

Open Study Comparing 5% Sodium L-Ascorbyl-2-Phosphate Lotion Versus 1% Clindamycin Phosphate Lotion for Acne Vulgaris

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Among the multiple roles of vitamin C in keratinocyte and dermal tissue, the role of scavenging active oxygen species is one of the most important. We postulated that 5% sodium L-ascorbyl-2-phosphate lotion (APS), a vitamin C derivative, would be an effective topical agent for treating patients with acne vulgaris because of its active oxygen scavenging property. As a result, we conducted a multicenter, open-label clinical trial comparing the efficacy and tolerability of APS versus 1% clindamycin phosphate lotion (CL) in the treatment of facial acne vulgaris. APS demonstrated efficacy in the topical treatment of acne vulgaris and superiority to CL for this indication.

Recently, the many roles of vitamin C in human skin processes have been reported in several dermatologic journals.¹⁻³ Among the multiple roles of vitamin C in keratinocyte and dermal tissue, the role of scavenging active oxygen species appears to be one of the most important. We hypothesized that this scavenging effect inhibits sebum oxidation and would thus prevent comedone formation. Previously, we have reported on the efficacy of 5% sodium L-ascorbyl-2-phosphate lotion (APS), a vitamin C derivative, in the treatment of

acne vulgaris and acne scarring.⁴⁻⁶ The study presented in this article was a multicenter, open-label clinical trial comparing the efficacy and tolerability of APS and 1% clindamycin phosphate lotion (CL) in patients with facial acne vulgaris.

METHODS

Patients

Eighty patients (77 women and 3 men aged 16–37 years) with at least 10 and fewer than 50 inflammatory lesions, at least 10 and fewer than 100 noninflammatory lesions, and no more than 2 nodulocystic lesions on the face were enrolled in this study. Patients had not used any other topical treatment for 4 weeks, systemic antibiotics for 4 weeks, or systemic retinoids for at least 6 months prior to participating in the study. Women participating in the study were not pregnant or lactating and had discontinued oral contraceptives for at least 3 months prior to entering the study.

Seventy patients completed the study (37 in the APS group and 33 in the CL group). Ten patients discontinued the study; 7 patients were unable to come to the clinic as

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APS VS CL FOR ACNE VULGARIS

scheduled, and 3 patients wanted to take an oral contraceptive against the protocol.

Enrolled patients were randomized to apply either APS or CL in the morning and in the evening for 12 consecutive weeks. Any other topical or oral treatments were not allowed during the study period. Efficacy, tolerability, and lesion-count evaluations were performed by a blinded investigator.

Efficacy

Efficacy and cutaneous tolerability were assessed at baseline and at weeks 4, 8, and 12 by counting and observing the changes in inflammatory and noninflammatory facial lesions. Clinical global assessment was performed by the blinded investigator for each patient at week 12 and was compared with baseline using the following scale: 0=worsening; 1=poor improvement; 2=mild

TABLE 1

Global Improvement Scores and Mean Lesion Count Reduction (N=70)*†‡

	APS Group, No. of Patients (%)	CL Group, No. of Patients (%)
Global Improvement		
0	1 (2.70)	5 (15.15)
1	4 (10.81)	8 (24.24)
2	4 (10.81)	2 (6.06)
3	20 (54.05)	17 (51.52)
4	8 (21.62)	1 (3.03)
Mean Lesion Reduction, % (±SD)		
IFL	65.7 (±25.9)	39.4 (±57.2)
NIFL	58.1 (±31.1)	40.7 (±31.0)

*Seventy patients completed the study (37 in the APS group and 33 in the CL group).

†Global improvement was graded according to the following scale: 0=worsening; 1=poor improvement; 2=mild improvement; 3=good improvement; 4=excellent improvement.

‡APS indicates 5% sodium L-ascorbyl-2-phosphate lotion; CL, 1% clindamycin phosphate lotion; IFL, inflammatory lesion; NIFL, noninflammatory lesion.

