Efficacy and Safety of 30% Supramolecular Salicylic Acid Peel in the Treatment of Severe Acne Vulgaris: A Multicenter, Randomized, Evaluator-Blinded, Parallel-Controlled Trial

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Abstract

Background: Acne vulgaris (AV) is a common and highly prevalent disease with many unmet treatment needs.

Objective: To evaluate the efficacy and safety of 30% supramolecular salicylic acid (SSA) peel in treating severe AV.

Methods: In this study, we enrolled participants aged 18 to 40 years with severe AV, which was defined according to Pillsbury's International Modified Classification as Grades III or IV. All participants were randomized in a 1:1:1 ratio to receive either 30% SSA peel combined with acne extraction (needle-cleaning), 30% SSA peel alone, or acne extraction (needle-cleaning) alone weekly for 8 weeks. The primary outcomes were the overall effective rate and the global acne grading system (GAGS) score. Safety assessments were conducted throughout the treatment period.

Results: A total of 240 patients were randomized into three groups: combined group (79 patients), SSA peel group (82 patients), and acne extraction group (79 patients). After 8 weeks, the combined group had a significantly higher effective rate compared with the acne extraction group (74.68% vs. 34.18%; $P < 0.0001$). The efficacy in the combined group was similar to that in the SSA peel group (74.68% vs. 68.29%; $P = 0.3695$). GAGS scores were significantly lower in the combined and SSA peel groups compared with the group ($P < 0.0001$). Only one case of mild facial dermatitis was reported in the SSA peel group. No serious adverse events occurred in any of the three groups during this trial.

Conclusion: 30% SSA monotherapy or in combination with acne extraction (needle-cleaning) has a significant effect in the treatment of severe AV. The combined treatment achieved numerically higher efficacy than 30% SSA monotherapy, although the difference did not reach statistical significance. This study is registered in the Chinese Clinical Trial Registry as "efficacy and safety of Broda 30% SSA in the treatment of severe acne" (ChiCTR2100042950).

Keywords: 30% supramolecular salicylic acid; acne extraction (needle-cleaning); severe acne vulgaris

Introduction

Acne vulgaris (AV) is a prevalent chronic inflammatory disease that affects the follicles and sebaceous glands[1]. It is particularly common among adolescents and young adults[2], primarily appearing on the face. The etiopathogenesis of AV is multifactorial and involves follicular hyperproliferation, increased sebum production, inflammation, and microbial overgrowth[3]. The clinical presentation can range from mild facial comedonal lesions, with or without sporadic inflammatory lesions, to severe, widespread, and inflammatory disease accompanied by systemic symptoms[4]. Acne often leads to scarring and post-inflammatory hyperpigmentation (PIH), which can significantly affect the individual's quality of life[5]. Severe AV can also result in psychological and physical consequences that greatly burden those affected. Therefore, early intervention is crucial in the treatment of AV to improve the quality of life and alleviate the psychological and physical burden.

There are various treatment options available for acne, including oral isotretinoin, which effectively targets all the underlying pathways of acne but carries a risk of severe teratogenicity[5]. Therefore, it is important to explore therapies that offer rapid onset, good efficacy, and minimal adverse reactions. Chemical peeling is a widely used cosmetic procedure in medical practice and has been employed for many years[6]. Salicylic acid (SA) is known to remove intercellular lipids, reduce the adhesion of keratinocytes, and promote the loosening and subsequent shedding of these cells[7]. Additionally, it possesses antibacterial, antifungal, and certain anesthetic properties[8]. SA plays a role in preventing acne scar formation and improving existing atrophic scars[9,10]. Furthermore, it can help reduce PIH, which often occurs

after acne lesions have resolved[11]. Traditional synthetic SA has limited solubility in water and is typically dissolved in organic solvents such as ethanol. However, alcoholic solutions can cause skin irritation, leading to poor patient compliance[12]. Supramolecular salicylic acid (SSA) differs from traditional SA as it contains reversible noncovalent bonds. This unique property allows SSA to be soluble in water and released steadily and slowly, maximizing its activity through bond exchange reactions. Moreover, SSA can minimize skin irritation caused by organic solvents, making it suitable for individuals with sensitive skin[13].

Traditional Chinese Medicine has utilized fire needles or acupuncture to treat patients with AV, yielding positive therapeutic outcomes[14,15]. In our study, we conducted a multicenter, randomized, evaluator-blinded, parallel-controlled trial to evaluate the efficacy and safety of 30% SSA in combination with acupuncture, as well as each treatment alone, for the management of severe AV. The results are presented as follows.

Materials and methods

The study received approval from the ethics committee of the First Hospital of China Medical University, and written informed consent was obtained from all participating patients.

Patient selection

The study was conducted from April 2021 to March 2023, recruiting patients with severe AV from the dermatology outpatient clinics of 17 hospitals, defined as Grades III or IV based on Pillsbury's International Modified Classification.

Inclusion criteria

Patients aged 18 to 40 years with a clinical diagnosis of severe AV (Pillsbury Grades III and IV) voluntarily participated in this research and provided written informed consent.

Exclusion criteria

Patients would be excluded if they met the following criteria: (1) the face was suffering from other skin diseases that may aggravate the disease, or the researchers believed that this disease may affect the judgment of the test results; (2) patients allergic to the test drug or hypersensitive system; (3) pregnant or lactating patients; (4) patients with secondary acne, such as occupational acne and acne caused by systemic steroids; (5) patients who took oral antibiotics, glucocorticoids, spironolactone, anti-androgens, and other acne drugs within 4 weeks before the trial; or patients who used physical therapy for acne; or patients who were treated with SA and fruit acid; or patients who used other acne drugs for external use within 2 weeks; (6) patients who took isotretinoin orally within 2 months before the trial (or viaminate within 6 months); (7) patients who had a history of facial injection or surgery 2 months before the trial; (8) patients with immunodeficiency disease; (9) scar constitution and fear of acupuncture.

Elimination criteria

(1) Patients who seriously violated the protocol's criteria and requested withdrawal.

(2) Patients with poor compliance.

(3) Patients who lacked primary indicators, making efficacy evaluation impossible.

(4) Patients who used prohibited drugs during the study, preventing efficacy assessment.

(5) Patients who were randomly enrolled but did not use drugs or lacked follow-up data.

Termination and discontinuation criteria

(1) Patients who had undergone at least four rounds of treatments and follow-up assessments, with the severity of various acne lesions judged by researchers to have worsened or improved by at least one grade (according to the global acne grading system [GAGS]), were classified as early termination subjects.

