

Evaluation of role of priming agents in salicylic acid peel: A comparative study

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Abstract

Introduction: Salicylic acid is increasingly used as a superficial peeling agent for acne. Widespread use has caused increasing awareness about the adverse events associated with SA like erythema, exfoliation, itching, redness etc. Appropriate use of priming agents like retinoids, hydroquinone etc., can help in reduction of ADRs and can affect final treatment result.

Aim: Evaluation of efficacy and safety of salicylic acid (SA) peel with or without priming agents in patients of acne.

Methodology: A prospective, randomized, open-label, parallel-group study was carried out in patients with acne. Total 72 patients were randomized in to three groups A, B and C to receive 30% salicylic acid (SA) peel with either 0.05% tretinoin or 4% hydroquinone or without any priming agent. Objective and subjective assessment in improvement in acne was compared. For safety analysis, all reported adverse drug events were compared.

Results: Mean age of patients was 22.46±5.32 years. Both non-inflammatory and inflammatory acne lesions reduced with SA peel in all three groups. Improvement in total acne score is significantly higher in SA peel with priming agents (p<0.05). The change in total acne score (Week 0-12) was 81.45% with SA alone, 94.3% with isotretinoin and 90.2% with hydroquinone priming (p<0.05). Total adverse event reported were 10(58.82%), 4 (23.53%) and 3(17.65%) in SA peel without priming agent, with isotretinoin and with hydroquinone respectively. Rate of occurrence of adverse events was significantly high in SA without priming agent (p<0.05). Mean visual analogue score was 91.47, 94.31 and 83.46 in group A, B and C respectively. SA peel with priming agent was rated as significantly more effective by patients rather than SA without priming agent (p<0.05).

Conclusion: Appropriate priming agents should always be used with superficial peeling agents like SA in management of acne which enhances the effectiveness and reduces the adverse effects of therapy.

Keywords: Acne, Salicylic acid peel, Priming agents, Tretinoin, Hydroquinone.

Introduction

Chemical peels are considered as adjuvant therapy in treating all forms of acne. The addition of chemical peels leads to a faster clinical response and patient satisfaction in acne patients.¹ Salicylic acid (SA) as a peeling agent has been studied by various dermatologists. Being a lipophilic agent and having an ability to concentrate in the pilosebaceous apparatus, SA peels are a good therapeutic option for comedonal acne, and can be a good adjunctive modality for treating open and closed comedones, post-acne erythema, and hyperpigmentation.¹

Different studies have reported effectiveness of SA peel as superficial chemical peel for acne. Aronsohn used 50% SA ointment with excellent results in 81 patients with pigmentation, freckles, and photoaging of the hands.² Swinehart used a 50% SA ointment paste containing buffered methyl salicylate and croton oil for the treatment of actinically damaged skin, lentigenes, and pigmented keratosis on the forearms and dorsal aspect of the hands, and reported excellent results.³ The efficacy of SA in the treatment of photoaging and acne has been described in patients with Fitzpatrick skin types I-III as well as in skin types V and VI.⁴ Kligman and Kligman used SA as a superficial peeling agent in 50 women with mild to moderate photodamage, and reported improvement in surface roughness and pigmented lesions, along with a reduction in fine lines.⁵

Grimes treated 25 patients from a darker racial ethnic group who had acne vulgaris, melasma, or post-inflammatory hyperpigmentation with 20% and 30% SA peels, and reported good efficacy with minimal side effects.⁶ SA peel has been increasingly used in different concentration ranging from 0.5% to 30% for various skin problems like acne, melasma, post-inflammatory hyperpigmentation, freckles, lentigenes, photodamage etc.

Widespread use of SA as a superficial peeling agent has caused increasing awareness about the adverse events associated with SA like erythema, exfoliation, itching, redness etc. Appropriate use of priming agents like retinoids, hydroquinone etc can help in reduction of ADRs. Use of priming agents has direct relevance to the final treatment result and the rate of complications therefore, the importance of a consistent pre-treatment phase cannot be underestimated.⁷

The advent of new and potent topical therapeutic agents and therapeutic procedures such as chemical peeling has resulted in significant improvement in the treatment of acne and it is a still developing field. Various researchers have studied role of priming agents along with chemical peels but very few studies published for their comparative evaluation. Therefore, this study was aimed at the comparative evaluation of efficacy and safety of SA peel with or without priming agents in patients of acne.