TABLE 2

Mean Lesion Counts at Baseline and Week 12 (N=70)*

	Mean IFL Count at Baseline	Mean IFL Count at Week 12	Mean NIFL Count at Baseline	Mean NIFL Count at Week 12
APS Group (n=37)	29.0	10.2	27.8	10.5
CL Group (n=33)	24.6	15.1	21.2	12.5

*IFL indicates inflammatory lesion; NIFL, noninflammatory lesion; APS, 5% sodium L-ascorbyl-2-phosphate lotion; and CL, 1% clindamycin phosphate lotion.

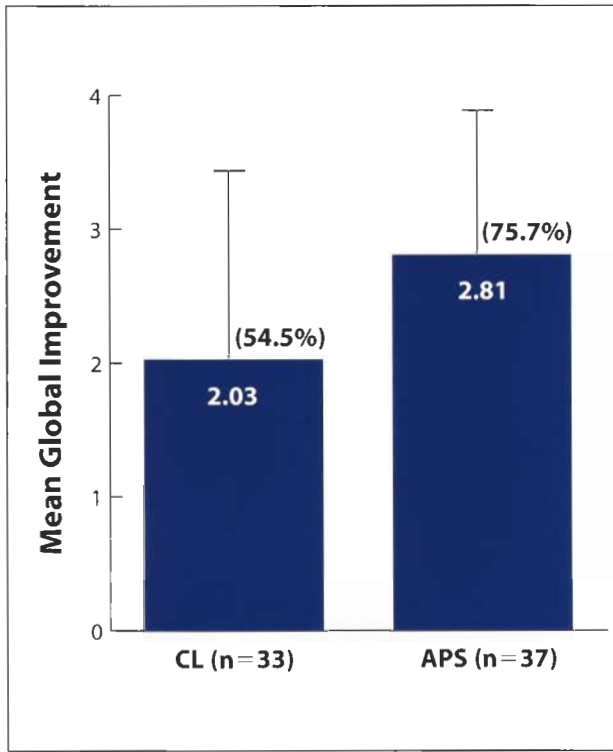


Figure 1. Mean global improvement scores after 12 weeks of treatment with APS and CL. Difference between APS and CL treatment groups is statistically significant ($P < .01$). Values in parentheses indicate percentage of patients with good and excellent improvement scores; bars, deviations; CL, 1% clindamycin phosphate lotion; APS, 5% sodium L-ascorbyl-2-phosphate lotion.

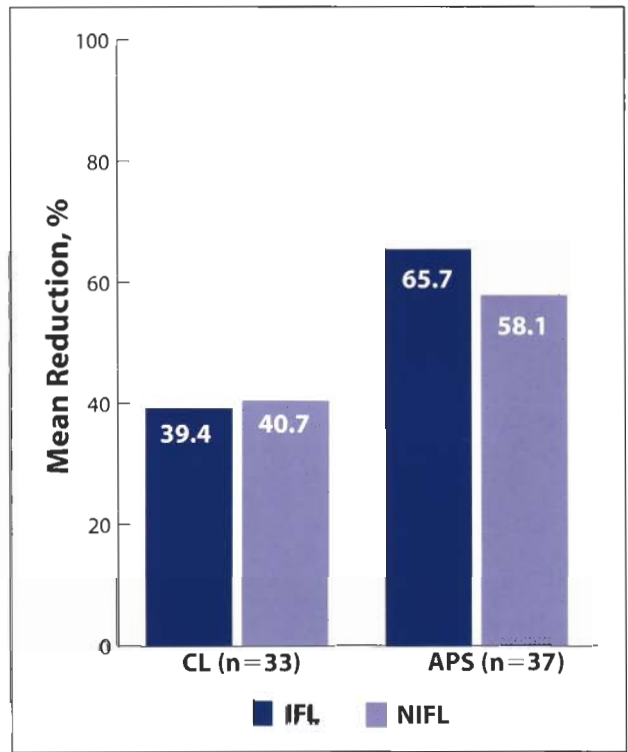


Figure 2. Mean percentage reduction of inflammatory and noninflammatory lesions after 12 weeks of treatment. Values for the APS treatment group are statistically significantly higher than those of the CL treatment group ($P < .01$ and $P < .05$, respectively). IFL indicates inflammatory lesions; NIFL, noninflammatory lesions; CL, 1% clindamycin phosphate lotion; APS, 5% sodium L-ascorbyl-2-phosphate lotion.

improvement; 3=good improvement; and 4=excellent improvement. Cutaneous tolerability was assessed by observation of burning, erythema, or scaling and was graded according to the following scale: 0=none; 1=mild; 2=moderate; and 3=severe.