(2) Early termination subjects were included in the statistical analysis as completed cases.

(3) Subjects had the option to withdraw from the trial at any time for any reason.

(4) Occurrence of severe or intolerable adverse events.

(5) Presence of any exclusion criteria during the study.

(6) Researchers had the authority to withdraw subjects based on medical necessity.

(7) Patients who had achieved 100% reduction in skin lesions could prematurely terminate the study and would be included in the statistical analysis as completed cases.

Treatment

Eligible participants were randomized in a 1:1:1 ratio to receive either 30% SSA peel combined with acne extraction (combined group), 30% SSA peel alone (SSA peel group), or acne extraction alone (acne extraction group) once a week for 8 weeks. Firstly, patients were instructed to thoroughly clean their faces. Secondly, digital facial photographs, including the frontal and lateral faces, were obtained using the VISIA® Skin Analysis System before each treatment session and at follow-ups. All parameters of the epidermal barrier function, such as skin water content, transepidermal water loss (TEWL), potential of hydrogen (pH), and sebum levels, were measured on the forehead, nose, left cheek, right cheek, and chin. Finally, the average values of the five sites were calculated for this study. Given the distinct procedural characteristics of the three interventions, participant and treating-physician blinding was not achievable; only outcome evaluators remained blinded to group allocation, so this trial was evaluator-blinded rather than double-blinded. A modification application has been submitted to the Chinese Clinical Trial Registry to revise the blinding description of trial ChiCTR2100042950.

Combined group

For the combined group, participants were initially treated with acne extraction (needle-cleaning) following disinfection. This local cutaneous procedural intervention, termed acne extraction (needle-cleaning), consists of puncturing superficial acne lesions including comedones, pustules, and cysts with the needle of a 1-mL sterile syringe, followed by gentle evacuation of lesion contents. It differs substantially from traditional meridian acupuncture, which employs fine needles for subcutaneous stimulation of acupoints. Cysts were punctured at the most prominent part, and pus and blood were drained with a cotton swab. After acne extraction (needle-cleaning), disinfection was repeated, and a cold compress with liquid dressing (Broda, Shanghai Ruizhi Pharmaceutical Technology Company, China) was applied for 15–20 min. Inflammatory papules and lesions in the dangerous triangle area were excluded from acne extraction (needle-cleaning) treatment.

Following this, 30% SSA (Broda, Shanghai Ruizhi Pharmaceutical Technology Company, China) was evenly applied to the patient's facial lesions. A layer of water was then brushed onto the face and massaged for 8–15 min simultaneously. During the process, water could be repeatedly added with massage to promote the absorption of SSA. In the chemical peeling procedure, the therapeutic endpoint was defined as the appearance of uniform erythema or frost-like whitening (Grade I frosting) on the target lesions, indicating adequate penetration of the agent. If any discomfort arose, a fan and cold spray could be used to alleviate irritation, and treatment would end after 8 min. Once the endpoint was reached, the peel was removed by rinsing with cold water, followed by a 15–20 min cold compress with liquid dressing and the application of moisturizing cream.

SSA peel and acne extraction (needle-cleaning) group

The SSA peel group received 30% SSA treatment alone, while the acne extraction (needle-cleaning) group received acne extraction (needle-cleaning) treatment. All three groups were treated once a week for a total of eight sessions. After each acne extraction session in the acne-extraction-alone group, patients received identical post-procedural skin care including 15–20 min cold compress with liquid dressing and moisturizing cream application, consistent with the care provided in the combined group and SSA peel-alone group.

Compensatory treatment

Patients in the acne extraction (needle-cleaning) group were eligible for free 30% SSA treatment for 2 months (once every 2 weeks, totaling 4 sessions) after discontinuing acne extraction (needle-cleaning).

Drug combination

Subjects in the trial were restricted from taking oral antibiotics such as minocycline, doxycycline. The combined group was also prohibited from using oral retinoic acid drugs, topical fusidic acid cream, azelaic acid, and retinoic acid. Participants were not allowed to undergo physical therapy or other chemical peeling treatments. Clinical evaluation was done weekly during the study.

Clinical assessment of efficacy

Primary outcomes

The primary outcomes included the overall effective rate and the GAGS score. Improvement in lesions was evaluated by counting comedones, inflammatory papules, pustules, erythema, nodules, and cysts. Two senior dermatologists, who were blinded to group allocation, counted the acne lesions. The clearance rate of skin lesions (%) was calculated using the formula: (number of lesions before treatment−number of lesions after treatment)/number of lesions before treatment × 100%. The efficacy index was determined based on cure (≥ 90%), significant effect (60%–89%), effective (20%–59%), and invalid (< 20%). The effective rate was the sum of cure and significant effect. Patients were scored according to the GAGS proposed by Doshi *et al.* in 1997[16], which divided the face, chest, and back into six regions. Evaluation was performed on facial regions I to V, graded on a 0–4 scale based on the most severe lesion within each location. Patients were classified as mild, moderate, severe, or very severe based on their total score. All images and scores were simultaneously saved and uploaded to the Electronic Data Capture (EDC) system.

Secondary outcomes

The secondary outcomes included disease improvement assessed using VISIA (rated as very satisfied, relatively satisfied, satisfied, and dissatisfied); epidermal barrier function indicators such as skin water content, TEWL, pH, and sebum levels; self-evaluation of efficacy (rated as excellent, good, average, and poor) and symptoms (rated as none, mild, moderate, and severe).

Assessment of adverse effects

Potential adverse events in this study may include pruritus, burning, pain, erythema, swelling, dryness, desquamation, pigmentation, and crusting during and after SSA peel treatment. These events must be documented in the EDC system and reported to the project director. Researchers will provide guidance or treatment to patients experiencing adverse events and follow up until their discomfort is relieved.

Statistical analysis

Statistical analysis of data sets

The intention-to-treat (ITT) population included all randomized cases that underwent treatment and had at least one follow-up record. The per-protocol (PP) population was a subset of the ITT, consisting of cases that adhered to the trial protocol, showed good compliance, and did not receive prohibited drugs or treatments. Both ITT and PP populations were analyzed for primary and secondary efficacy indicators.

Methods of statistical analysis

The Statistical Analysis System (SAS) 9.4 was used to describe and analyze the data in this study. Quantitative indicators were described using mean, standard deviation, median, minimum, and maximum values. Qualitative indicators were presented as the number of cases and percentage in each category. All statistical tests were two-sided, with $P \leq 0.05$ considered statistically significant. Homogeneity among the three groups was compared using analysis of variance (ANOVA), χ^2 test, or rank sum test.

