

## **Efficacy of Salicylic Acid 25% Concentration Peeling with and without Systemic Azithromycin with Zinc sulphate& Topical Benzoyl Peroxide Therapy in Management of Mild to Moderate Acne Vulgaris Scars**

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### **Abstract**

**Background:** Acne vulgaris is the most common skin condition affecting the pilosebaceous system in adolescents and young age and characterized by different skin lesions and might result in permanent scars. Chemical peeling is an effective option in the management of active acne. The mechanism of action lies in causing desquamation by targeting the corneosomes and keratinocytes, enhancing breakdown and decreasing cohesiveness. It also increases epidermal activity of enzymes, leading to epidermolysis and exfoliation and induces improvement of skin texture, pore size and reduces sebum production. Proper and successful treatment of acne involves choosing the right medication.

**Objectives:** This study aims to evaluate the clinical efficacy and safety of using topical 25% Salicylic acid alone, in comparison with a combination of systemic Azithromycin and topical 25% salicylic acid, Zinc sulphate, and Benzoyl peroxide gel, in treatment of mild to moderate acne lesions.

**Subjects and methods:** This study is a prospective, randomized clinical trial included a hundred patients diagnosed with mild-to-moderate facial acne vulgaris and randomly divided into two equal groups Group A, treated by 25% Salicylic Acid peeling in combination with systemic Azithromycin in addition to Zinc sulphate and topical Benzoyl peroxide gel. Group B, treated by 25% salicylic peeling only. All patients received at least 6 peeling sessions performed 2 weeks apart in 12-weeks duration.

**Results:** Number of peeling sessions was significantly lower in group A than group B ( $p= 0.03$ ). Improvement rate (92%) 46 cases in group A vs. (20%) 10 cases in group B. Improvement score after 6<sup>th</sup> session was 4.71 in group A vs. 2.67 in group B ( $p<0.001$ ). Also, there was a highly significant improvement after each session in group A as 15 cases (30%) needed only 4 sessions for complete improvement. Group B showed only significant improvement after 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> sessions, while there was no improvement in score after 5<sup>th</sup> and 6<sup>th</sup> sessions. There were no statistically significant differences regarding risk factors of acne such as; psychological distress, family history, dairy product consumption, fast food, cosmetics, regular exercise and special diet habits ( $p>0.05$ ). Disease duration were matched in both groups as mean duration in group A was 26.8 versus 27.5 months in group B. Back & shoulder lesion were found in 34 cases in group A while they present in 31 cases in group B. There were no differences regarding lesions characteristics between both studied groups except for pustules that were predominant in group A in 34/50 cases (68%) whereas, they found in 24/50 cases (48%) in group B ( $p=0.04$ ).

**Conclusion:** Topical 25 % of salicylic acid is more efficient to treat mild to moderate acne vulgaris and in combination with systemic Azithromycin in addition to Zinc sulphate and topical Benzoyl peroxide gel is significant than alone and both protocols equal in safety and tolerability.

**Keywords:** Acne Vulgaris, Salicylic Acid, Chemical Peeling, Benzoyl Peroxide.

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### **I. INTRODUCTION**

Acne vulgaris is a longstanding disorder of the pilosebaceous system as a result of abnormal desquamation of follicular epithelium which leads to the obstruction of the pilosebaceous canal, resulting in inflammation and subsequently the formation of papules, pustules, nodules, comedones, and scarring<sup>(1)</sup>.

Acne vulgaris has a great effect on the quality of life so, it is very important to manage patients with acne vulgaris properly to avoid persistent complications and psychological consequences<sup>(2)</sup>.

Acne vulgaris is the most common skin condition affecting late adolescents across the globe. Almost 85% of general population develop an acne episode in their lives, which mainly involved the face, upper back and chest<sup>(3)</sup>. Acne vulgaris is caused by overactivity of the sebaceous glands and blockage in the ducts, which leads to the formation of comedones that later on inflamed, by *Propionibacterium acnes*<sup>(4)</sup>.

