

Effectiveness and tolerability of adapalene cream 0.1% in the treatment of female skin ageing: A randomised controlled trial

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Abstract

Background: Adapalene has been used off-label by dermatologists to manage skin ageing.

Objectives: To evaluate the effectiveness and tolerability of adapalene cream 0.1% in the treatment of skin ageing.

Methods: We conducted a randomised controlled trial on women with moderate skin ageing. Subjects were randomly assigned to either adapalene cream 0.1% or no treatment. All participants from both groups followed a daily skincare regimen that included use of sunscreen, moisturiser, and facial cleanser. Skin ageing was assessed at 1, 2, 4, and 6 months using the Skin Ageing Score (SAS) and Dermoscopic Photoaging Score (DPAS). Safety and tolerability were also assessed by systematic recording of adverse events at each follow-up visit, patient-reported symptoms, and clinical examination for signs of peeling, stinging, erythema, acne, and hyperpigmentation.

Results: A total of 58 subjects completed the study. While the mean (SD) total SAS of the treatment arm decreased from 38.2 (5.5) to 32.5 (3.2) after 6 months of treatment in the adapalene group, it remained unchanged in the control arm (baseline 38.5 (4.2), 6 months 37.9 (4.2)). The difference in total SAS between the two arms at 6 months was significant (mean difference -5.40, 95% CI -7.26 to -3.54; $p < 0.001$). Pigmentation and wrinkles significantly improved in the treatment arm. The mean DPAS decreased over time in both arms but the difference between two arms was not significant. Stinging sensation and xerosis were the most common side effects (64.3% and 25%, respectively), that mostly improved after 2 months.

Limitations: Small sample size, short treatment follow-up period, and single-centre validation

Conclusions: Adapalene cream 0.1% cream significantly improved signs of skin ageing, particularly wrinkles and pigmentation, and was well-tolerated. It can be a promising treatment for skin ageing.

Keywords: Adapalene, dermoscopic photoaging scale (DPAS), pigmentation, skin ageing, skin ageing score (SAS), wrinkles

Introduction

Skin ageing results from genetic degeneration and accumulation of environmental damage, leading to the gradual deterioration of the structural and physiological

function of the skin.¹ Among the topical drugs used for skin ageing, retinoids are the most studied. Tretinoin is the only FDA-approved retinoid for the treatment of photoaging. However, due to its potential for irritation, alternative

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retinoids such as adapalene, retinol, and retinaldehyde are increasingly preferred for their improved tolerability.

Adapalene, a third-generation synthetic retinoid, selectively binds to retinoic acid receptor- β/γ and features a multi-aromatic structure, without unsaturated hydrocarbon chains, making it more photostable compared to other retinoids. Due to its selective effect on the receptor, it is less irritating to the skin. Some studies have demonstrated the effectiveness and high tolerability of adapalene in skin rejuvenation, though limited data exist on its use in Vietnamese populations.²⁻⁶ This study evaluates the effectiveness and tolerability of adapalene cream 0.1% for moderate skin aging in Vietnamese women.

Methods

Study design

We conducted an open-label randomised controlled trial at the National Hospital of Dermatology and Venereology (Hanoi, Vietnam) involving women between 30 and 65 years with Glogau classification II and III. Exclusion criteria included pregnancy, breastfeeding, using topical or oral retinoids, α -hydroxy acid, β -hydroxy acid, or doing facial cosmetic procedures (such as peel, laser, thread lift, filler, or botox) within 6 months before study enrollment. Participants with significant systemic diseases, including uncontrolled diabetes mellitus, severe hypertension, liver or kidney dysfunction, autoimmune disorders, or on medications such as systemic corticosteroids, immunosuppressants, anticoagulants, or photosensitising drugs that could affect treatment outcomes were also excluded.