Sample-size calculation

Sample size was calculated based on the primary endpoint, the overall effective rate. We hypothesized that the overall effective rate would be 70% for combined treatment, 60 % for SSA monotherapy, and 35% for acne extraction (needle-cleaning) alone. Setting $\alpha = 0.05$ (two-sided), power = 80 %, and anticipating a 10 % dropout rate, a total sample size of 240 participants (80 subjects per

group in 1:1:1 randomization) was required. Sample-size calculation was performed using PASS 15 software.

Results

There were no statistically significant differences among the three groups in age, sex, height, and weight at baseline, indicating comparability ($P > 0.0500$) (Tables 1 and 2).

Patients

A total of 240 patients were enrolled in this study, recruited from 17 medical research centers across China (see Table S1 for detailed information). Patients were divided into three groups: 79 in the acne extraction group, 82 in the SSA peel group, and 79 in the acne extraction group. Among them, 218 patients completed the trial (73, 74, and 71

Table 1: Baseline characteristics of the 240 patients with acne vulgaris.

Characteristic	ITT			PP		
	Combined group	SSA peel group	Acne extraction group	Combined group	SSA peel group	Acne extraction group
Age (year)						
N (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
Mean ± SD	24.89 ± 5.04	23.98 ± 4.73	25.01 ± 4.39	24.69 ± 4.82	23.98 ± 4.60	25.12 ± 4.50
Median	23.90	22.85	24.30	23.70	22.95	24.30
Min, Max	18.10, 39.90	18.00, 37.30	18.20, 39.50	18.10, 39.90	18.00, 37.30	18.20, 39.50
Sex						
Male *N* (%)	32 (40.51)	41 (50.00)	31 (39.24)	30 (41.10)	37 (50.00)	27 (38.03)
Female *N* (%)	47 (59.49)	41 (50.00)	48 (60.76)	43 (58.90)	37 (50.00)	44 (61.97)
Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
Height (cm)						
N (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
Mean ± SD	168.32 ± 7.78	169.78 ± 8.60	167.59 ± 8.62	168.52 ± 7.89	169.78 ± 8.63	167.44 ± 8.52
Median	168.00	170.00	168.00	168.00	170.00	166.00
Min, Max	150.00, 183.00	150.00, 189.00	152.00, 183.00	150.00, 183.00	150.00, 189.00	152.00, 183.00
Weight (kg)						
N (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
Mean ± SD	60.22 ± 10.29	63.02 ± 14.60	62.41 ± 12.95	60.52 ± 10.36	63.29 ± 14.92	62.52 ± 12.92
Median	59.20	60.00	58.00	59.20	60.00	58.00
Min, Max	41.50, 96.00	44.00, 130.00	45.00, 104.00	41.50, 96.00	44.00, 130.00	45.00, 104.00

Abbreviations: ITT, intention-to-treat; PP, per-protocol; SSA, supramolecular salicylic acid; *N*, number of patients; SD, standard deviation.

Table 2: Results of Intergroup comparisons of demographic characteristics.

Variable	Method	ITT		PP	
		Statistic	*P*	Statistic	*P*
Age (year)	ANOVA	1.137	0.3226	1.114	0.3300
Sex	χ^2	2.280	0.3198	2.301	0.3165
Height (cm)	ANOVA	1.437	0.2396	1.434	0.2406
Weight (kg)	ANOVA	1.057	0.3492	0.900	0.4080

Abbreviations: ITT, intention-to-treat; PP, per-protocol; ANOVA, analysis of variance.

in the three groups respectively), while 22 dropped out (6, 8, and 8 in the three groups respectively), resulting in a dropout rate of 9.17% (7.59%, 9.76%, and 10.13% in the three groups, respectively). Reasons for dropping out included patient choice ($n = 10$), unrelated accidents ($n = 6$), protocol violation ($n = 3$), not meeting criteria ($n = 2$), and loss to follow-up ($n = 1$). All enrolled cases were included in the ITT and safety analysis (Fig. 1 and Table 3).

Evaluation of clinical efficacy

After 8 weeks of treatment, the overall effective rates in the combined group were significantly higher than those in the acne extraction group (74.68% vs. 34.18% in the ITT population, 95% confidence interval [*CI*]: 26.32% to 54.70%, $P < 0.0001$; 79.45% vs. 38.03% in the PP population, 95% *CI*: 26.82% to 56.03%, $P < 0.0001$). The efficacy of the combined group was similar to the SSA peel group (74.68% vs. 68.29% in the ITT population, 95% *CI*: −7.52% to 20.30%, $P = 0.3695$; 79.45% vs. 74.32% in the PP population, 95% *CI*: −8.47% to 18.73%, $P = 0.4610$), with no significant difference between them (Fig. 2 and Table 4). GAGS scores of the combined and SSA peel groups were significantly lower than those in the acne extraction (needle-cleaning) group at the end of the eighth week ($P < 0.0001$) (Fig. 3 and Table 5).

The therapy improvement assessed by VISIA gradually increased in all three groups. The combined and SSA peel groups showed more significant improvement than the acne extraction (needle-cleaning) group ($P < 0.0001$) (Fig. 4). Changes in skin barrier function indicators such as TEWL, skin sebum levels, and skin water content improved in all groups compared with pre-treatment, with no statistical difference among the groups ($P > 0.0500$) (Fig. 5).

The clinical symptoms of the three groups gradually improved with treatment duration. After 8 weeks, the proportion of patients with severe symptoms decreased significantly in the combined group (from 75.95% to 10.96%) and in the acne extraction (needle-cleaning) group (from 81.01% to 28.17%) compared to baseline. Patients' self-evaluation of efficacy in the combined group showed 50.68% graded as excellent and 38.36% as good by the end of the eighth week. In the acne extraction (needle-cleaning) group, 16.90% were excellent and

