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 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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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 contained gelling agent. The homogenized A. vera leaf gel was dispersed using a double bladed mixer (Ika-Werk, Germany) 300 rpm for 30 min. The resulting mixture was then cleaned with deionized water. The rind was removed with a sharp blade. The clear pulp was homogenized with a mixer.

Clinical assessment
0 = No lesion
1 = ≥ 1 comedon
2 = ≥ 1 papule
3 = ≥ 1 pustule
4 = ≥ 1 nodule

Sum of local scores = global score

Severity
None
Mild acne
Moderate acne
Severe acne
Very severe acne

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):

\[ \text{TLC} = \text{comedones} + \text{papules} + \text{pustules} \]

\[ \text{ASI} = \text{papules} + \left( 2 \times \text{pustules} \right) + \left( \text{comedones} / 4 \right) \]

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 used to compare the efficacy of AVG to carbopol.
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 \( \pm 4.53 \) and 10.63 \( \pm 3.23 \), 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 \( (p < 0.000 \text{ and } p = 0.003, \text{ respectively}) \).

**Non-inflammatory lesion ( comedone) scores.**

At baseline, the mean scores of non-inflammatory lesions in case and control groups were 6.23 \( \pm 1.92 \) and 5.36 \( \pm 2.06 \), 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 \( (p = 0.041 \text{ and } p = 0.001, \text{ respectively}) \).

**Inflammatory lesion scores.**

At baseline, the mean scores of inflammatory lesions in case and control groups were 6.08 \( \pm 4.13 \) and 5.07 \( \pm 3.13 \), respectively
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 ($8.10 \pm 2.52$ and $9.23 \pm 2.75$, 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 ($4.94 \pm 1.59$ and $4.36 \pm 2.17$, 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 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.
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 = 0.330 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 topical application. The presence of glycerin (20%) in P can promote the skin hydration in treated area.

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 adverse experiences 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.

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

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>TR/AVG (case)</th>
<th>TR/P (control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 2</td>
<td>Week 4</td>
</tr>
<tr>
<td>Scaling</td>
<td>No. (%)</td>
<td>Mean scale ± SD</td>
</tr>
<tr>
<td>Erythema</td>
<td>9 (30%)</td>
<td>0.47 ± 0.82</td>
</tr>
<tr>
<td>Edema</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Burning</td>
<td>5 (16.7%)</td>
<td>0.27 ± 0.64</td>
</tr>
<tr>
<td>Itching</td>
<td>1 (3.3%)</td>
<td>0.03 ± 0.18</td>
</tr>
</tbody>
</table>

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