Methodology

A randomized open label study spreaded over six months was carried out in dermatology department of a tertiary care teaching hospital in western India. The study protocol was approved by Human Research Ethics Committee of the institute prior to commencement of study. Permission from the hospital superintendent and head of the dermatology department was also obtained before conducting the study.

Participant Selection: Total 72 patients attending the dermatology outpatient department and diagnosed with acne vulgaris were included in the study.

Inclusion Criteria: Diagnosis of acne was mainly based on clinical examination by the qualified dermatologist. Patients of age 12 years and more and both gender with mild to moderate acne with facial lesions only were included in the study.

Exclusion Criteria: Pregnant and lactating mothers, patients with known history of hypersensitivity reaction to salicylates or aspirin, patients with history of herpes simplex, patients with drug induced acne and patients with history of keloid formation were excluded from the study. Patients not willing to participate in the study and not willing to give written informed consent were also excluded.

Patient Screening Procedure: Appropriate patient selection and assessment of each individual's skin condition was carried out before considering a chemical peel. The treating dermatologist had evaluated the patient for the possible indications, looked for any contraindications, and discussed the procedure in detail, and assessed the patient's expectations and anticipation of results. The potential risks of the procedure as well as the limitations were also discussed. The patient's skin type was evaluated using Fitzpatrick's classification.⁸ Evaluation of active acne was done using a method devised by Michaelsson and colleagues.⁹ By multiplying number of each type by its severity index and adding each sum, a total acne score was obtained. Assessment of acne lesions was done at baseline (0 weeks) and at each visit (2, 4, 6, 8, 10 and 12 weeks). Prior to the chemical peel, a detailed history and cutaneous examination was performed in all patients. A written informed consent was obtained before enrolling the patient in the study and performing the peeling procedure. All the patients were advised to avoid smoking, minimize their exposure to sunlight, and apply broad-spectrum sunscreens daily. Any topical medications like antibiotics were discontinued before 15 days of the peeling.

Group Allocation and Priming Agents: All patients were randomly assigned into group A, B and C of 24 patients each using random number table.

Group A: Patients with mild to moderate acne vulgaris and primed with retinoids before SA peel (30%) application. Topical preparation of tretinoin (0.05%) was prescribed for 2 weeks prior to peeling and discontinued 1 week before peeling session started.

Group B: Patients with mild to moderate acne vulgaris and primed with hydroquinones before SA (30%) peel application. 4% hydroquinone is applied twice daily for 2 weeks prior to the peel and discontinued before 1 week before peeling session started. It was resumed 2 days post-peel, if needed.

Group C: patients with mild to moderate acne treated with SA peel (30%) without any priming agent.

SA Peeling Procedure: After priming with the allocated agent for 2 weeks the patient was started with SA peeling procedure. At the first visit of enrollment, hypersensitivity testing was done in all patients. A hypersensitivity test with 10% SA peel both commercially available and freshly prepared performed on small 1 cm area in the right retro-auricular area. The patients were reviewed after 1 week, and if they tolerated the peel well, they were taken up for full face peels. Patients were asked to first wash their face with water then asked to lie down in a 45° semi-reclining position with eyes closed. All patients were given a surgical cap to pull back their hair and cover the ears. Degreasing was done by scrubbing with cotton gauze soaked with spirit, followed by one soaked with cleansing lotion. Sensitive areas of face like the lips and nasolabial folds were protected with a thin layer of petrolatum. Commercially or freshly prepared SA peel will be then applied over the face using a fan-shaped sable brush in a predetermined clockwise manner starting over the forehead, right cheek, chin, left cheek, nose, upper lip, and lastly the infraorbital areas, taking 30 to 35 seconds to accomplish and using approximately 0.8 to 1 ml solution per session. With SA peeling, the patients experience a stinging sensation that usually lasted for 3 to 5 minutes. After the cessation of this stinging sensation, most patients developed a uniform white crystalline precipitate, "pseudofrost," in the peeled areas (indicating the deposition of salicylic acid after its hydroethanolic vehicle had volatilized) which was considered as the end point of peeling. In patients who did not develop the pseudofrost, the cessation of the stinging sensation was considered the end point. The total duration of the peeling sessions varied from 3 to 5 minutes with SA peeling. As soon as the end point reached, the peel was neutralized by asking the patients to wash their faces with copious amounts of cool tap water. Patients were then asked to pat, and not rub, the face dry. After rinsing, a bland moisturizer is applied to the skin. The patients were asked to apply a sunscreen with a sun protection factor (SPF) of greater than 30 on their faces before leaving the dermatology department. Patients were allowed to go home with instructions to apply a moisturizing cream if the facial skin felt too dry, to avoid or minimize sun exposure, and to apply sunscreen one hour before getting exposed to the sun. They were cautioned not to apply any cream or face wash containing AHAs, salicylic acid, or retinoids. All the

patients were followed up every 15 days till 3 months and improvement in acne was recorded.