Intervention

The intervention was topical adapalene 0.1% cream (Differin®, Galderma) applied to the entire face with increasing frequency: every 3 days in the first week, every other day in the second week, and daily from the third week on. Both intervention and untreated control patients also used a facial cleanser (Physioderm Cleansing Gel®, Ziaja), a moisturiser (Cetaphil Moist Cream®, Galderma), and a sunscreen (Farmona Sun Face Cream SPF 50®, Farmona) daily.

Study procedures

Eligible patients were randomised 1:1 to intervention or control arms using sequentially numbered, opaque sealed envelopes. Patients selected one envelope from a thoroughly shuffled box and opened it in the study coordinator's presence to reveal their group assignment.

Baseline data collection included skin care, lifestyle habits, and skin examination; then, patients were followed up at 1, 2, 4, and 6 months. At all visits, the participants were photographed in a standardised way, and skin ageing was assessed using the Skin Ageing Scale (SAS) and Dermoscopic Ageing Score (DPAS).^{7,8} Dermoscopic examination in this study was done by the Dino-Lite Edge AM4515ZT4. Adverse events were also recorded.

Study outcomes

The primary outcome was the total Skin Ageing Score (SAS), which evaluates 17 clinical signs of skin ageing including various types of comedones, pigmentation, wrinkles, sagging, and elasticity. Each criterion is scored from 1-3 based on severity, with total scores ranging from 24-66.⁷

Secondary outcomes included component scores of SAS, total DPAS score, and side effects. The DPAS looks for the presence of dermoscopic signs of skin ageing. It evaluates four facial regions (forehead, both cheeks, and chin) using 12 binary criteria (1=present, 0=absent): yellowish discolouration, diffuse redness, white lines, lentigo, pigmentation changes, telangiectasia, yellowish papules, actinic keratosis, senile comedones, and three types of wrinkles. Total scores range from 0 to 48.⁸

Sample size

The sample size was calculated for a two-sided comparison of the mean SAS total score at 6 months between the intervention and control arm. Assuming a difference of 4 points in the SAS total score, a standard deviation of 5 points, a significance level (alpha) of 0.05, and a power of 80% (beta = 0.2), the minimum sample size calculated in each arm was 32 patients.

Statistical analysis

We described categorical variables as count (percentage) and quantitative variables as mean (SD) or median (IQR). Group differences were analysed using chi-squared, t-test, or Mann-Whitney U tests as appropriate.

For effectiveness outcomes, we compared mean scores between groups over time using generalised estimating equations (GEE) with time interactions. Treatment effects were calculated using linear combinations of GEE coefficients with 95% confidence intervals. Subgroup analyses of the primary outcome examined changes at 6 months stratified by sunscreen use frequency, Fitzpatrick skin type, and Glogau classification.

Adverse events were reported as frequencies without statistical testing. Analyses were performed using IBM SPSS Statistics 22.0 with plots created in Python 3.10.7. P-values <0.05 were considered significant, without adjustment for multiple testing.

Results

Patient characteristics

A total of 60 patients were enrolled in the study, among which 58 completed the 6 months of treatment. Two subjects in the treatment group discontinued due to side effects during the first month (1 xerosis and 1 acne) and were excluded from the analysis [Figure 1].

The mean age was 42.4 years. Nearly half of participants had >1 hour daily sun exposure. While 60-80% rarely sought shade, wore sunglasses, or avoided late nights, sunscreen use

