Excellent Clinical Results with a New Preparation for Chemical Peeling in Acne: 30% Salicylic Acid in Polyethylene Glycol Vehicle

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BACKGROUND Chemical peeling by salicylic acid in ethanol or another vehicle may be accompanied by stinging and burning followed by postinflammatory hyperpigmentation in the treated area, or salicylism. We have developed a new formulation: 30% salicylic acid in polyethylene glycol (SA-PEG). A topical application of SA-PEG remodels photodamaged skin in mice and humans, without systemic absorption.

OBJECTIVE The objective was to evaluate the safety and efficacy of SA-PEG for clinical use in the treatment of acne.

MATERIALS AND METHODS We evaluated the effects of the preparation histologically in mice and its safety and efficacy in 44 volunteers with normally aged skin and in 436 patients with acne.

RESULTS Histologic studies in animals showed no inflammatory changes in the skin following topical application of SA-PEG. Volunteers noted an improved skin texture. In the acne patients, the comedones and papules disappeared, resulting in an excellent outcome. There was a notable absence of stinging and burning, edema, bleeding, or crusting in the treated area.

CONCLUSION The SA-PEG preparation appeared to be safe and effective, with minimal associated inflammation or adverse effects, even in Asian patients who tend to develop hyperpigmentation or keloids. This preparation is thus ideal for chemical peeling.

The authors have indicated no significant interest with commercial supporters.

Because of its keratolytic and anti-inflammatory effects, salicylic acid (ortho-hydroxybenzoic acid) has been used at low concentrations for chemical peeling of the facial skin. There has been an increased interest and demand for this procedure, because patients with such conditions as acne, freckles, and wrinkles have obtained a satisfactorily rejuvenated or improved cosmetic appearance. However, salicylic acid and various other chemical peeling agents may cause stinging and burning in patients with acne. Recently, salicylic acid has been used to obtain a superficial wounding of the skin at the relatively high concentrations of 20% to 30% formulated in 95% ethyl alcohol,¹ utilizing its corrosive action on the skin. While cosmetically very effective, such high concentrations of salicylic acid in ethyl alcohol may cause stinging, burning, redness, and frosting (Figure 1) followed by crusting and pigmentation of the treated area.¹—³ Another problem, especially in Asian patients, is the residual hyperpigmentation that frequently develops after inflammation of the skin, which can adversely affect the clinical outcome.³ Furthermore, application of salicylic acid to large areas of the skin, or repeated applications, can lead to absorption, which might cause salicylate intoxication.⁴

We previously developed a new formulation consisting of 30% salicylic acid in polyethylene glycol vehicle (SA-PEG).⁵—⁷ The ability of SA-PEG to
exfoliate the cornified cells in hairless mice is comparable to that of salicylic acid in ethanol vehicle. Polyethylene glycol (PEG) is a vehicle with a fairly strong affinity for phenol compounds including salicylic acid, which is itself capable of retaining the agent. Thus, a topical preparation of SA-PEG would not release salicylic acid onto the skin. We have confirmed that there is only minimal absorption of 30% SA-PEG through the intact skin of hairless mice in experiments using 14C-labeled 30% SA-PEG.

In ultraviolet (UV)B-irradiated skin of hairless mice, which served as a model for sun-damaged skin, the structural atypia and expression of p53 protein in keratinocytes induced by UVB irradiation were intensely suppressed in the SA-PEG–treated mice when compared to that in the control UVB-irradiated mice. Incomplete expression of filaggrin and loricrin in keratinocytes from the UV-irradiated control mice was also improved in keratinocytes from the SA-PEG–treated mice. In photoexposed human facial skin, immature cornified envelopes (CEs) were replaced with mature CEs 4 weeks after treatment with SA-PEG. Moreover, skin specimens treated with SA-PEG exhibited a unique connective tissue layer composed of fine collagen fibers beneath the epidermis without evidence of inflammatory infiltrates. These results indicate that chemical peeling with SA-PEG leads to reorganization of the epidermis and a rebuilding of the superficial dermal connective tissue.

