Open Study Comparing Sodium L-Ascorbyl-2-Phosphate 5% Lotion Versus Adapalene 0.1% Gel for Acne Vulgaris

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We are reporting on an evaluator-blinded, multicenter, open-label clinical study to compare the efficacy and safety of sodium L-ascorbyl-2-phosphate (APS) 5% lotion with that of adapalene (ADP) 0.1% gel for facial acne treatment. Sixty patients were randomized to apply either APS or ADP for 12 weeks. Among 53 patients who completed the study, APS treatment was consistently superior to ADP treatment in inflammatory acne lesion reduction at any study period. The overall study results show the superior efficacy and safety of APS 5% lotion compared with that of ADP 0.1% gel in the treatment of acne vulgaris. APS is a vitamin C derivative and is very effective in removing active oxygen species. Oxidation of squalene or fatty acid is thought to induce comedogenesis and is, therefore, pathogenic of acne. The efficacy of APS in acne treatment may be attributed to its oxidation inhibitory action on squalene and fatty acid by removing the active oxygen species.

An increase in UV radiation resulting from the destruction of the ozone layer has caused harmful effects to our environment, as well as to human skin, which is also subject to damage. Whereas UVB radiation generates superoxide anion radicals, hydrogen peroxide, and hydroxyl radicals,[1,2] UVA radiation generates singlet oxygen.[3] Arakane et al[4] reported that UV radiation on coproporphyrin, a metabolite from *Propionibacterium acnes*, also causes singlet oxygen.

Oxidation of squalene and fatty acid is reported as one of the pathogeneses of acne.[5] Some reports suggest those peroxide substances may be comedogenic.[6] If active oxygen species caused by UV radiation triggers oxidation of squalene and fatty acid, removal of these active oxygen species from the sebum, corneal layer, and infundibulum and from the inside of follicles may lead to suppression of, and prevention of, the initial onset of facial acne lesions. According to this hypothesis, antioxidative substances that can remove active oxygen species in the previously mentioned areas may be of clinical benefit. We have reported on the efficacy of sodium L-ascorbyl-2-phosphate (APS) lotion for acne treatment since 1997[7-9] and now conclude that it is an effective antioxidative substance to remove active oxygen species. Suppression of acne progression with overall improvement has also been observed, which may be attributed to its action of inhibiting the advanced stage of lipid hyperoxidation.

Now, we report on an evaluator-blinded, multicenter, randomized, parallel-group clinical study comparing the efficacy and the safety of APS 5% lotion with that of adapalene (ADP) 0.1% gel for facial acne treatment.

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The authors report no conflicts of interest in relation to this article.

Table 1

Global Improvement at Week 12 for Patients Treated With Sodium L-Ascorbyl-2-Phosphate (APS) 5% Lotion or Adapalene (ADP) 0.1% Gel for Facial Acne

	Worsening	Poor Improvement	Mild Improvement	Good Improvement	Excellent Improvement
APS (N=28), n (%)	0 (0)	5 (17.9)	2 (7.1)	13 (46.4)	8 (28.6)
ADP (N=25), n (%)	4 (16.0)	3 (12.0)	2 (8.0)	13 (52.0)	3 (12.0)

METHODS

Patients

Sixty female patients, 17 to 34 years of age, with at least 10 but fewer than 50 inflammatory acne lesions, at least 10 but fewer than 100 noninflammatory acne lesions, and no more than 2 nodulocystic acne 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. Patients participating in the study were not pregnant or lactating and had discontinued oral contraceptives for at least 3 months prior to entering the study.

Fifty-three patients completed the study (28 in the APS group and 25 in the ADP group). Seven patients discontinued the study: 3 patients were unable to come to the clinic as scheduled, 2 patients wanted to take an oral contraceptive against the protocol, and 2 patients in the ADP group were not able to continue because of adverse effects.

Enrolled patients were randomized to apply either APS or ADP 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.