Outcome Measures: The treating physician made an objective assessment of the changes in active acne lesions, post-acne scarring, and hyperpigmentation at each visit and total acne scores were compared at each visit. The patient's subjective assessment was also made using 100 cm visual analogue scale. It was graded as excellent (>80%), good (60-80%), average (30-60%), poor (<30%), no change and worse. All the spontaneously reported or physician identified adverse drug events were also compared among three groups.

Statistical Analysis: All data were analyzed with the help of Microsoft excel 2010. Data were represented as actual frequency, mean, percentage, standard deviation as appropriate. Chi-square test was used for analysis and association of qualitative data. Unpaired t test was used for comparison between the groups, and paired t test was used for within group comparisons. P values < 0.05 were considered significant.

Results

Total of 72 patients were enrolled and randomly divided into three groups A, B and C according to priming agent used. The mean age of the patients was 22.46 ± 5.32 years. More than half of patients (54.32%) patients belong to 21-30 years of age with female preponderance. Majority of patients has skin type IV (53%), followed by type III (26%) and type V (21%). Comedones and papules were most common presentation of acne in almost all the patients while pustules and nodules were present only in 12% of study patients.

Objective evaluation of treatment outcomes done by the treating physician revealed that the use of priming agent improves therapeutic outcome as discussed below. As shown in table 1, there was reduction of both non-inflammatory and inflammatory acne with SA peel in all three groups which establishes efficacy of SA as peeling agent. It showed improvement in superficial scarring and skin texture. It also resolved post acne hyperpigmentation to some extent. Although SA peel alone without any priming agent led to highly significant ($p < 0.001$) improvement in the total acne score, the improvement is significantly higher when it is used with priming agents either isotretinoin or hydroquinone ($p < 0.05$). The change in total acne score (Week 0 to Week 12) was 81.45% with SA alone, 94.3% with isotretinoin priming and 90.2 % with hydroquinone priming ($p < 0.05$).

Out of total 72, 16 (22.22%) patients developed some or other ADRs. Total 17 adverse events were reported in these 16 patients. Total adverse event reported in SA peel without priming agent were 10(58.82%) while 4 (23.53%) in those having priming with isotretinoin and 3(17.65%) in those having priming with hydroquinone as shown in table 2. Rate of occurrence of adverse events was significantly high in SA without priming agent ($p < 0.05$).

Subjective Assessment: The visual analog scale scores as assessed by the patient have been shown in table 3. Mean VAS score was 91.47, 94.31 and 83.46 in group A, B and C respectively. SA peel with priming agent was rated as significantly more effective by patients rather than SA without priming agent ($p < 0.05$). If pictures were there it would have been a best study, try to put pictures.

Table 1: Comparison of efficacy of SA peel with and without priming agent

Follow up visit	Group A	Group B	Group C
Day 0	Improvement mean \pm SD	Improvement mean \pm SD	Improvement mean \pm SD
Day 0	-		
At 2 week	33.47 \pm 5.62	33.45 \pm 4.5	28.47 \pm 6.62
At 4 week	48.43 \pm 7.77	45.27 \pm 6.33	43.67 \pm 4.92
At 6 weeks	60.22 \pm 6.82	59.15 \pm 5.4	55.47 \pm 7.88
At 8 weeks	70.56 \pm 8.89	68.7 \pm 6.4	63.54 \pm 5.28
At 10 weeks	83.34 \pm 6.9	81.47 \pm 5.42	75.32 \pm 7.87
At 12 weeks	94.3 \pm 1.46	90.2 \pm 2.32	81.45 \pm 3.36
Within group comparison	P<0.05*	P<0.05*	P<0.05*
Between group comparison#	P<0.05	P<0.05	P<0.05

Group A: SA peeling with priming agent tretinoin (0.05%);

Group B: SA peeling with priming agent hydroquinone (4%);

Group C: SA peeling without any priming agent

*Paired t test; P value: < 0.05 was considered significant. (for within group comparison from baseline to 12 weeks)