Chemical peeling is an effective option in the management of active acne. The mechanism of action lies in causing desquamation by targeting the corneosomes and keratinocytes, enhancing breakdown and decreasing cohesiveness. It also increases epidermal activity of enzymes, leading to epidermolysis and exfoliation and induces improvement of skin texture and pore size and reduces sebum production<sup>(5,6)</sup>.

Salicylic acid is 2-hydroxybenzoic acid or orthohydroxybenzoic acid. It is a lipophilic agent, which induces desquamation of upper lipophilic layers of stratum corneum. The salicylic acid peel is one of the safest superficial chemical peels in addition, salicylic acid has anti-inflammatory effect which could help in speed up the treatment of inflamed lesions<sup>(7)</sup>.

Benzoyl peroxide is well established as an effective topical agent and it can be provided in different formulations. It is an effective broad spectrum bactericidal agent which is due to its oxidizing activity<sup>(8)</sup>. The drug has also an anti-inflammatory, keratolytic, and comedolytic activities, and is indicated in mild-to-moderate acne vulgaris<sup>(9,10)</sup>.

Azithromycin is documented as a potent therapy for skin infections in both adult and pediatric age groups due to its remarkable efficacy and pharmacokinetics. It has a long tissue half-life and requires less frequent dosage, which is useful in increasing the compliance and tolerability of the patient<sup>(11,12)</sup>. Oral azithromycin has approved good efficacy and safety in treatment of mild to moderate acne vulgaris in adolescents, with excellent patient compliance<sup>(13,14)</sup>.

The aim of this comparative randomized clinical trial is to evaluate the clinical efficacy and safety of using topical 25% Salicylic acid alone, in comparison with combination of systemic Azithromycin and topical 25% salicylic acid, Zinc sulphate and Benzoyl peroxide gel, in treatment of mild to moderate lesions of acne vulgaris.

## **II. PATIENTS AND METHODS**

This study is a prospective, randomized clinical trial included a hundred patients; 75 females and 25 males with mean age of 21.8 years diagnosed with mild-to-moderate facial acne vulgaris. The study carried out at private outpatient Dreams Center of Dermatology and Cosmetology in contribution with Libyan academy for postgraduate studies, in the period from March till September 2020 after approval of the Libyan National Committee for Biosafety and Bioethics (LNCBB) and informed consent was taken from every patient. The study was carried out following the recommendations of the Declaration of Helsinki in October 2000.

**Inclusion criteria:** Patients included in this study had mild to moderate facial acne vulgaris and had not taken any treatment either topical or systemic at least two months before the study. All patients were healthy and had no other skin lesions.

**Exclusion criteria:** patients with severe acne vulgaris (abscesses and nodulo-cystic lesions), patients who were on any anti-acne therapy since last 2 months, pregnancy and lactation, patients with history of hypersensitivity to formulations used, and patients with conditions like photosensitivity and active dermatoses such as facial warts or herpes simplex infection.

Each patient was subjected to detailed history by being interviewed for age, sex, occupation, sun exposure, duration of the disease, family history, any precipitating factors such as use of cosmetics, dairy product consumption, fast food, regular exercise, special diet habits, and psychological distress. Patients were then subjected to a proper general, systemic, and dermatological examination to assess skin type, post-acne hyperpigmentation, and scars followed by a full explanation of the procedure.

The severity of acne in all the patients was graded on clinical grounds as; grade 1- Comedones, occasional papules, grade 2- Papules, comedones, few pustules, grade 3- Predominant pustules, nodules & abscess and grade 4- Mainly cysts, abscess and widespread scarring<sup>(15)</sup>.

A pre-peeling test was performed by application of the peeling agent on a 1 cm × 1 cm area in the right retro-auricular area. The patients were examined after 1 week and if they tolerated the peel well, they received facial peeling.

### **Treatment Protocol:**

Patients were randomly divided into two groups of 50 patients each, based on computerized randomization. Group A, treated by 25% Salicylic Acid peeling in combination with systemic Azithromycin 500 mg once per day orally for 3 days in 10 days apart in 1 month duration in addition to Zinc sulphate and topical Benzoyl peroxide gel. Group B, treated by 25% salicylic peeling only. Any other systemic and topical acne treatments were banned. All patients received 6 peeling sessions or less according to improvement scale, sessions performed 2 weeks apart in 12-weeks duration.