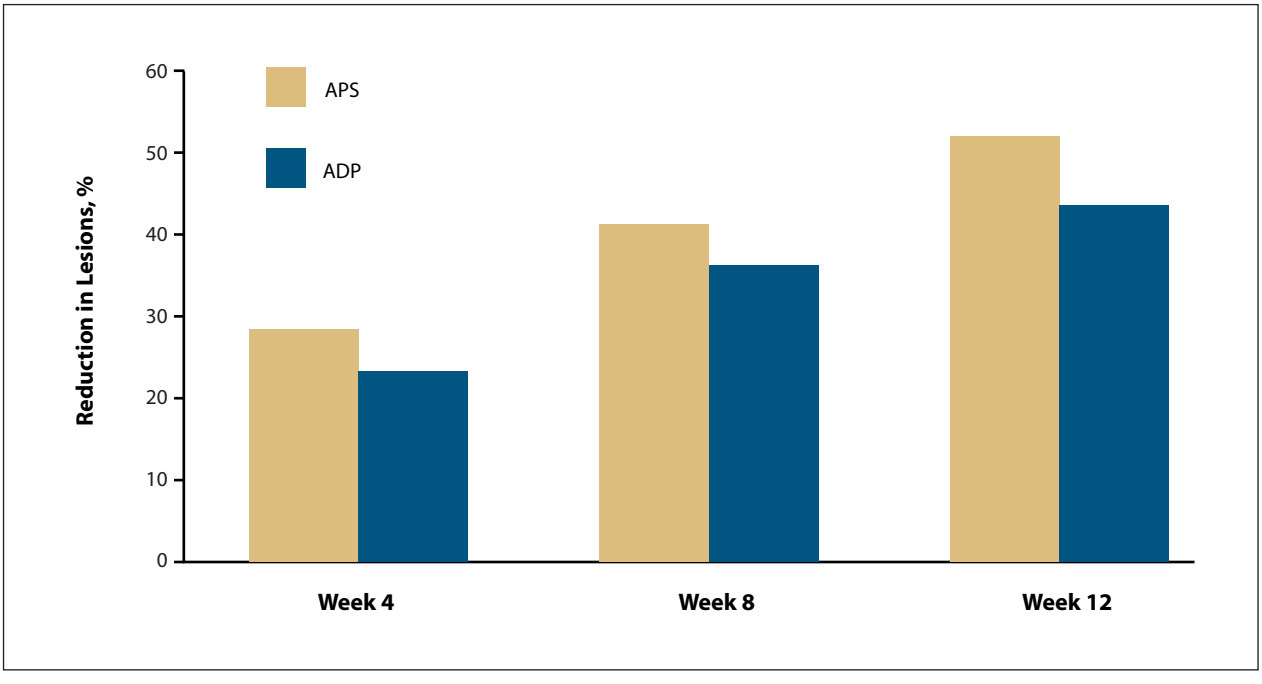

Figure 1. Mean percentage reduction in inflammatory acne lesions at weeks 4, 8, and 12 for patients being treated with sodium L-ascorbyl-2-phosphate (APS) 5% lotion or adapalene (ADP) 0.1% gel. Values for the APS treatment group are significantly higher than those of the ADP treatment group throughout the study period.