#Unpaired t test for comparison between group A and group C; $p < 0.05$

#unpaired t test for comparison between group B and group C; $p < 0.05$

unpaired t test for comparison between group A and group B: $p < 0.05$

Table 2: comparison of adverse events in patients undergoing SA peel with or without priming:

S.No.	Reported reaction	Group A	Group B	Group C	Total
1	Exfoliation	1	0	2	3
2	Burning sensation	1	1	1	3
3	Erythema	1	1	2	4
4	Itching	0	1	1	2
5	Photosensitivity	1	0	1	2
6	Hyperpigmentation / skin darkening	0	0	1	1
7	Dry skin	0	0	1	1
8	Maculopapular Rash	0	0	1	1
	Total	4 (23.53%)	3 (17.65%)*	10 (58.82%)	17 (100%)

*chi-square test, p value<0.05: total number of adverse events reported was significantly higher in SA without priming agent as compare to use of SA peel with any priming agent

Group A: SA peeling with priming agent tretinoin (0.05%);

Group B: SA peeling with priming agent hydroquinone (4%);

Group C: SA peeling without any priming agent

Table 3: Comparison of subjective assessment using visual analogue scores for SA peel with and without priming agent:

Follow up visit	Group A	Group B	Group C
	Mean VAS score	Mean VAS score	Mean VAS score
Day 0	-	-	-
At 2 week	35.00	37.00	24.23
At 4 week	42.16	48.83	36.42
At 6 weeks	56.32	55.35	46.87
At 8 weeks	79.98	78.65	68.12
At 10 weeks	86.17	89.12	74.67
At 12 weeks	91.47	94.31	83.46
Within group comparison	P<0.05*	P<0.05*	P<0.05*
Between group comparison#	P<0.05	P<0.05	P<0.05

Group A: SA peeling with priming agent tretinoin (0.05%);

Group B: SA peeling with priming agent hydroquinone (4%);

Group C: SA peeling without any priming agent

*Paired t test; P value: < 0.05 was considered significant. (for within group comparison from baseline to 12 weeks)

#Unpaired t test for comparison between group A and group C; p<0.05

#unpaired t test for comparison between group B and group C; p<0.05

unpaired t test for comparison between group A and group B: p<0.05

VAS: visual analogue scale

Discussion

Many chemical peels used increasingly in treatment of acne vulgaris like salicylic acid, glycolic acid etc. Peeling outcomes is dependent on many factors such as patient condition, stage of acne, peeling agent and its concentration, preparation before peeling and follow up after peeling procedure as well as the skillful level of aesthetician or dermatologist.¹⁰ It is easy to achieve great chemical peel results without complications when appropriate pre-peel and post-peel consideration is contemplated. This study was designed to evaluate the efficacy and safety of salicylic acid as peeling agent with and without priming agent.

SA is one of the most commonly used chemical peel used in treatment of acne vulgaris which is a Beta-hydroxyl acid with both keratolytic properties and anti-inflammatory also could infiltrate simply to pilosebaceous layers and is not toxic, self-neutralizing with minimal dermal infiltration.¹¹ Previous study showed that SA can be used for all stages of active acne due to its anti-inflammatory and comedolytic properties.¹¹ The adverse events of salicylic acid are minor and temporary like dryness and erythema. Salicylic acid toxicity (Salicylism) occurs when applied to large area due to systemic absorption of the acid and is usually associated with high concentrations.¹¹

In this study, it was found that SA peel alone without any priming agent led to highly significant

($p < 0.001$) improvement in the total acne score, the improvement is significantly higher when it is used with priming agents either tretinoin or hydroquinone ($p < 0.05$). The change in total acne score (Week 0 to Week 12) was 81.45% with SA alone, 94.3% with tretinoin priming and 90.2 with hydroquinone priming ($p < 0.05$). Efficacy of SA as peeling agent has been established by many researchers.^{3,6,7,10} A split face, blinded study by Kessler E et al compared a series of six glycolic acid 30% peels on one side of the face vs. six salicylic acid 30% peels on the other side in patients with facial acne ($n = 20$).¹² Both treatments were effective, but the effect of salicylic acid was sustained longer and this peel was associated with fewer side-effects compared with that of glycolic acid.¹² Also lipophilic form of salicylic acid could increase the effect of superficial peeling; this effect may be attributable to a better penetration into the sebaceous follicle. The anti-inflammatory activity of SA makes it useful in rapidly decreasing facial erythema.¹³