This study evaluated the safety and efficacy of the SA-PEG in hairless mice, studying the histologic changes in cornified cells on the surface of the skin and in the hair follicles. We then evaluated the safety and efficacy of this new preparation in 44 volunteers with normally aged skin and in 436 patients with acne. Finally, measurements of the skin barrier function (in terms of the transepidermal water loss [TEWL]) and changes in the skin elasticity were conducted in 15 additional treated volunteers.

**Materials and Methods**

**SA-PEG**

A homogeneous and stable 30% SA-PEG formulation (pH 1.16) was provided by Keisei Inc. (Shinagawa, Tokyo, Japan). If prepared under inadequate conditions, SA crystals separate out and this leads to a reduction in the concentration of SA, while the crystals can irritate the skin at the application site.

**Animal Experiments**

Eight-week-old hairless Skh/hr1 male mice were purchased from Hoshino Laboratory Animals Co. (Saitama, Japan). After cleansing the back of each UVB-irradiated animal (n = 6) with 70% ethyl alcohol, we applied 30% SA-PEG to the right side, while the left side received only the PEG vehicle and served as a control. In 20 minutes, the preparation was rinsed off with distilled water, and the skin was gently dried with cotton gauze. Next, specimens were excised from the two sites on the backs of anesthetized animals. Specimens were obtained immediately following treatment and again at 1, 3, 12, and 24 hours and at 14 days. Each specimen was cut in half, with one-half being snap-frozen in liquid nitrogen, embedded in ornithine carbamyl transerase (OCT) compound, cut into 4-μm-thick slices,
and stained with hematoxylin-eosin. These frozen sections were used to evaluate the morphology of the cornified cells on the surface of the animals' skin and in the hair follicles. The other half of the specimen was fixed with 10% formaldehyde in phosphate-buffered solution (pH 7.2), embedded in paraffin, cut into 4-μm-thick slices, and stained with hematoxylin-eosin. These sections were used to evaluate the histologic characteristics of the animal's skin according to the standards established for paraffin-embedded sections.

**Human Patients and Healthy Volunteers**

A 33-year-old healthy man received chemical peeling for 5 minutes with 30% salicylic acid in ethanol vehicle on his left forehead and with 30% SA-PEG on the other side in standard protocol. Forty-four Japanese women, aged 44 to 80 years, who presented for cosmetic peeling of the facial skin, were evaluated for aesthetic effect in the procedure shown below. Fifteen healthy Japanese women, aged 19 to 52 years, were evaluated for physiologic functions of their skin in the study. A 24-year-old man was evaluated macroscopically for the cornified plugs during four courses of 30% SA-PEG chemical peeling. A total of 436 Japanese patients with acne, 410 females and 26 males, aged 17 to 46 years (a mean of 32.3 years), were evaluated for clinical effects of the treatment in the study. A total of 436 patients with acne, 410 females and 26 males, aged 17 to 46 years (a mean of 32.3 years), were evaluated for clinical effects of the treatment in the study. A total of 2,572 peelings (mean, 5.9/patient) were performed on the patients. All of them were provided informed consent for participation in this study and were asked to report any adverse effects, including stinging or burning of the treated area.

**Method of Facial Peeling**

The patient’s face was cleansed with soap and water, and the lips and eyelids were covered with a layer of petrolatum as protection. Next, 30% SA-PEG was applied to the patient’s forehead, nose, and zygomatic area, distally to the chin. Approximately 3 g of the agent was required to completely cover the face. Five minutes later, the peeling agent was carefully wiped off with ice-cold cotton gauze, and the face was rinsed with generous amounts of tap water. Ice-cold cotton gauze was then applied for 5 minutes. Patients were ordered to apply sunscreen and to avoid excessive sun exposure for 48 hours after peeling. They were also instructed to refrain from applying cosmetics for 12 hours. In cases with repetitive treatment, 4-week or longer intervals were set between each application.