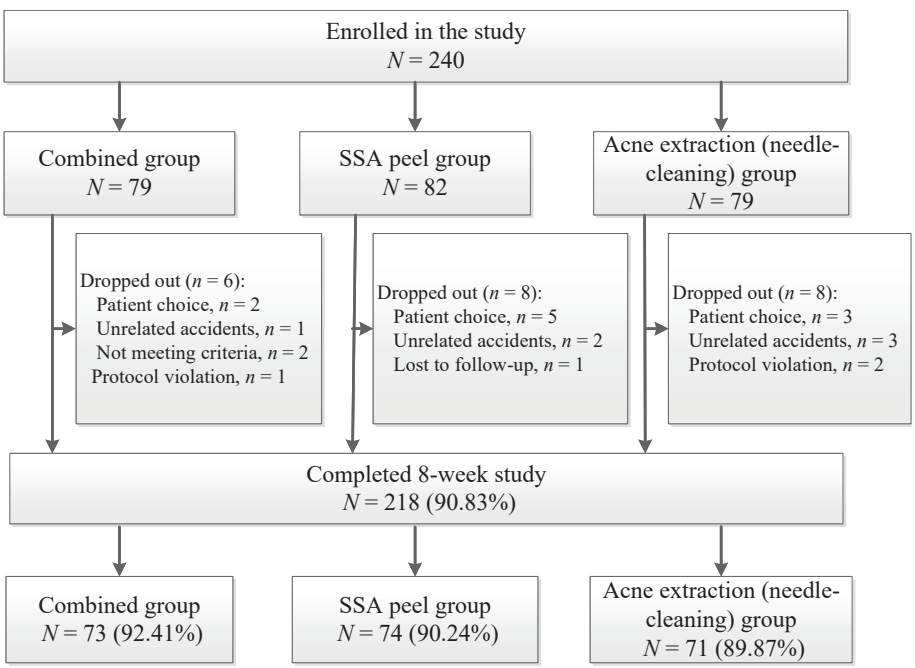


Figure 1: Patient flow diagram for the 8-week study of Chinese patients with severe AV treated with either 30% SSA peel combined with acne extraction (needle-cleaning), or each treatment alone.

Abbreviations: SSA, supramolecular salicylic acid; AV, acne vulgaris; *N and n*, number of patients.

Table 3: Number of enrolled cases and reasons for dropout.

Reason	Combined group *N* (%)	SSA peel group *N* (%)	Acne extraction group *N* (%)	Sum *N* (%)
Total	79 (100.0)	82 (100.0)	79 (100.0)	240 (100.0)
Dropouts during the trial	6 (7.59)	8 (9.76)	8 (10.13)	22 (9.17)*
Patient choice	2 (2.53)	5 (6.10)	3 (3.80)	10 (4.17)
Adverse events	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Unrelated accidents	1 (1.27)	2 (2.44)	3 (3.80)	6 (2.50)
Not meeting criteria	2 (2.53)	0 (0.00)	0 (0.00)	2 (0.83)
Protocol violation	1 (1.27)	0 (0.00)	2 (2.53)	3 (1.25)
Lost to follow-up	0 (0.00)	1 (1.22)	0 (0.00)	1 (0.42)
Withdrawal of informed consent	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Dead	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Others	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

* Comparison of inter-group dropout rates, Fisher's $P = 0.8855$.

Abbreviations: *N*, number of patients; SSA, supramolecular salicylic acid.

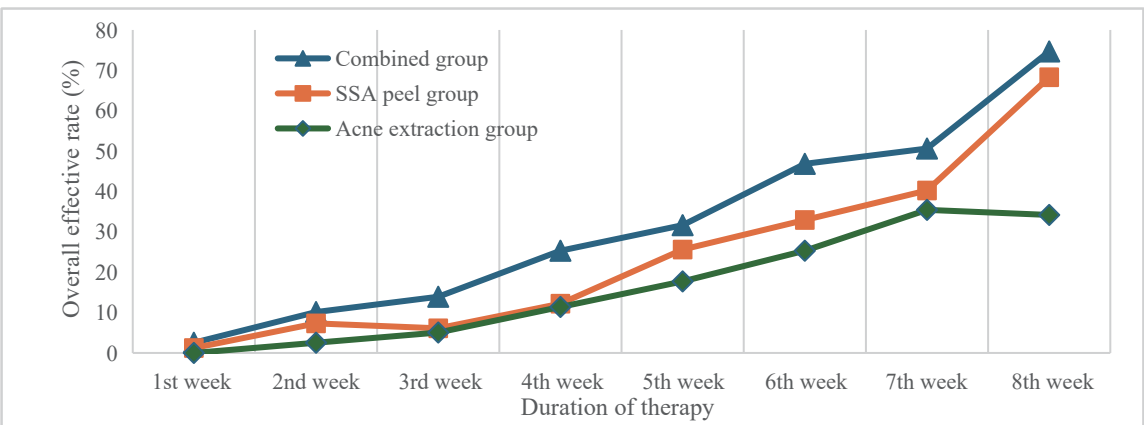


Figure 2: Changes in the overall effective rate throughout the treatment period.

Abbreviations: SSA, supramolecular salicylic acid.

35.21% were good. Self-evaluation in the combined and SSA peel groups was superior to the acne extraction (needle-cleaning) group, with a significant difference between the groups ($P < 0.0500$) (Fig. 6). Before-after clinical photographs of two patients from each group are displayed in Figure 7.

Adverse effects

There was only one adverse event in the SSA peel group (incidence rate of 1.22%), which presented with mild pruritus, burning sensation, facial erythema, and desquamation. No other participants reported clinically significant pruritus, burning, persistent erythema, desquamation, pigmentation, or crusting. No adverse events occurred in the combined group and the acne extraction (needle-cleaning) group, and no serious adverse events were reported. Mild transient and self-limiting redness and dryness occurring immediately after peeling (expected procedural irritation) were not classified as adverse events in accordance with our pre-specified safety case-report form definition.

Table 4: The overall effective rate in ITT and PP populations.