Statistical analysis was performed using the Mann-Whitney *U* test and the paired Student *t* test. All statistical tests were 2-sided, and *P* values of .05 or less were considered statistically significant.

RESULTS

Table 1 shows the mean percentage reductions in inflammatory and noninflammatory lesions, as well as global improvement at week 12. Table 2 shows mean inflammatory and noninflammatory lesion counts at baseline and week 12. The percentage of patients in the APS treatment group showing either good or excellent improvement was 75.7% (28/37) compared with 54.5% (18/33) in the CL treatment group (Figure 1). Differences were analyzed using the paired Student *t* test, and *P* values of .05 or less were considered statistically significant. The mean percentage reductions in inflammatory and noninflammatory

lesions are shown in Figure 2. Figures 3 through 5 show overall improvement of patients in the APS treatment group at week 12. Mean percentage reductions in inflammatory and noninflammatory lesion counts were statistically significant in the APS treatment group compared with the CL treatment group ($P < .01$ and $P < .05$, respectively).

Cutaneous Tolerability

Irritation was generally mild in both treatment groups, and none of the 70 patients enrolled discontinued the study because of adverse events. Global cutaneous tolerability scores are shown in Table 3. Tolerability was good in both treatment groups, and global tolerability in the APS group was excellent.

Statistical Analysis

Global improvement scores, as well as inflammatory and noninflammatory lesion counts were compared. Mean values were analyzed using the paired Student *t* test, and *P* values of less than .05 were considered statistically significant.

TABLE 3

Global Cutaneous Tolerability Scores*†‡

	Score				Average
	0	1	2	3	
APS Group, No. of Patients (%)					
Burning	29 (78.4)	7 (18.9)	1 (2.7)	0 (0)	0.24
Erythema	25 (67.6)	10 (27.0)	2 (5.4)	0 (0)	0.38
Scaling	30 (81.1)	7 (18.9)	0 (0)	0 (0)	0.19
CL Group, No. of Patients (%)					
Burning	22 (66.7)	7 (21.2)	3 (9.1)	1 (3.0)	0.49
Erythema	18 (54.5)	13 (39.4)	2 (6.1)	0 (0)	0.52
Scaling	18 (54.5)	12 (36.4)	3 (9.1)	0 (0)	0.55

*Seventy patients completed the study (37 in the APS group and 33 in the CL group).

†APS indicates 5% sodium L-ascorbyl-2-phosphate lotion; CL, 1% clindamycin phosphate lotion.

‡Cutaneous tolerability was assessed by observation of burning, erythema, or scaling and graded according to the following scale: 0=none; 1=mild; 2=moderate; 3=severe.



Figure 3. Patient at baseline (A) and after (B) 12 weeks of twice-daily topical treatment with 5% sodium L-ascorbyl-2-phosphate lotion.