**Clinical Evaluation**

For aesthetic evaluation, each subject received a single application of 30% SA-PEG on the left side of the face only. The results of chemical peeling were evaluated in a representative case by scanning electron microscopy of the skin surface 1 week after peeling. All acne patients were photographed before and after each (single to 12 times) application of SA-PEG chemical peeling. A questionnaire containing 6 questions about adverse effects of the peeling and 11 questions about efficacy of the peeling was filled out by 42 patients, 40 females and 2 males, aged 24 to 46 years (mean, 30.8 years), with acne who had received SA-PEG chemical peeling in a certain month. The evaluation scores for each question were divided into five answer categories: not at all, 0%; a little, 0% to 25%; some, 25% to 50%; quite a lot, 50% to 75%; and very much, 75% to 100%. In representative cases, 1 patient had comedonal and inflammatory acne (Patient 1), and 2 patients had severe inflammatory acne (Patients 2 and 3). Patient 1 was treated with 30% SA-PEG on both sides of the face. Patient 2, who had severe pustular acne, received an oral antibiotic together with a single chemical peeling with 30% SA-PEG on only the left side of the face. Patient 3, who had severe inflammatory nodular acne, received an oral antibiotic and underwent three separate treatments with 30% SA-PEG on both sides of the face.

**Physiologic Evaluation**

We measured the elasticity and the TEWL of a defined area of the skin before and after treatment. Measurements were carried out before the treatment.
and then repeated at 1 hour, 1 day, 1 week, 2 weeks, and 4 weeks after the first chemical peeling. After the second chemical peeling, further measurements were 2 and 4 weeks later. TEWL was determined with a skin evaporative water recorder, TEWL probe (DermaLab, Cortex Technology, Hadsund, Denmark). Measurements were performed for 30 seconds, and the mean value (g/m²/hr) determined of the last stable 8-second period was used as TEWL. The elasticity of the skin was measured with an elasticity probe (DermaLab, Cortex Technology). Measurement of this unit is based on suction applied to the skin surface, whereby the probe provides a vacuum chamber. Calculation of the elasticity module was based on the differential force necessary to elevate the skin surface 1.5 mm between two infrared detection levels inside the probe chamber. Measurements were repeated five times in immediate sequence on the same area. Each value was a mean of the last four measurements (kPa/s).

Results

Experimental Observations

Immediately after the application of SA-PEG to the skin of hairless mice, the cornified cell layer showed a temporary thickening. Beneath that layer, vacuolar changes were occasionally seen and the cornified cell layer became detached (Figure 2A). Three hours after application, the epidermis showed a marked thinning. The cornified cells that plugged the hair follicles became macerated and then became detached above the granular cells. Twelve hours after the application, the epidermis showed a marked thinning. The cornified cells that plugged the hair follicles became macerated and then became detached above the granular cells. Twelve hours after the application, the skin showed a thickening of the granular cell layer. The cornified cells within the hair follicles are almost dissolved and are becoming detached from the follicles (B). Twenty-four hours after application, a new cornified cell layer appears above the granular cells. The cornified cells within the hair follicles, which adhered firmly before peeling, have been removed almost completely (C). Formalin-fixed specimen of UVB-irradiated mouse skin two weeks after the application. The new cornified cell layer consists of fine, regularly arranged cells above the thickened granular cell layer (D).

Two weeks after the application, a cornified cell layer consisting of new, fine, and regularly arranged cells appeared above the hypertrophic granular cell layer (Figure 2D). Adhesion of the cornified cell layer to the epidermis was not seen. No inflammatory changes were observed in the epidermis or dermis.

Clinical Response in Volunteers

Chemical peeling with SA-PEG on one side of the face produced marked cosmetic improvement within 1 week compared with the other, untreated side of the face (not shown). There were no complaints of
pain, burning, or stinging and no signs of edema, bleeding, crusting, or postinflammatory pigmentation. Scanning electron microscopy of the treated skin surface 1 week after chemical peeling revealed a restoration of the regular grooves (glyphics) of the skin and the removal of the cornified plugs from the hair follicles (Figure 3). Adherent cornified cells have been removed from the skin surface and hair follicles. Macroscopically, cornified plugs were also removed, and the appearance of facial pores was minimized after peeling four times (Figure 4).

The SA-PEG preparation achieved the desired rejuvenated appearance of aging skin in the majority (98%) of subjects, who showed a smoothing of texture, an increase in elasticity, and an improvement in color of the skin. Follow-up for 1 to 3 months showed that the majority of subjects were satisfied with the results. Only 2% showed no change.