Time point	Outcome	ITT			PP		
		Combined group	SSA peel group	Acne extraction group	Combined group	SSA peel group	Acne extraction group
1st week							
	Effective *N* (%)	2 (2.53)	1 (1.22)	0 (0.00)	2 (2.74)	1 (1.35)	0 (0.00)
	Invalid *N* (%)	77 (97.47)	81 (98.78)	79 (100.00)	71 (97.26)	73 (98.65)	71 (100.00)
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
2nd week							
	Effective *N* (%)	8 (10.13)	6 (7.32)	2 (2.53)	8 (10.96)	6 (8.11)	2 (2.82)
	Invalid *N* (%)	71 (89.87)	76 (92.68)	77 (97.47)	65 (89.04)	68 (91.89)	69 (97.18)
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
3rd week							
	Effective *N* (%)	11 (13.92)	5 (6.10)	4 (5.06)	11 (15.07)	5 (6.76)	4 (5.63)
	Invalid *N* (%)	68 (86.08)	77 (93.90)	75 (94.94)	62 (84.93)	69 (93.24)	67 (94.37)
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
4th week							
	Effective *N* (%)	20 (25.32)	10 (12.20)	9 (11.39)	20 (27.40)	10 (13.51)	9 (12.68)
	Invalid *N* (%)	59 (74.68)	72 (87.80)	70 (88.61)	53 (72.60)	64 (86.49)	62 (87.32)
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
5th week							
	Effective *N* (%)	25 (31.65)	21 (25.61)	14 (17.72)	25 (34.25)	21 (28.38)	14 (19.72)
	Invalid *N* (%)	54 (68.35)	61 (74.39)	65 (82.28)	48 (65.75)	53 (71.62)	57 (80.28)
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
6th week							
	Effective *N* (%)	37 (46.84)	27 (32.93)	20 (25.32)	36 (49.32)	26 (35.14)	20 (28.17)
	Invalid *N* (%)	42 (53.16)	55 (67.07)	59 (74.68)	37 (50.68)	48 (64.86)	51 (71.83)
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
7th week							
	Effective *N* (%)	40 (50.63)	33 (40.24)	28 (35.44)	39 (53.42)	32 (43.24)	28 (39.44)
	Invalid *N* (%)	39 (49.37)	49 (59.76)	51 (64.56)	34 (46.58)	42 (56.76)	43 (60.56)
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
8th week							
	Effective *N* (%)	59 (74.68)	56 (68.29)	27 (34.18)	58 (79.45)	55 (74.32)	27 (38.03)
	Invalid *N* (%)	20 (25.32)	26 (31.71)	52 (65.82)	15 (20.55)	19 (25.68)	44 (61.97)
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)

Abbreviations: ITT, intention-to-treat; PP, per-protocol; SSA, supramolecular salicylic acid; *N*, number of patients.

Discussion

SA is a lipid-soluble component that can reduce the adhesion between keratinocytes, extract intercellular connecting bridging granule proteins, and disrupt the cohesion of epidermal cells. With properties such as reducing oil secretion, regulating keratinization, and having anti-inflammatory and antibacterial effects, SA

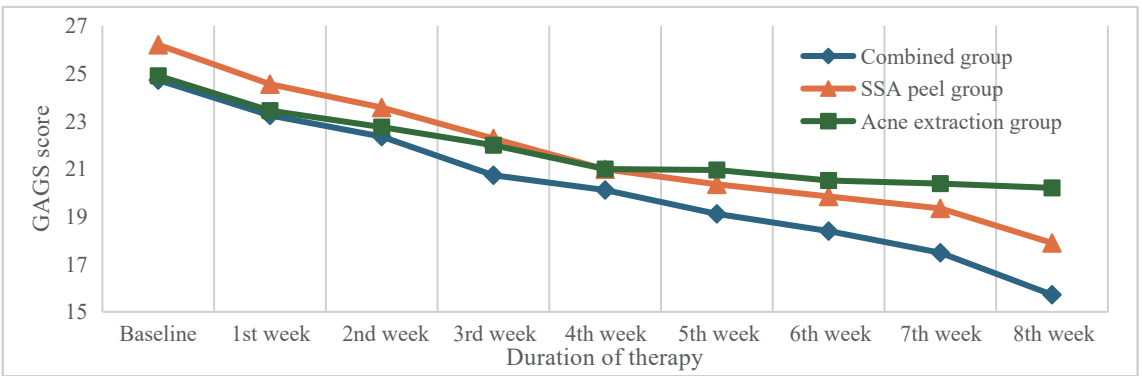


Figure 3: Changes in the GAGS scores throughout the treatment period.

Abbreviations: SSA, supramolecular salicylic acid; GAGS, global acne grading system.

Table 5: The global acne grading system (GAGS) scores in ITT and PP populations.

Time point	Statistic	ITT			PP		
		Combined group	SSA peel group	Acne extraction group	Combined group	SSA peel group	Acne extraction group
Baseline							
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
	Mean ± SD	24.72 ± 4.80	26.20 ± 4.66	24.90 ± 4.74	24.73 ± 4.81	26.39 ± 4.59	24.89 ± 4.71
	Median	25.00	27.00	26.00	25.00	28.00	26.00
	Min, Max	11.00, 32.00	13.00, 32.00	12.00, 32.00	11.00, 32.00	13.00, 32.00	12.00, 32.00
1st week							
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
	Mean ± SD	23.24 ± 4.68	24.55 ± 4.96	23.44 ± 5.05	23.18 ± 4.71	24.59 ± 4.91	23.39 ± 5.13
	Median	23.00	25.00	24.00	23.00	25.00	24.00
	Min, Max	12.00, 32.00	13.00, 32.00	12.00, 32.00	12.00, 32.00	13.00, 32.00	12.00, 32.00
2nd week							
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
	Mean ± SD	22.35 ± 5.00	23.57 ± 4.95	22.75 ± 4.87	22.29 ± 5.07	23.62 ± 4.96	22.70 ± 4.89
	Median	22.00	24.00	23.00	22.00	24.00	23.00
	Min, Max	10.00, 32.00	13.00, 32.00	13.00, 32.00	10.00, 32.00	13.00, 32.00	13.00, 32.00
3rd week							
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
	Mean ± SD	20.73 ± 5.14	22.27 ± 5.51	21.99 ± 5.31	20.60 ± 5.19	22.09 ± 5.47	21.80 ± 5.38
	Median	21.00	23.00	22.00	21.00	23.00	22.00
	Min, Max	7.00, 32.00	9.00, 32.00	10.00, 31.00	7.00, 32.00	9.00, 32.00	10.00, 31.00
4th week							
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
	Mean ± SD	20.11 ± 5.36	20.98 ± 5.26	20.99 ± 5.52	19.93 ± 5.41	20.89 ± 5.16	20.69 ± 5.57
	Median	20.00	20.00	22.00	20.00	20.00	21.00
	Min, Max	1.00, 31.00	11.00, 32.00	9.00, 31.00	1.00, 31.00	11.00, 32.00	9.00, 31.00

(*continued*)

Table 5

(continued)