### **Peeling Procedure:**

Vaseline is used to protect sensitive areas such as the inner canthus of the eyes and nasolabial folds then betadine following by alcohol swab were used for cleaning up the face and then face degreased with acetone. In both studied groups, the correspondant peeling agents were applied as a single coat, by using a cotton tip applicator,

sequentially starting from the forehead and progressing to the cheeks, chin, glabella, nose, and perioral area. Patients were observed for immediate whitening – salicylic acid frost, that is, pseudofrost after SA peeling and faint erythema were considered endpoints, in each group. The patients were also asked to report when they felt a stinging or burning sensation with peels, which was considered the alternative endpoint in patients in whom erythema could not be discerned (because of dark skin color). After achieving endpoints, patients were asked to pat and wash their faces with cool tap water. All patients were advised to protect from sunlight by using sunscreen regularly at daytime for the entire study duration.

**Assessment follow up:**

Each patient was assessed by the investigator by inspecting and feeling the skin. Non-inflammatory and inflammatory lesions were counted on each visit. Digital color facial photographs were taken. Left and right profile views were obtained at baseline, before the 1st session, after the 6th session, and at the end of the follow up period. For independent clinical assessment, three dermatologists evaluated the photographs. For assessment of improvement we proposed a new scoring scale based on global acne grading system according to counted number of lesions before and after peeling sessions in both studied groups as: mild lesions were considered when Papulo-pustular lesions <15 inflammatory lesions (Score 1 : 15 – 10, Score 2: 10 – 5, Score 3 : < 5, and Score 4 means completely improvement), and moderate lesions means presence of 15-50 inflammatory lesions (Score 1: 15-50, Score 2: 15-10, Score 3: 10-5, Score 4: < 5, and Score 5 means completely improvement)

Safety evaluations included assessment of erythema, dryness, exfoliation, burning sensation, crust, and dark pigmentation. Immediate and delayed side effects were recorded at each session and in the follow-up period.

**Statistical analysis:**

Analysis of data was done using Statistical Program for Social Science version 24. Quantitative variables were presented in the form of mean and standard deviation. Continuous variables were compared using Student's T test for independent groups was used in case of normal distribution or Mann Whitney test as a non-parametric alternative. Qualitative variables were described as number and percent. Qualitative variables were compared using chi-square ( $\chi^2$ ) and Fisher exact test, as indicated. When a variable was not normally distributed, a  $P$  value  $< 0.05$  is considered significant.

### **III. RESULTS**

A total of 100 cases of mild to moderate facial acne vulgaris 25 males and 75 females their ages ranged from 14 to 38 with mean age 21.8 years. There were no significant differences regarding age and sex distribution between both studied groups  $p>0.05$ . There were no statistically significant differences regarding risk factors of acne such as; psychological distress, family history, dairy product consumption, fast food, cosmetics, regular exercise and special diet habits  $p>0.05$  (Table. 1). Disease duration were matched in both groups as mean duration in group A was 26.8 versus 27.5 months in group B. Back & shoulder lesion were found in 34 cases in group A while they present in 31 cases in group B. There were no differences regarding lesions characteristics between both studied groups except for pustules that were predominant in group A in 34/50 cases (68%) whereas, they found in 24/50 cases (48%) in group B;  $p=0.04$  (Table. 2).