The skin barrier function, evaluated by TEWL, did not show significant changes, which provides further evidence of the safety of this preparation (Figure 5). Significant improvement in the skin elasticity was proved by this measurement (Figure 6).

**Clinical Response in Acne Patients**

None of the 436 acne patients treated by SA-PEG complained of pain, and there were no adverse effects such as erythema, bleeding, crusting, or

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**Figure 3.** Scanning electron micrographs of a 75-year-old Japanese woman with typical aged skin. The surface of the skin before treatment shows numerous adherent cornified cells masking the regular grooves of the skin surface (A). One week after treatment with SA-PEG, there is a restoration of the regular grooves in the skin surface, and the adherent cornified cells have been removed from the hair follicles (B).

**Figure 4.** Macroscopic effect of SA-PEG chemical peeling on cornified plugs and facial pores. The cornified plugs were evaluated macroscopically in a 24-year-old man before (A) and 2 weeks after four peelings with SA-PEG (B) on the right side of his face. As a control, the left side (C) was not treated with SA-PEG (D).
postinflammatory pigmentation of the skin.
The results of the questionnaire survey on perceived efficacy of SA-PEG chemical peeling indicate that the vast majority of 42 respondents noted a clinical improvement in acne, satisfaction in the treatment, and a spontaneous improvement in skin texture and color (Table 1). Some patients desired and received continuous treatment for cosmetic improvement after they were satisfied with a complete healing of acne.

Within 1 month of treatment, chemical peeling with 30% SA-PEG considerably reduced the development of comedones and papules in the patients. However, areas of inflammation consisting of erythema, papules, and pustules still persisted in Patient 1, who was treated with SA-PEG on both sides of the face (Figure 7). Patient 2 received an oral antibiotic and underwent a single chemical peeling with SA-PEG on only the left side of the face. Treatment produced marked improvement (Figures 8C and 8D) within 2 weeks compared with the right, untreated side (Figures 8A and 8B). The treated side exhibited a clearing of the pustules, papules, and comedones accompanied by a reduction in oiliness and in roughened, enlarged pores (Figure 8).

Patient 3, who had severe acne (Figure 9A), received an oral antibiotic together with the administration of three separate chemical peeling treatments on both sides of the face, given monthly for 3 months. After 3 months of the combined oral antibiotic–topical chemical peeling treatment, the pustules, papules, and comedones dissappeared, accompanied by a decrease in sebum and an improvement in skin texture and color (Figure 9B). All three individuals spontaneously reported an improvement in skin texture and color.

**Discussion**

This study showed that chemical peeling with SA-PEG was very effective in eradicating relatively
severe comedones and papules in patients with acne. Furthermore, new lesions were slow to emerge during repetitive treatments, even these were done only once a month. The combination of an oral antibiotic and chemical peeling produced excellent clinical results in both cases of acne with preexisting severe inflammation. There was no stinging or burning, even immediately after application of the prepara-

![Figure 8](image)

**Figure 8.** Photographs of Patient 2, a 20-year-old Japanese woman with papular and pustular inflammatory acne on the right (A) and left (C) sides of the face before treatment. Two weeks after the administration of an oral antibiotic, the comedones and papules persist on the untreated right side (B). Left side of face 2 weeks after a single application of SA-PEG with the concomitant administration of an oral antibiotic. The number of comedones and papules is now markedly reduced (D).

**Table 1.** The Results of a Questionnaire Survey on Adverse Effects and Perceived Efficacy of SA-PEG Chemical Peeling in 42 Patients (40 Females and 2 Males) with Acne