Time point	Statistic	ITT			PP		
		Combined group	SSA peel group	Acne extraction group	Combined group	SSA peel group	Acne extraction group
5th week							
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
	Mean ± SD	19.11 ± 5.16	20.35 ± 5.43	20.95 ± 5.64	18.85 ± 5.14	20.04 ± 5.32	20.65 ± 5.70
	Median	20.00	20.50	21.00	19.00	20.00	20.00
	Min, Max	6.00, 31.00	7.00, 32.00	9.00, 32.00	6.00, 30.00	7.00, 32.00	9.00, 32.00
6th week							
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
	Mean ± SD	18.39 ± 5.32	19.84 ± 5.36	20.51 ± 6.05	18.07 ± 5.27	19.51 ± 5.16	20.15 ± 6.12
	Median	18.00	19.00	21.00	18.00	19.00	21.00
	Min, Max	6.00, 31.00	8.00, 32.00	8.00, 31.00	6.00, 28.00	8.00, 32.00	8.00, 31.00
7th week							
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
	Mean ± SD	17.48 ± 5.04	19.34 ± 5.43	20.38 ± 5.91	17.08 ± 4.89	18.96 ± 5.10	20.01 ± 5.96
	Median	17.00	19.00	21.00	17.00	18.00	20.00
	Min, Max	6.00, 31.00	8.00, 32.00	8.00, 31.00	6.00, 27.00	8.00, 32.00	8.00, 31.00
8th week							
	Sum (missing)	79 (0)	82 (0)	79 (0)	73 (0)	74 (0)	71 (0)
	Mean ± SD	15.72 ± 4.55	17.89 ± 5.40	20.20 ± 5.81	15.18 ± 4.13	17.35 ± 4.92	19.82 ± 5.84
	Median	16.00	17.50	21.00	15.00	17.00	20.00
	Min, Max	3.00, 31.00	4.00, 30.00	7.00, 31.00	3.00, 25.00	4.00, 30.00	7.00, 31.00

Abbreviations: ITT, intention-to-treat; PP, per-protocol; SSA, supramolecular salicylic acid; SD, standard deviation.

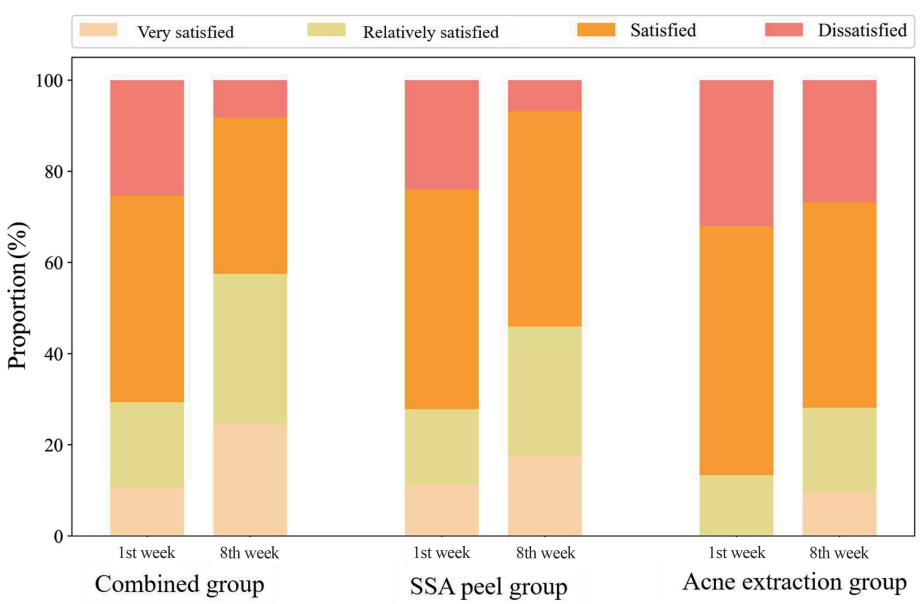


Figure 4: The degree of improvement of the treatment under VISIA.

Abbreviations: SSA, supramolecular salicylic acid.

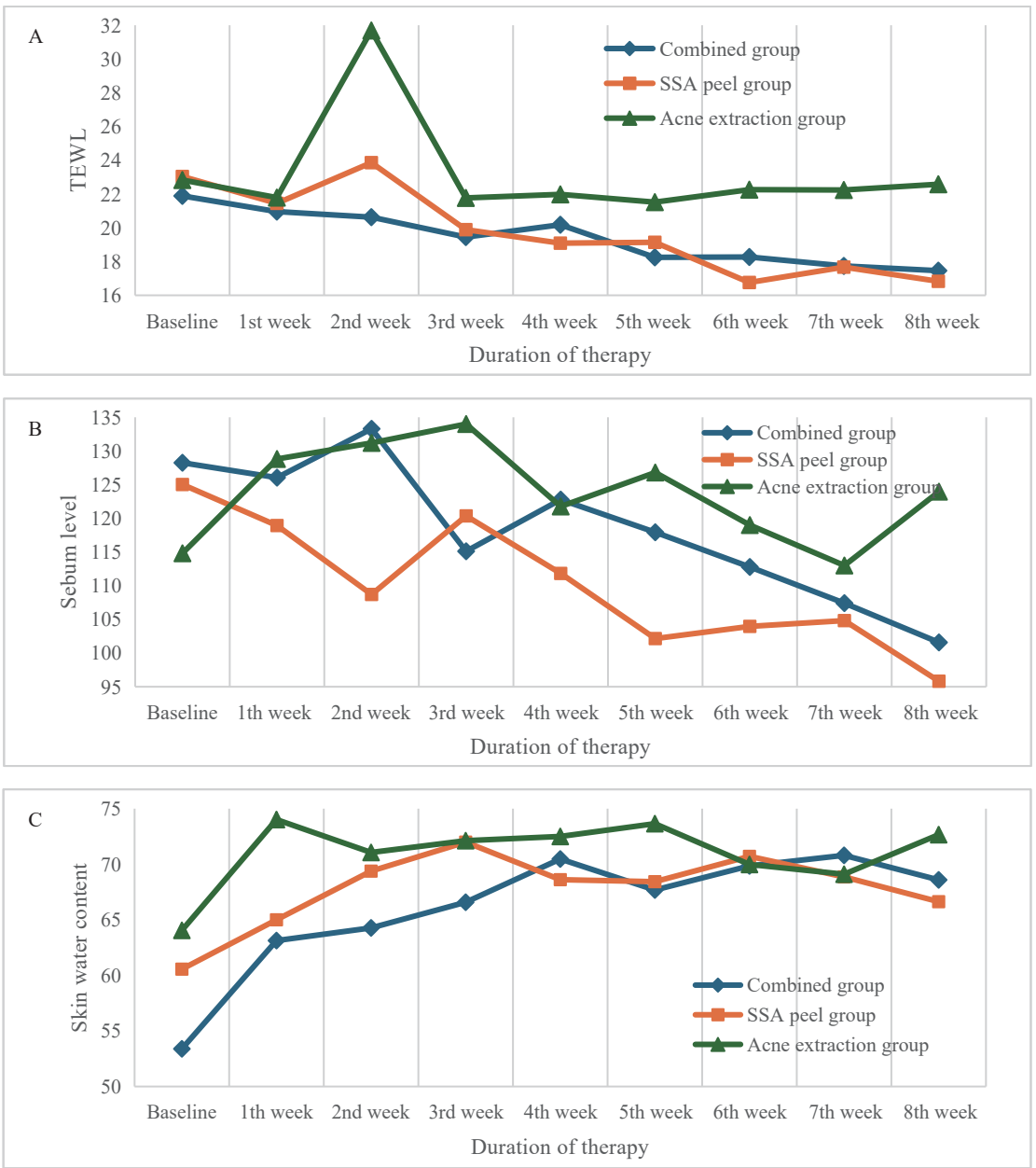


Figure 5: Parameters of the epidermal barrier function throughout the treatment period. (A) TEWL. (B) Sebum levels. (C) Skin water content.