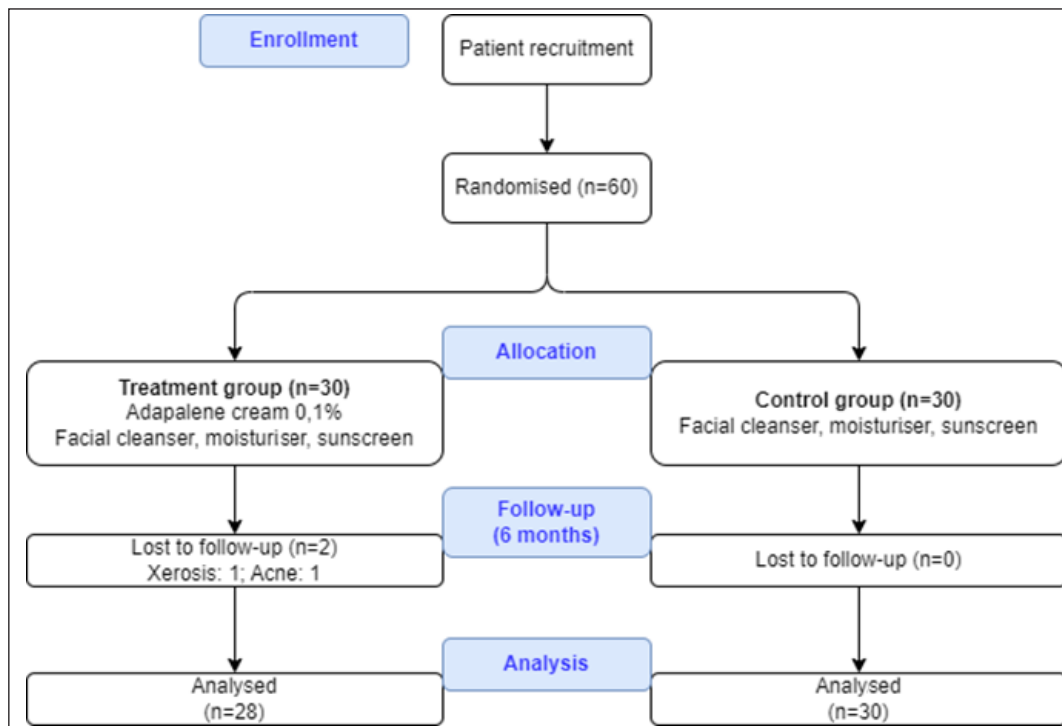


Figure 1: Consolidated standards of reporting trials (CONSORT) diagram of the study.

was common. Subjects had Fitzpatrick type III (50%) or IV (50%) skin, with approximately 30% classified as Glogau III [Table 1].

Effectiveness of adapalene

The mean (SD) baseline total SAS scores were 38.25 (5.52) and 38.47 (4.19) for the intervention and control arms, respectively. The total SAS score in the intervention arm consistently declined over time, while in the control arm, it remained unchanged [Figure 2]. The total SAS score in the intervention arm started to decline after 1 month, and the changes were remarkable at 4 and 6 months. At 6 months, the mean (SD) total SAS scores were 32.50 (3.17) and 37.90 (4.16) for the intervention and control arms. In the GEE analysis with time-treatment interactions, the mean difference in the total SAS score at 6 months was -5.40 (95% confidence interval (CI) -7.26, -3.54, p<0.001) [Supplementary Table 1]. In subgroup analysis, adapalene was effective in all subgroups. The mean difference was more prominent in patients with Fitzpatrick IV skin type compared to Fitzpatrick III type [Supplementary Figure 1].

Among the five component scores of SAS (pigmentation, wrinkle, erythema, sagging, and comedon-milia), pigmentation, wrinkle, and comedone-milia had clear improvement [Figure 3].

The mean total DPAS score gradually decreased over time in both arms [Figure 4]. The mean total DPAS score in the control arm appeared to be higher than in the intervention arm, but the differences were insignificant.

