ± 0.25
Erythema	No. (%)	9 (30%)	5 (16.7%)	1 (3.3%)*	8 (26.7%)	7 (23.3%)	6 (20%)*
	Mean scale ± SD	0.47 ± 0.82	0.2 ± 0.48	0.03 ± 0.18	0.33 ± 0.66	0.37 ± 0.81	0.23 ± 0.5
Burning	No. (%)	5 (16.7%)	5 (16.7%)	1 (3.3%)	13 (43.3%)	9 (30%)	3 (9.9%)
	Mean scale ± SD	0.27 ± 0.64	0.27 ± 0.64	0.03 ± 0.18	0.50 ± 0.63	0.33 ± 0.48	0.1 ± 0.31
Itching	No. (%)	1 (3.3%)	2 (6.6%)	0 (0%)	1 (3.3%)	1 (3.3%)	1 (3.3%)
	Mean scale ± SD	0.03 ± 0.18	0.06 ± 0.25	0.0 ± 0.0	0.06 ± 0.37	0.1 ± 0.55	0.06 ± 0.37

*Significant differences between case and control groups ($p = 0.046$).
AE = adverse event; AVG = *Aloe vera* gel; P = placebo; SD = standard deviation; TR = tretinoin.

The number of patients experiencing any AE, and the mean score of severity, are listed in Table II. In the TR/AVG group, there were 36, 27 and 11 AEs at weeks 2, 4 and 8 respectively; in the TR/P-treated group, there were 42, 27 and 21 such events in this period of study. Scaling, the most common AE, occurred with nearly equal severity in both groups at weeks 2, 4 and 8 ($p = 0.443$, $p = 0.330$ and $p = 1.000$, respectively). The second common AE was erythema, occurred less severe in case group after week 8 ($p = 0.046$). This difference was not significant at weeks 2 and 4 ($p = 0.491$ and $p = 0.337$, respectively). The results showed no significant differences in other AEs' severity (edema, burning and itching) between case and control groups.

Discussion

The purpose of this double-blind, randomized study was to compare the efficacy and tolerability of AVG 50% in combination with TR cream 0.025% in the treatment of mild to moderate acne vulgaris. In this study, TR/AVG and TR/P were associated with reduction in scores of total lesions, non-inflammatory lesions and inflammatory lesions. The TLC and ASI were decreased after 4 weeks too. The reductions in scores of both inflammatory and non-inflammatory lesions may be the result of TR's effects on the microcomedone, which is the precursor to both lesions. Topical retinoids reverse the hypercornification of the follicular canal as well as produce expulsion of existing comedones by inducing accelerated proliferation of the follicular epithelium. The unplugged follicle is less anaerobic, and this results in a reduction in the growth of *P. acnes* (5).

The differences between case and control groups in the change in lesion scores from baseline to weeks 2, 4 and 8 were statistically significant, with the exception of the similar changes in comedones at week 2 in two groups ($p = 0.578$). At the end of treatment, 78.7% of patients treated with the combination (TR/AVG) had clear skin as assessed with the GAGS scale; this compares favorably with 23.3% of subjects achieving this result in control group. This combination therapy was effective in treating both inflammatory and non-inflammatory lesions' score. These results show the synergistic effect of *A. vera* on treating action of TR in reducing lesions' score.

A. vera has thick leaves. When the green skin of a leaf is removed a clear mucilaginous substance appears that contains 99.3% water and 0.7% of solid materials (18). Anti-inflammatory, anti-irritant, healing of wounds and antibacterial effects are some of the pharmacological actions of this plant. Compounds isolated from the inner gel, such as salicylates, magnesium lactate, bradykinin, thromboxane inhibitors, sterols and a β-linked acetyl mannan (acemannan) have been reported as active anti-inflammatory components (19). The wound-healing effect of *A. vera* dressing on full-faced dermabrasion patients suffering from acne vulgaris, was reported in one study. This research showed the significant healing effect of *A. vera* dressing after 72 h in comparison with P (26). This healing effect was reported in patients with mild to moderate chronic psoriasis too. The cure rate in the patients receiving *A. vera* cream was 83% and only 7% in the P group ($p < 0.001$) (16). The mixture of *A. vera* extract and other six plants was used as a component of an Ayurvedic formulation. This study showed that oral and topical preparation significantly reduced acne lesions (21). *A. vera* in another Ayurvedic formulation showed *in vitro* antibacterial effect against *P. acnes*. However, *A. vera* was insignificant to suppress *P. acnes*-induced reactive oxygen species and proinflammatory cytokines (20,27). It seems that anti-inflammatory and healing effects of *A. vera* have promoted the efficacy of TR cream.

The combination therapy of TR cream and AVG was well tolerated. Adverse experiences were seen in 76.7% and 70% patients in case and control groups at week 2, respectively. Leyden et al. reported AE in 87.6% of subjects. The most common adverse experiences were dryness, scaling, burning, erythema, itching, sunburn and irritation (28). AVG caused less cutaneous AEs than P, in combination therapy with TR cream, especially in reducing erythema from week 2 to 8. The anti-inflammatory effect of AVG constituents can cause the relief of skin erythema.

Leyden et al. reported dryness and scaling as the most common mucocutaneous AE of TR (28). In present study, there were no significant differences in scaling between case and control subjects. The presence of glycerin (20%) in P can promote the skin hydration in treated area.

No withdrawals owing to adverse effects of *A. vera* were reported in several clinical trials. Some patients experienced burning after topical application, contact dermatitis and mild itching. All AEs were reversible and *A. vera* was generally very well tolerated (16). In this research, there were no significant differences between two groups in burning, itching and edema. These results proved that the mentioned AEs were not due to *A. vera* topical application.

Conclusion

The results of this randomized, double-blind trial demonstrate that the combination therapy of TR and *A. vera* was well tolerated and resulting in significantly greater improvement in mild to moderate acne vulgaris than drug and placebo. This combination therapy effectively treated both inflammatory and non-inflammatory lesions, and showed less AEs, especially in skin erythema.

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Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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