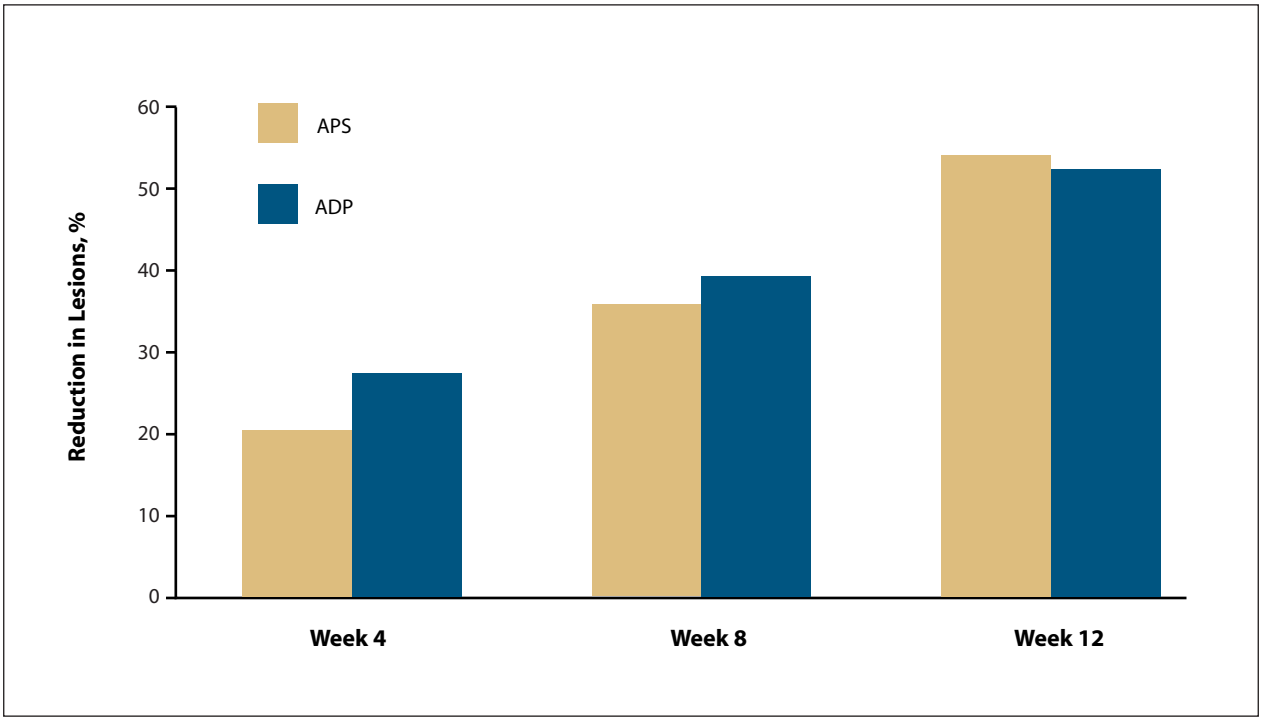

Figure 2. Mean percentage reduction in noninflammatory acne lesions at weeks 4, 8, and 12 for patients being treated with sodium L-ascorbyl-2-phosphate (APS) 5% lotion or adapalene (ADP) 0.1% gel. Values for the ADP treatment group are significantly higher than those of the APS treatment group until week 8. The APS treatment group shows a higher value at week 12.

Efficacy and Cutaneous Tolerability

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 acne lesions. A digital charge-coupled macro/micro device, which captures clinical digital photographic and microscopic images, was used. Clinical global assessment was performed by the blinded investigator for each patient at week 12 and was compared with that of baseline using the following scale: 0=worsening, 1=poor improvement, 2=mild 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. Global cutaneous tolerability was assessed by means of the average scores at week 12. Statistical analysis was performed using the paired Student *t* test. All statistical tests were 2-sided, and *P* values of .05 or less were considered statistically significant.

RESULTS

Efficacy

Table 1 shows global improvement at week 12. The percentage of patients in the APS treatment group showing either good or excellent improvement was 75% (21 of 28 patients) compared with 64% (16 of 25 patients) in the ADP treatment group. Figures 1 and 2 show the mean percentage reduction in inflammatory and noninflammatory acne lesions, respectively. The lesion counts were statistically significant in the APS treatment group compared with those in the ADP treatment group ($P=.01$ and $P=.05$, respectively). Figure 3 shows overall improvement of patients in the APS treatment group at week 12.