<table>
<thead>
<tr>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Some</th>
<th>Quite a Lot</th>
<th>Very Much</th>
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<tr>
<td><strong>Adverse effects</strong></td>
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<td>Bleeding</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>Pain on peeling</td>
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<td>7</td>
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<td>Pain after peeling</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Rush</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Dryness</td>
<td>35</td>
<td>6</td>
<td>1</td>
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<td>0</td>
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<tr>
<td>Pigmentation</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td><strong>Efficacy on the skin</strong></td>
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<td></td>
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<td>Nascent acne decreased</td>
<td>0</td>
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<td>0</td>
<td>4</td>
<td>37</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>35</td>
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<td>Acne scar minimized</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>7</td>
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<td>Excess oil disappeared</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>11</td>
<td>25</td>
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<tr>
<td>Pores shrank</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>12</td>
<td>23</td>
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<tr>
<td>Skin turned smooth</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>37</td>
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<tr>
<td>Elasticity increased</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>37</td>
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<tr>
<td>Skin color improved</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>10</td>
<td>22</td>
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<td>Skin clarity improved</td>
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<td>5</td>
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<td>Skin turned comfortable for makeup</td>
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<td>Degree of satisfaction</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>42</td>
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*The question about makeup was asked only of female patients.*
tion, nor other adverse effects including scaling, crusting, or postinflammatory pigmentation. Although some patients felt a minimum tingling, the degree of pain was comparably weaker than the penetrating pain caused by salicylic acid in ethanol.

We previously reported that chemical peeling with SA-PEG in animals leads to an alteration in epidermal morphology by inducing a loss of cornified cells.5–7 Inflammatory infiltrates are occasionally seen in areas of skin treated with 30% salicylic acid in ethyl alcohol vehicle.1,5 However, treatment with SA-PEG infrequently produces such infiltrates.5–7 PEG has a high affinity for salicylic acid and therefore binds this agent, releasing only a small amount into the living tissue layer of the epidermis.6 This may explain why SA-PEG does not cause the burning pain that is usually encountered with the ethyl alcohol vehicle.1–3 This may also help to explain why patients undergoing chemical peeling with the new preparation do not immediately experience pain, in contrast to those treated with the ethyl alcohol vehicle.

Our studies on using radiolabeled salicylate in animals have shown plasma levels of radioactivity well below the toxic level and demonstrated by microautoradiograms that the highest level of radioactivity was present in the cornified cell layer of the hair follicles. One may anticipate that this new formulation of salicylic acid may be used as a chemical peeling agent without the risk of inducing salicylism.7 No clinical evidence of salicylism was observed in any of our treated subjects to date.

In addition to a disappearance of comedones and papules, the acne patients showed an improvement in skin texture after treatment. Similarly, the 44 volunteers reported a smoother skin texture. There was also an obvious increase in skin elasticity and an improved skin color. In 15 additional volunteers, measurement of TEWL showed little change in water barrier function, and a significant improvement in skin elasticity was demonstrated. We previously showed that peeling with SA-PEG leads to the production of new collagen fibers in the papillary dermis of UV-irradiated mouse skin.6 This observation may explain how this chemical peeling serves to improve the texture of the skin.

In conclusion, SA-PEG used for facial peeling in patients with acne was safe and effective when used in conjunction with an oral antibiotic. Although few procedures have been employed to remove comedones, this innovative preparation, which can specifically remove the cornified layer even on infundibulum with little absorption, offers significant adjunctive benefits for all acne patients affected at various degrees of severity without exception. The skin of middle-aged or elderly volunteers without acne showed cosmetic improvement in repetitive,
long-time treatment without any adverse effects. This preparation will present an advantage in chemical peeling especially for Asian patients who tend to develop hyperpigmentation or keloids related to acne inflammation.

References


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COMMENTARY

In a time when new laser technologies appear to be the wave of the future, it is interesting to see something new in the world of chemical peeling. Salicylic acid peeling is an old therapy, but this article shakes up some of the traditional ideas of its use. These authors have methodically examined, in detail, the clinical and histologic effects of this particular chemical peel solution. Rarely have we seen this much science behind a peeling agent. They have effectively shown that much of what we thought was required for chemical peeling to be effective (i.e., redness, stinging, peeling) is completely unnecessary.

It is a very intriguing concept that keeping salicylic acid from penetrating deeply into the skin does not negate its positive effects, only its side effects. It would be interesting to see if continued application of this peel over a series of 8 to 10 treatments would give cumulative clinical benefits for photoaged skin, particularly rhytides.

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