Abbreviations: SSA, supramolecular salicylic acid; TEWL, transepidermal water loss.

has therapeutic effects on both non-inflammatory and inflammatory lesions of AV[10]. However, these functions are limited to the epidermis. The reversible noncovalent bonding used by 30% SSA allows it to penetrate deeper but makes it difficult to reach the dermis, and the slow-release effect prolongs the time it takes to take effect[17].

Our study evaluated the efficacy and safety of 30% SSA alone or combined with acne extraction (needle-cleaning) in treating severe AV. After 8 weeks of treatment, the combined group and SSA peel group had significantly higher overall effective rates compared with the acne extraction (needle-cleaning) group. A significant increase in the overall effective rate was seen after 4 weeks of therapy in the combined group, with no significant difference between the combined group and the SSA

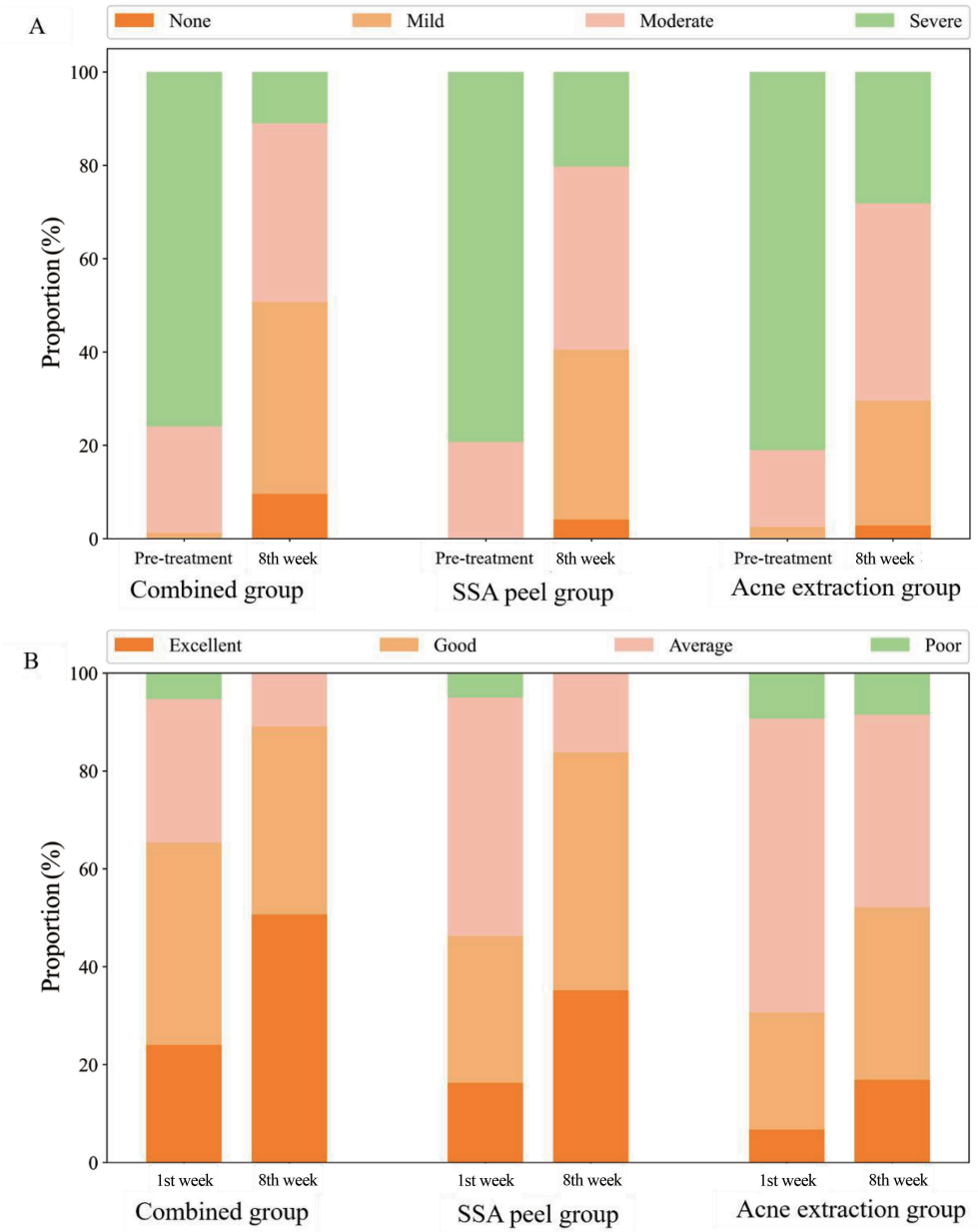


Figure 6: The proportion of patients' self-evaluation of symptoms (A) and efficacy (B) before and after treatment.

Abbreviations: SSA, supramolecular salicylic acid.

peel group at the end of therapy. This shows that 30% SSA has a certain efficacy in treating severe AV, which is consistent with previous findings supporting SSA as an effective treatment for severe AV[18–22]. Moreover, 30% SSA can be absorbed more effectively after pre-therapy acne extraction (needle-cleaning), with the two treatments complementing each other. This may contribute to the numerically better outcomes of combined therapy compared to SSA alone, though no statistically significant difference was observed. The GAGS score is a commonly used index for assessing acne severity and treatment effectiveness. Our results indicated that the GAGS scores decreased significantly more in the combined group and SSA peel group compared with the acne extraction (needle-cleaning) group, further confirming the efficacy of 30% SSA in alleviating AV. We hypothesize that the therapeutic effect of 30% SSA peel in severe AV may be attributed to its ability to improve the skin