Cutaneous Tolerability

Irritation was generally mild in both treatment groups; however, 2 patients in the ADP treatment group discontinued the study because of severe burning. Mean scores of cutaneous tolerability are shown in Table 2. Global tolerability in the APS group was excellent.

COMMENT

APS is one of the ascorbyl phosphate derivatives. With enzymatic actions, the phosphate group of APS is easily separated in the epidermis and acts as pure vitamin C in the body tissue. Miwa[10] found that APS is able to elevate intracellular vitamin C concentration and called that function the "enriching effect." Other types of ascorbyl phosphate derivatives have lower transcutaneous absorption and lower enzymatic conversion efficiency into vitamin C.[11] Unlike ascorbic acid-6-palmitate, ascorbyl phosphate derivatives do not damage skin, nor do they have cellular toxicity, and their safety has been demonstrated.[10]

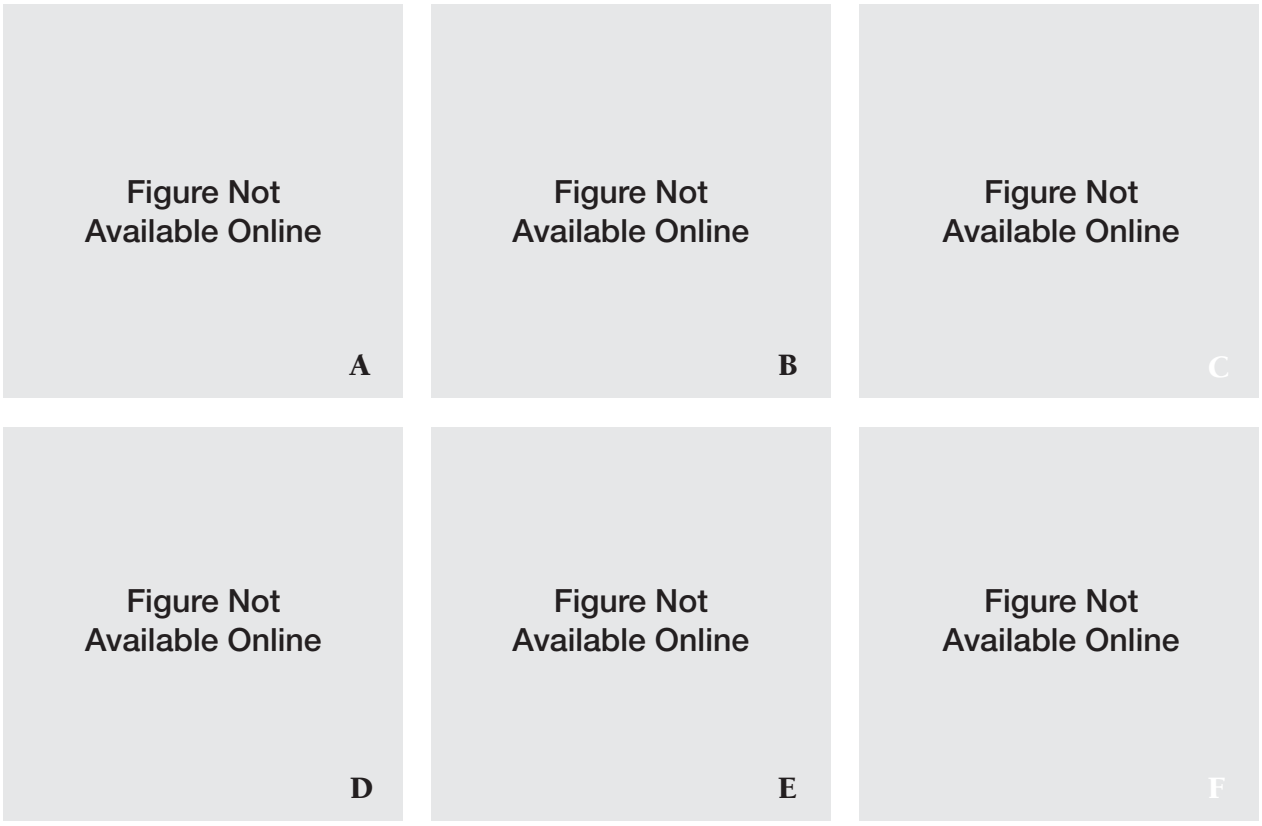

Figure 3. Patients at baseline (A, B, C) and after 12 weeks of twice-daily topical treatment with sodium L-ascorbyl-2-phosphate 5% lotion (D, E, F).