Table 1: Baseline characteristics between the intervention and control arms

Characteristics	Intervention (n=28)	Control (n=30)
Age (years), mean (SD)	42.4 (6.8)	42.2 (6.1)
Average daily duration of exposure to sunlight, n (%)		
1 hour or below	16 (57.1)	16 (53.3)
Above 1 hour	12 (42.9)	14 (46.7)
Sunscreen use, n (%)		
Frequent (≥3 times/day)	16 (57.1)	18 (60.0)
Infrequent (<3 times/day)	12 (42.9)	12 (40.0)
Wearing sunglasses, n (%)		
Frequent (≥50% of outdoor time)	6 (21.4)	4 (13.3)
Infrequent (<50% of outdoor time)	22 (78.6)	26 (86.7)
Staying under the shade, n (%)		
Frequent (≥50% of outdoor time)	9 (32.1)	11 (36.7)
Infrequent (<50% of outdoor time)	19 (67.9)	19 (63.3)
Staying up late, n (%)		
Frequent (≥3 days/week)	11 (39.3)	6 (20.0)
Infrequent (<3 days/week)	17 (60.7)	24 (80.0)
Stress, n (%)		
Low level	24 (85.7)	26 (86.7)
High level	4 (14.3)	4 (13.3)
Fitzpatrick skin type, n (%)		
Fitzpatrick III	13 (46.4)	14 (46.7)
Fitzpatrick IV	15 (53.6)	16 (53.3)
Glogau classification, n (%)		
Glogau II	17 (60.7)	23 (76.7)
Glogau III	11 (39.3)	7 (23.3)

SD: Standard deviation.

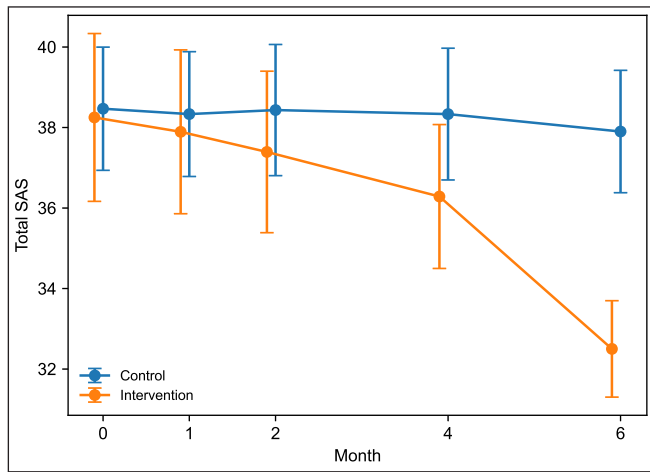


Figure 2: Mean total SAS scores over time between the intervention and control arm. The error bars were 95% CI of the means. (CI: Confidence interval.)

Safety

Adverse events were predominantly observed in intervention patients. Only one patient in the control arm had acne. The most common adverse events during the first 2 months were stinging and peeling (stinging 64% and peeling 25% in 1st month) that subsided afterwards [Table 2]. Some patients developed acne (10.7%) and hyperpigmentation (10.7%), but the adverse effects resolved after 2 months.

Discussion

In this randomised trial, we evaluated the effectiveness of adapalene in improving the signs of skin ageing measured by objective scales, including SAS and DPAS. We found that the mean total SAS score decreased significantly after 6 months. Patients complained of peeling and stinging, but the symptoms often resolved after 2 months.