**Table 1: Demographic characteristics and risk factors of both studied groups.**

		Group A N=50		Group B N=50		t-test MW <sup>#</sup>	P
Age\ years Mean ±SD Range		$22.2 \pm 5.1$ 14 - 31		$21.4 \pm 4.3$ 14 - 38		0.89	0.37 NS
		N	%	N	%	$\chi^2$	P value
Gender	Male	10	20	15	30.0	1.33	0.25 NS
	female	40	80	35	70.0		
Psychological distress		28	56	21	42.0	1.96	0.16 NS
Positive family history		31	62	26	52.0	1.02	0.31 NS
Dairy product consumption		41	82	39	78.0	0.25	0.62 NS
Fast food		41	82	36	72.0	1.41	0.24 NS
Daily makeup use		32	64	23	46.0	3.27	0.07 NS
Regular exercise		23	46	22	44.0	0.04	0.84 NS
Special diet habits		25	50	29	58	0.64	0.42 NS

NS: P-value>0.05 is not significant, MW#: Mann–Whitney U-test

**Table 2: Disease characteristics among both studied groups.**

	Group A N=50		Group B N=50		MW <sup>#</sup>	P
	N	%	N	%	$\chi^2$	P value
Disease duration\ months Mean ± SD Range (median)	$26.8 \pm 17.98$ 1 – 60 (24)		$27.5 \pm 27.4$ 1 – 120 (24)		0.83 <sup>#</sup>	0.41 NS
Face acne	50	100	50	100	-----	-----
Back & shoulder acne	34	68.0	31	62.0	0.39	0.53 NS
Post-acne scar	35	70	31	62.0	0.71	0.39 NS
Hyperpigmentation	44	88	42	84.0	0.33	0.56 NS
Comedones	50	100	50	100	----	----
Inflammatory papules	36	72	28	56.0	2.78	0.09 NS
Non-inflammatory papules	50	100	50	100	----	----
Pustules	34	68	24	48	4.11	0.04 S

NS: P-value>0.05 is not significant

S: P-value<0.05 is significant

Number of peeling sessions was significantly lower in group A as mean number of sessions was **5.4** session while it was **5.8** sessions in group B; **p= 0.03**. improvement was found in 46 cases (92%) in group A treated with combination therapy, while only 10 cases (20%) in group B improved by salicylic acid only peeland 40 cases (80%) did not show improvement. There was no significant difference regarding side effects between both studied groups as only 10 cases of whole study population showed side effects as follows; IngroupAthere were three cases of hyperpigmentation, two cases of erythema, and only one case of dryness, while in group B only two cases of hyperpigmentation and two cases of erythema were reported (**Table. 3**).

**Table 3: Treatment data among both studied groups.**

		Group A N=50		Group B N=50		t-test	P
Number of peeling Mean ±SD Range		$5.4 \pm 0.93$ 4 – 6		$5.8 \pm 0.66$ 4 – 6		2.24	0.03 S
Side effects	No	N	%	N	%	$\chi^2$	P value
Side effects	Hyperpigmentation	3	6	2	4.0	1.24	0.74 NS
	Erythema	2	4	2	4.0		
	Dryness	1	2	0	0.0		
	Improvement	Yes	92	20.0	Fisher	<0.001 HS	
		No	8	80.0			

NS: P-value>0.05 is not significant

HS: P-value<0.001 is high significant

There was a statistically significant increase in disease improvement score in group A treated with combination therapy than in group B treated with 25% salicylic acid peel only, after first session and before and after each subsequent session as showed in **table 4**.