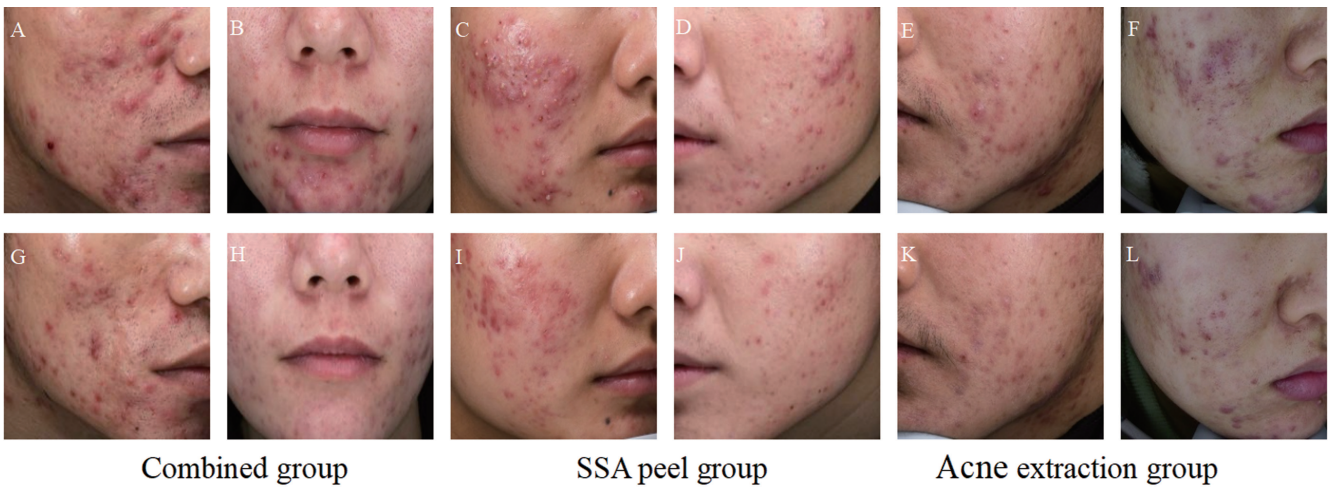


Figure 7: Improvement in lesions of acne vulgaris before (A–F) and after eight rounds of treatment (G–L).

Abbreviations: SSA, supramolecular salicylic acid.

microenvironment and modulate the skin microbiome, thereby reducing local inflammation.

Additionally, VISIA was utilized to evaluate disease improvement in the three groups. The results indicated that the combined group and SSA peel group demonstrated significantly greater improvement compared to the acne extraction (needle-cleaning) group. VISIA assessment offers an objective measure of disease improvement, reinforcing the effectiveness of SSA in acne treatment. Patients' self-assessments also corroborated these findings, with individuals in the combined group and SSA peel group reporting superior efficacy compared with those in the acne extraction (needle-cleaning) group, consistent with the GAGS score results. Patients' subjective evaluations act as a valuable supplementary indicator, reflecting their genuine perceptions of treatment outcomes. Therefore, our results further substantiate the efficacy of SSA in treating severe AV.

Based on the analysis of skin barrier function indicators, although TEWL, sebum level, and skin water content showed varying degrees of improvement, there was no statistical difference among the three groups. The lack of significant difference could be attributed to several possible reasons from a clinical perspective. Firstly, the three treatments may have similar effects on skin barrier function indicators. Secondly, significant effects in acne treatment often require a certain observation period. Our study and observation lasted only 8 weeks, which may not have been sufficient to detect noticeable differences. Additionally, the selected skin barrier function indicators may not comprehensively assess treatment effects, suggesting the need for additional outcome measures or methods.

In terms of side effects, only one case of mild facial dermatitis was reported in the SSA peel group. No patients experienced any serious adverse effects that required discontinuation of therapy.

However, our study had limitations. Firstly, we did not conduct follow-up to determine the recurrence rate among the patients after the trial ended. It would have been beneficial to observe the efficacy and side effects over a longer period. Secondly, we did not obtain skin microbial samples and lesional skin biopsies at the beginning and end of the treatment, which prevented the analysis of the cutaneous microbiome richness and tissue expression of inflammatory factors. Thirdly, there was no blank or placebo control group in our trial. We selected acne extraction (needle-cleaning) alone as the active comparator. Therefore, we cannot separate the true therapeutic effect of 30% SSA peel from the natural disease course or placebo response. Future studies incorporating placebo control are needed to further validate the magnitude of treatment effect of SSA for severe AV. Therefore, further long-term follow-up studies are needed to validate our results.

Conclusion

This clinical study confirms that 30% SSA monotherapy or in combination with acne extraction (needle-cleaning) can significantly reduce inflammatory lesions and improve clinical symptoms in patients with severe AV. The combined treatment achieved numerically higher efficacy than 30% SSA monotherapy, although the difference did not reach statistical significance. Additionally, the treatment was found to be safe, with no serious adverse events reported. Therefore, 30% SSA monotherapy or combined with acne extraction (needle-cleaning) is considered an effective and safe treatment for severe AV, recommended for clinical use.

Author contributions

Xiaoqian Zhao: writing–original draft, investigation, and methodology; Litao Zhang, Enpin Yang, Yan You, Weihui Zeng, Haixia Jing, Xian Jiang, Hongzhong Jin, Rong Xu, Shiqin Tao, Jin Chen, Wei Lai, Nan Yu, Bingjiang Lin, Gang Wang, Juan Tao, and Zhu Shen: data curation, formal analysis. All authors reviewed, edited, and approved the final version of the manuscript and agreed to its publication; Li Zhang: funding acquisition, methodology, writing–review and editing, and project administration.

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Ethics statement

This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of the First Hospital of China Medical University (Approval No. AF-SOP-07-1.1-01).

All figures are either original to this work or properly attributed. No original images have been previously published, and all images comply with research integrity standards without inappropriate manipulation or misrepresentation.

Patient consent statement

Written informed consent was obtained from the patient/all participants for publication of this case presentation and accompanying images.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

AI statement

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the preparation, analysis, writing, image generation, or image processing of this manuscript.

Conflicts of interest

Gang Wang serves as Associate Editor-in-Chief of this journal. Litao Zhang, Yan You, Xian Jiang, Hongzhong Jin, Jin Chen, Nan Yu, Juan Tao, Zhu Shen, and Li Zhang are members of the Editorial Board of this journal. These authors were not involved in the editorial review or decision-making process for this manuscript. All editorial decisions were made independently by other members of the Editorial Board who have no relevant conflicts of interest. The remaining authors declare no conflicts of interest.

Supplementary files

Supplementary material is available in the online version of this article at https://doi.org/10.2738/SKIN.2026.0043 and is accessible for authorized users.

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