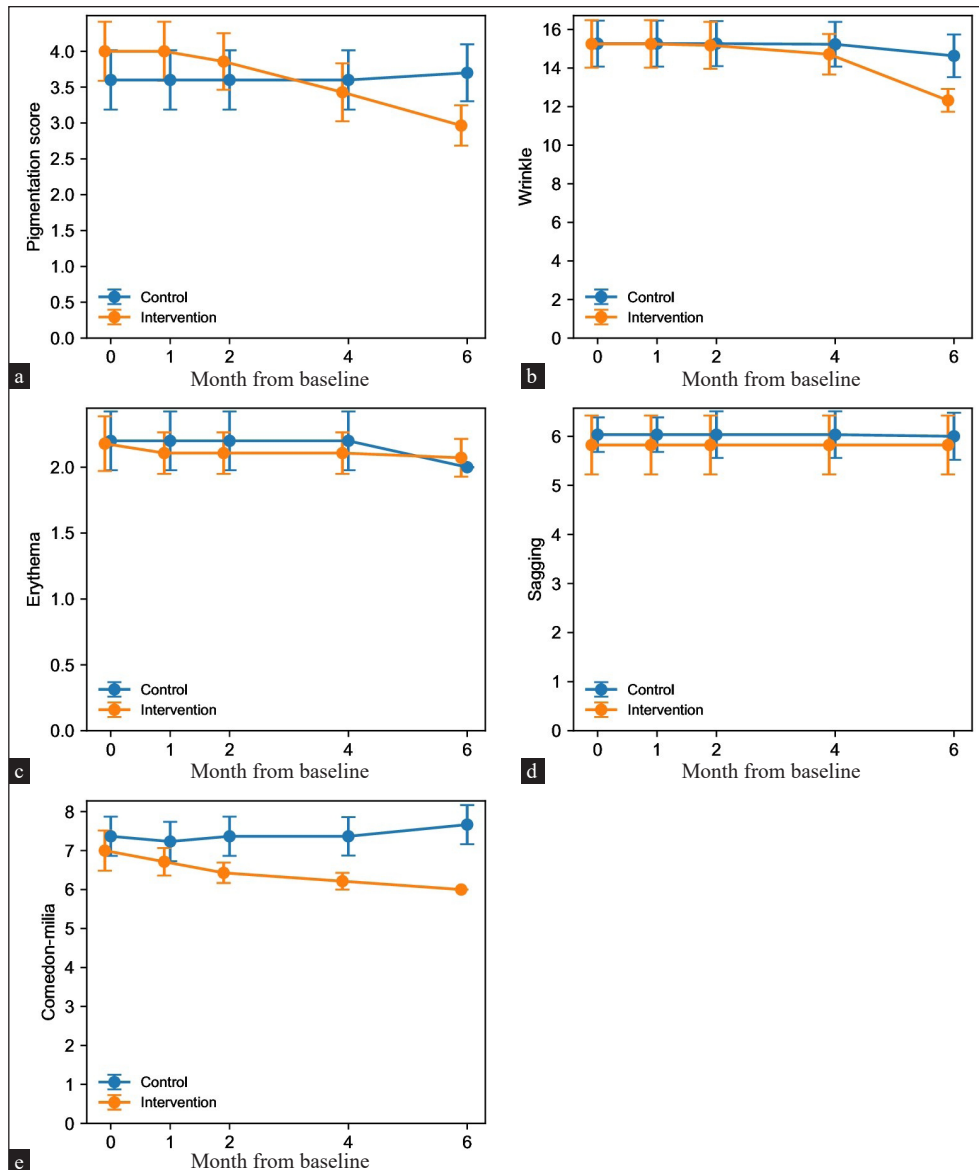


Figure 3: Changes in the mean component scores of SAS over time between the intervention and control arm. The error bars represent 95% confidence intervals of the means. (a) Pigmentation, (b) Wrinkle, (c) Erythema, (d) Sagging, (e) Comedon-milia. (CI: Confidence interval.)

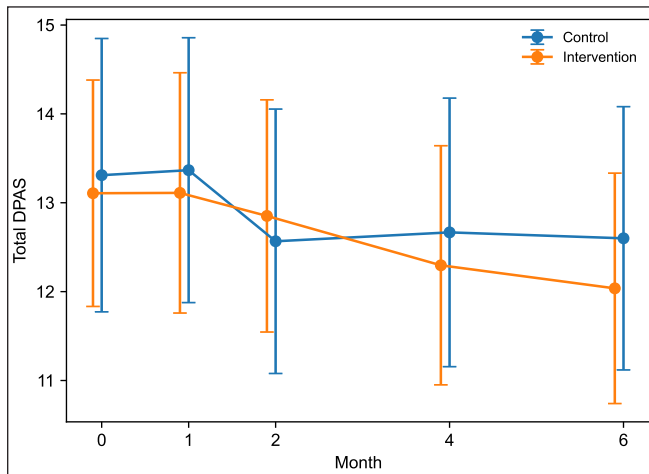


Figure 4: Mean total DPAS scores over time between the intervention and control arm. The error bars were 95% CI of the means. (CI: Confidence interval.)