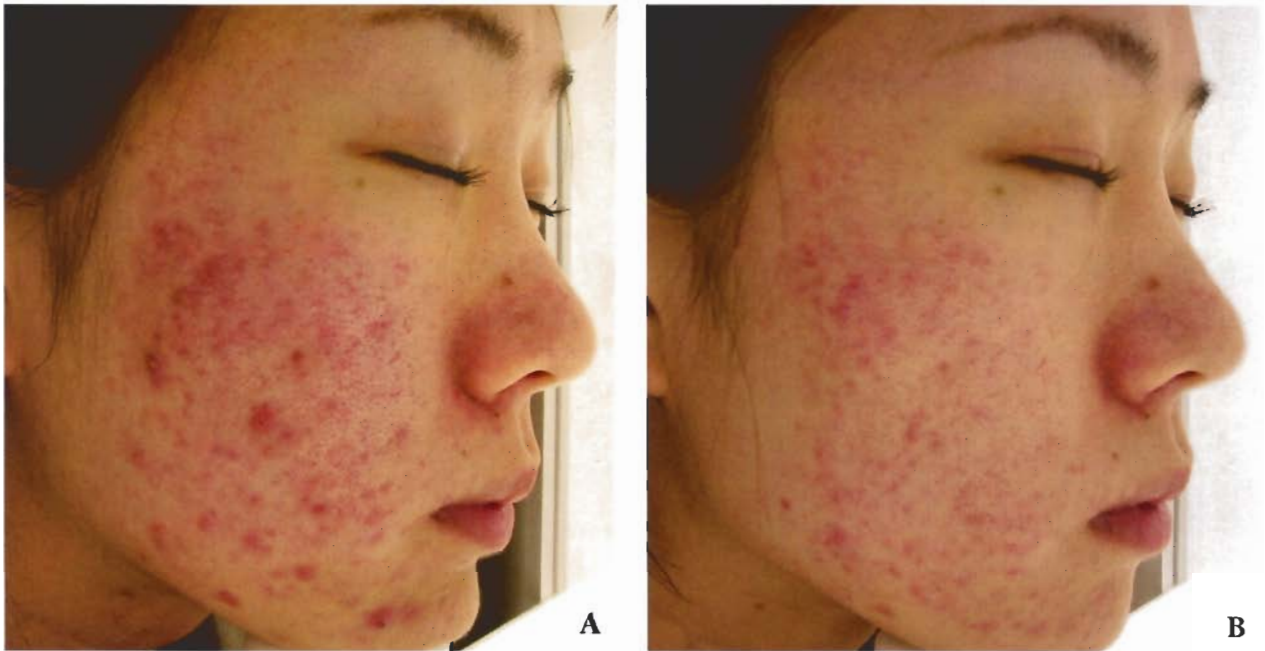


Figure 4. Patient at baseline (A) and after (B) 12 weeks of twice-daily topical treatment with 5% sodium L-ascorbyl-2-phosphate lotion.

Study results demonstrated the superiority of APS over CL in the treatment of facial acne. APS was shown to be superior to CL in percentage reductions in inflammatory and noninflammatory lesions, as well as global improvement scores (Figures 1 and 2; Tables 1 and 2).

COMMENT

The etiology of acne vulgaris involves complex interactions among several phenomena and factors. The oxidation of

sebum and free fatty acids causes follicular keratinization,^{7,8} resulting in sebum retention and proliferation of *Propionibacterium acnes*. However, the main cause of triglyceride oxidation in the follicles and consequently abnormal follicular keratinization remains unclear. Downing et al⁹ explained that relative shortage of linoleic acid causes excessive keratinization of follicles. Motoyoshi¹⁰ asserted that squalene in sebum is hyperoxidized and epidermal hypercornification is accelerated in