Our study demonstrated that APS treatment is clearly superior to ADP treatment in efficacy and in reduction rates of both inflammatory and noninflammatory acne lesions. APS treatment was consistently superior to ADP treatment at any study period in inflammatory acne lesion reduction. However, ADP treatment was superior to APS treatment up to week 8 in noninflammatory acne lesion reduction, and the APS group demonstrated slightly better improvement at week 12. In tolerability, the APS group experienced fewer adverse effects, whereas 2 patients in the ADP group discontinued the study because of burning and erythema.

Table 2

Mean Scores of Adverse Effects of Patients Treated With Sodium L-Ascorbyl-2-Phosphate (APS) 5% Lotion or Adapalene (ADP) 0.1% Gel For Facial Acne*

	Burning	Scaling	Erythema
APS	0.21	0.89	0.43
ADP	1.63	1.93	1.29

*Scores are based on a scale of 0 to 3, where 0=none, 1=mild, 2=moderate, and 3=severe.

Table 3 lists the ingredients of APS 5% lotion. The main ingredient of the formula, ascorbyl phosphate, shows some excellent mechanisms of pharmaceutical actions against acne. As described above, APS shows an excellent scavenging effect to remove active oxygen species from the skin surface, epidermis, and inside the follicles. Masatsuji-Kato et al[12] reported on the excellent scavenging effect of APS on removal of singlet oxygen. If oxidation of squalene or fatty acid is one of the pathogenic factors of comedogenesis, we hypothesize that APS may play a significant role in treating acne by scavenging singlet oxygen. It is reported that patients with acne often demonstrate abnormal intercellular lipid barriers,[13] as seen in ceramide deficiency. If we hypothesize that ceramide deficiency may lead to a pathogenic factor for comedogenesis, ceramide synthesis with APS, as reported by Ponec et al,[14] may prevent comedogenesis and further help improve acne treatment. It was noted clinically that purulent pustules and red papules were significantly

TABLE 3

Composition of Sodium L-Ascorbyl-2-Phosphate (APS) 5% Lotion (100 mL)

Ascorbyl phosphate	5 g
Ethanol	3 mL
Propylene glycol	2 mL
Glycerin	5 mL
10% methylparaben	2 mL
Sterile purified water	≈88 mL

reduced among the patients whose improvement was rated as excellent or good in our study. This may involve 2 pharmacologic actions of APS: (1) antioxidative action of APS against highly oxidative fatty acids and hyperoxide lipids in the comedones and follicles may lower the oxidative levels and further reduce inflammatory causes and (2) the excellent active oxygen-scavenging effect of APS may eradicate hydroxyl radicals generated from numerous neutrophils conglomerated around the purulent pustules and red papules. Along with these effects, destruction of normal peripheral tissue by hydroxyl radicals, as well as acne scars, may well be prevented. As shown previously, the APS group was consistently superior to the ADP group in reduction rates of inflammatory acne lesions throughout the study period.

APS may have additional clinical advantages for patients with acne. It may improve postinflammatory hyperpigmentation with its melanogenesis-inhibitory action. Patients may be encouraged to continue using APS if they witness the improvement in hyperpigmentation as well as in acne lesion reduction.

CONCLUSION

Our study results show the superior efficacy and safety of APS 5% lotion compared with that of ADP 0.1% gel in the treatment of acne vulgaris. APS is well tolerated, and it appears to be of benefit to patients as an excellent antiacne drug.

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