Table 2: Percentages of adverse events in the intervention arm

Adverse event, n (%)	Month 1	Month 2	Month 4	Month 6
Peeling	7 (25.0)	3 (10.7)	1 (3.6)	0 (0.0)
Stinging	18 (64.3)	12 (42.9)	6 (21.4)	2 (7.1)
Erythema	3 (10.7)	2 (7.1)	1 (3.6)	0 (0.0)
Acne	3 (10.7)	2 (7.1)	0 (0.0)	0 (0.0)
Hyperpigmentation	3 (10.7)	1 (3.6)	0 (0.0)	0 (0.0)

Figure 3 demonstrates reductions in all five SAS component scores after 6 months of adapalene treatment compared to controls, with wrinkle improvement notable from the fourth month onward. Previous studies have confirmed retinoids' effectiveness for skin aging.⁹⁻¹² While tretinoin 0.05% cream showed significant improvements in photodamaged skin after 12 weeks,⁹ and Bhawan *et al.* suggested significant results require 6 months of tretinoin treatment,¹⁰ our findings indicate adapalene's effect on wrinkles may be comparable to tretinoin—the only FDA-approved retinoid for photoaging. We noticed improvement in fine wrinkles on our patient's photos [Figure 5].

Our study demonstrated adapalene's efficacy in improving pigmented lesions. Retinoids reduce pigmentation by accelerating epidermal turnover, inhibiting melanosome transport, and enhancing UV resistance.^{11,12} These improvements aligned with Kang *et al.*'s findings (2003), which showed significant lentiginous reduction within 4 weeks of adapalene treatment.⁴

We used adapalene cream 0.1% in our study. Previous research by Herane *et al.* (2012) examined adapalene 0.3% gel in photoaging, while Bagatin *et al.* (2018) compared adapalene 0.3% gel with tretinoin 0.05% cream.^{5,6} Our findings demonstrate that even the lower 0.1% concentration can effectively improve skin aging parameters, particularly in Asian skin types while maintaining efficacy.

Similar to SAS, the average DPAS index decreased in the intervention arm after 6 months, though not significantly. As DPAS only detects the presence of aging lesions without grading severity, it requires more time to show marked changes. While DPAS excels at early detection of skin aging, it appears less effective for monitoring treatment response.

The commonest side effects in the intervention arm were stinging and xerosis, with less frequent occurrences of skin redness, acne, and hyperpigmentation during the first month of treatment. These manifestations, collectively known as retinoid dermatitis, result from the free carboxylic acid radical in the retinoid structure triggering proinflammatory cytokines including IL-1, TNF- α , IL-6, and IL-8.¹³ Compared to other studies, our results demonstrate that adapalene produced significantly fewer side effects than tretinoin, the first-line retinoid for skin rejuvenation. While tretinoin causes irritation in up to 90% of users during the first 24 weeks and 74% thereafter, adapalene showed a considerably better tolerability profile.¹⁴ This confirms adapalene's superior tolerability compared to tretinoin due to its receptor selectivity.



Figure 5: Under-eye wrinkles before (left) and after 6 months of treatment (right).

Limitations

Limitations including small sample size, short treatment follow-up period, and single-centre validation, should be considered when interpreting the results of this study. Further research with larger sample sizes, longer follow-up periods, and multi-centre designs are recommended to confirm and expand upon these findings.

Conclusion

Adapalene 0.1% was effective in improving signs of skin ageing. The treatment appeared to be well-tolerated in almost all patients. Our study adds unique value to the existing literature by evaluating a lower concentration (0.1%) of adapalene, which may be more suitable for long-term use, including both clinical and dermoscopic assessments, and focusing on Asian skin types, which may respond differently to retinoid treatments. In conclusion, topical adapalene is a promising treatment for skin ageing.

Ethical approval: The research/study was approved by the Institutional Review Board at Ethics Committee of the National Hospital of Dermatology and Venereology, Hanoi, Vietnam, number 369/ HĐĐĐ -BVDLTW, dated 17 August 2021.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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