In this study, significantly higher number of adverse effects was reported in the SA peel without priming agent group as compare to use of priming agents ($p < 0.05$). Most commonly encountered side effects were erythema and exfoliation. According to literature, superficial peels very rarely cause complications, which are usually not severe – transient mild hyperpigmentation, redness during the first night and a flare-up of pimples have been reported.¹⁴ All peels should be managed with care to minimize the potential for side-effects; the level of expertise in administering peels is vitally important to ensure a good outcome. Generally, the depth of peel correlates with the potential for side-effects and the benefit/risk ratio changes with increasingly deeper peels.¹⁴ Medium peels cause marked redness for several days, followed by significant desquamation, and also associated with high risk of hyperpigmentation and solar lentigines following treatment. Therefore, a stringent photoprotection with sunscreens is recommended for several weeks. Because of the risk of hyperpigmentation, medium-depth peels are unsuitable for phototype V or VI patients.¹⁵ While for deep peels, risk of complications like frequent early transient hyperpigmentation followed by hypopigmentation, or even total and permanent achromia is quite high.¹⁵ Medium and deep peels are less used now-a-days because of the complications. Even techniques for prevention of complication like use of priming agents have been increasingly implemented with superficial peels also. On analyzing subjective assessment for peels, the mean visual analog scale scores were significantly higher for SA with priming agents rather than SA peel alone group ($p < 0.05$). Use of priming agent also enhances subjective wellbeing feeling of the patient undergoing peeling procedure.

Various studies and literature has reported that the biggest drawback with the use of chemical peels is post

inflammatory hyperpigmentation (PIH). Various measures have been suggested to address this problem like the concomitant use of depigmenting agents, maintenance chemical peels, photoprotection and so on. Priming or preparing the skin prior to the peel is a useful adjunctive measure which also enhances the effect of the peeling agent apart from decreasing the PIH.¹⁶ It involves the application of a topical depigmenting agent like hydroquinone or tretinoin two weeks prior to the planned day of peel. In this study topical tretinoin and hydroquinone were used as priming agents and both showed significantly more effectiveness in both subjective and objective outcomes ($p < 0.05$). Priming ensures uniform penetration of the peeling agent, enhances healing and maintains the effects achieved with the chemical peel¹⁷⁻¹⁹ It is believed that isotretinoin improves the appearance of photoaged skin through collagen synthesis, dermal vascularization increase, cell differentiation and extracellular matrix stabilization.²⁰⁻²² Isotretinoin has been associated with increased incidence of delayed wound healing and scarring when combined with medium and deep chemical peels or dermabrasion, whereas the combination of superficial chemical peels and topical isotretinoin therapy has been reported to be safe, causing negligible or no adverse effects such as erythema during the few first days or transient, mild hyperpigmentation.¹⁹⁻²⁴ Studies have been conducted to assess the benefit of priming agents as adjuncts to chemical peels. In a study by Garg et al,²⁵ 60 Indian patients with melasma were randomly allocated into three groups, receiving only glycolic peel, GA primed with 0.025% tretinoin and 2% hydroquinone, respectively. The fall in MASI was highest in the group receiving 2% hydroquinone as a priming agent with minimum relapse and PIH. In another study by Nanda et al²⁶ better improvement was seen with 2% hydroquinone as a priming agent as compared to 0.025% tretinoin when used as an adjunct with 10-30% trichloroacetic acid peel peels. Appropriate use of priming agent can help in reducing the side effects and enhance the effectiveness of superficial peels. Because of the small sample size, it was not possible to compare the isotretinoin and hydroquinone as priming agents in this study. Larger studies with more number of patients are required to evaluate and compare the different priming agents in superficial peeling.

Conclusion

Chemical exfoliation resulting in the reduction of keratotic plugs using salicylic acid as a superficial peeling agent with appropriate priming serves as an add-on therapy for the treatment of acne.

In conclusion, three steps are essential in superficial peeling procedure: 1) Clinical diagnosis and appropriate patient selection for the peeling should be done which require special training of the dermatologists 2) Pre and post peeling: care which

includes use of priming agents which enhances objective and subjective outcome of peeling. It also helps determine the level of re-epithelialization, remodeling effects as well as scarring/recovery time. 3) Side effects: the dermatologist should be expert in early and prompt diagnosis and treatment of the side effects. The level of expertise of a dermatologist is crucial for the rate of side-effects and for the final peel results. Superficial peels are easy to perform and their benefit/ratio risk is very good.

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