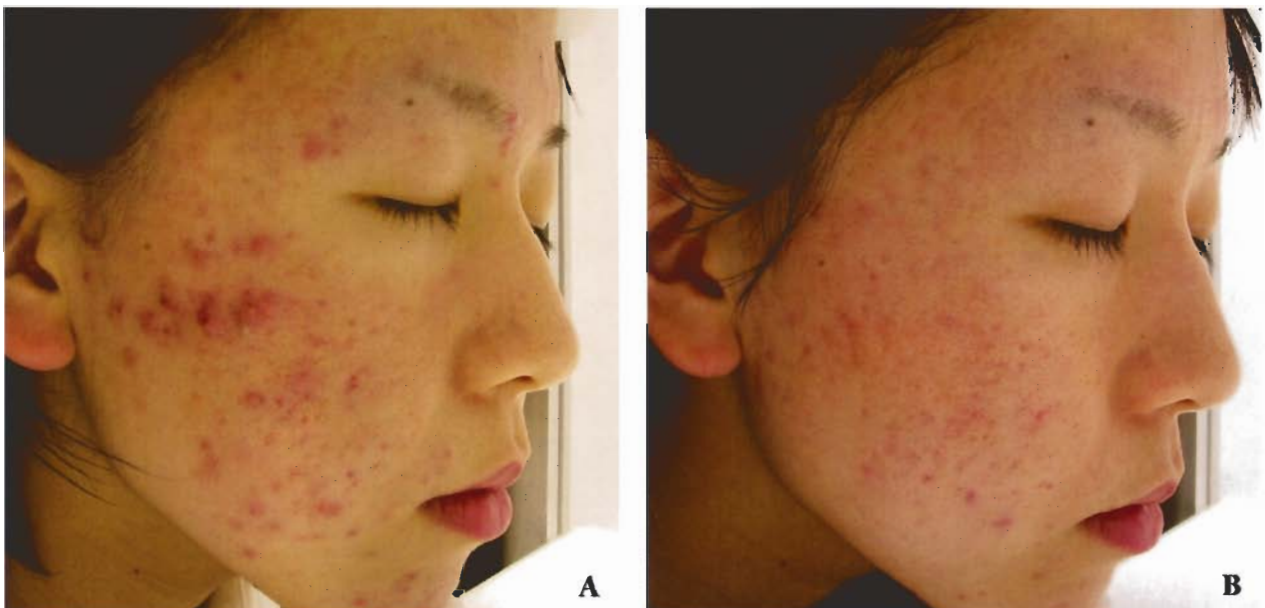


Figure 5. Patient at baseline (A) and after (B) 12 weeks of twice-daily topical treatment with 5% sodium L-ascorbyl-2-phosphate lotion.

APS VS CL FOR ACNE VULGARIS

relation to *P acnes*. Arakane¹¹ reported that singlet oxygen is generated when coproporphyrin derived from *P acnes* existing on the skin surface is exposed to UV light.

We hypothesized that sebum oxidation by singlet oxygen is the main cause of progressive oxidative reactions of triglycerides. These reactions trigger inflammation; progressive inflammation causes abnormal follicular hyperkeratinization, resulting in comedone formation.

We have postulated that APS, a vitamin C derivative, works as a scavenger of singlet oxygen derived from coproporphyrin.¹² In addition, APS simultaneously becomes a powerful scavenger of a large amount of free radicals (especially hydroxyl radicals) generated by neutrophils that migrate to the lesion area in the process of inflammation, which further progresses from the comedone. Because APS works as a scavenger of singlet oxygen, it inhibits sebum oxidation and also works as a scavenger of free radicals derived from neutrophils. Therefore, we speculate that tissue damage also is inhibited. In the future, when we consider topical acne treatments, the inhibition of active oxygen generated by UV light must be considered as a critical issue.

APS is a stable vitamin C derivative generated by the esterification of the second class of ascorbic acid by phosphoric acid. APS is absorbed in the skin, enzymatically converted into vitamin C on the surface of the cell membrane, and continuously taken up into the cells. Miwa¹³ found that APS increases the intracellular concentration of ascorbic acid and regarded it as the enriching effect, which might enhance the inhibition of melanin production. We emphasize that the effects of APS, which is immediately converted into large amounts of vitamin C in the corneal and epidermal layers, can inhibit progressive sebum oxidation and the resulting epidermal hypercornification and abnormal hyperkeratinization.^{1,14,15} Other vitamin C derivatives are not as effective as APS,^{12,15} as they are neither absorbed cutaneously nor converted into pure vitamin C in the epidermal layer.

Ponec et al³ reported that vitamin C is required in the formation of barrier lipids in epidermal reconstruction. Vitamin C also aids in ceramide synthesis, an important component of the barrier lipids. As mentioned previously, APS as a singlet oxygen scavenger can inhibit progressive sebum oxidation and abnormal follicular keratinization. Moreover, APS is involved in ceramide synthesis, which also inhibits abnormal follicular keratinization.^{16,17}

CONCLUSION

Both APS and CL were well tolerated by the study participants. In addition, APS was found to be more efficacious

than CL in the treatment of facial acne vulgaris. APS is a stable vitamin C derivative that has the potential to treat acne by targeting its etiology.

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