**Table 4: Disease score assessed before and after peeling sessions among both studied groups.**

	Group A N=50	Group B N=50	t-test MW <sup>#</sup>	P
Basic score				
Mean ± SD	1.0 ± 0.0	1.0 ± 0.0	----	-----
Range (Median)	1	1		
After 1 session				
Mean ± SD	1.22 ± 0.42	1.0 ± 0.0	3.71	<0.001
Range (Median)	1 – 2 (1)	1		HS
P- value (basic score vs. after 1 session)	<0.001 HS	----		
After 2 sessions				
Mean ± SD	1.98 ± 0.68	1.68 ± 0.47	2.55	0.02
Range (Median)	1 – 3 (2)	1 – 2 (2)		S
P- value (after 1 vs. after 2 sessions)	<0.001 HS	<0.001 HS		
After 3 sessions				
Mean ± SD	2.68 ± 0.55	2.16 ± 0.77	3.36 <sup>#</sup>	0.001
Range (Median)	2 – 4 (3)	1 – 3 (2)		S
P- value (after 2 vs. after 3 sessions)	<0.001 HS	<0.001 HS		
After 4 sessions				
Mean ± SD	3.56 ± 0.73	2.64 ± 0.9	5.61	<0.001
Range (Median)	1 – 5 (4)	1 – 4 (3)		HS
P- value (after 3 vs. after 4 sessions)	<0.001 HS	<0.001 HS		
After 5 sessions	(n=35)	(n=42)		
Mean ± SD	3.83 ± 0.51	2.76 ± 1.25	4.27 <sup>#</sup>	<0.001
Range (Median)	2 – 4 (4)	1 – 4 (3)		HS
P- value (after 4 vs. after 5 sessions)	<0.001 HS	0.131 NS		
After 6 session	(n=35)	(n=42)		
Mean ± SD	4.71 ± 0.86	2.67 ± 1.26	6.63 <sup>#</sup>	<0.001
Range (Median)	2 – 5 (5)	1 – 5 (2)		HS
P- value (after 5 vs. after 6 sessions)	<0.001 HS	0.47 NS		

NS: *P*-value>0.05 is not significant

S: *P*-value<0.05 is significant

HS: *P*-value<0.001 is high

significant

Also, there was a highly significant improvement after each session in group A as 15 cases (30%) needed only 4 sessions for complete improvement. group B showed only significant improvement after 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> sessions, while there was no improvement in score after 5<sup>th</sup> and 6<sup>th</sup> sessions (Table. 4).

#### IV. DISCUSSION

This comparative trial is the first to evaluate clinical efficacy and safety of 25% Salicylic acid Peeling, complemented with; systemic Azithromycin, Zinc sulphate and topical Benzoyl peroxide gel in comparison with 25% Salicylic Acid alone in treatment of mild to moderate acne vulgaris.

The results of current study revealed that there was no statistically significant difference among both studied groups in disease duration, distribution, and lesion characteristics except significant prevalence of pustules among 68% of group A patients versus 48% in group B, also has been revealed that insignificant differences in all disease characteristics as, duration of disease, and baseline acne score (*P*> 0.05)<sup>(16)</sup>. Similarly, there was no statistical difference in the mean baseline comedone, papule, and pustule counts (*P* value > 0.05), and hence, the two groups were comparable before starting the therapy. Also, similar results reported<sup>(17)</sup> as baseline non-inflammatory and inflammatory lesion counts were not different between the two groups (sides of the face) in their study noninflammatory lesion counts: 18.6 vs 22.7, *p* = 0.96; and inflammatory lesion counts: 14.2 vs 12.5, *p*= 0.38. Therefore, patients had symmetrical involvement for this split face study.

The assessment of the severity of acne vulgaris is considered a challenge for dermatologists. No grading system has been accepted universally<sup>(18)</sup>, so we evolved a new grading system according to follow up improvement of number of lesions as Mild lesions are considered when Papulo-pustular lesions <15 inflammatory lesions (Score1: 15 – 10, Score 2: 10 – 5, Score 3 : < 5, and Score 4 means completely improvement), whereas, Moderate lesions means presence of 15-50 inflammatory lesions( Score 1 : 15-50, Score 2: 15-10, Score 3: 10-5, Score 4: < 5, and Score 5 means completely improvement). According to this classification our study revealed that there was a high statistically significant increase in acne improvement score among group A on subsequent peeling sessions than the other group, as basic score was 1 in each group before treatment and after six sessions it increased to 4.71 ± 0.86 in group A versus, 2.67 ± 1.26 in group B; *p*<0.001. Also, our study results showed significant association between combination therapy and reduction of number of peeling sessions, and highly significant increase of improvement rate (92% versus 20% respectively).

These results are in agreement with other study<sup>(19)</sup> who compared the clinical efficacy and safety of combination chemical peels vs single agent peel in treatment of mild to moderate acne the study included 45 patients divided into three equal groups. Group B which is comparable to our study was treated by combination peels of salicylic (20%) mandelic (10%) (SM) mixture on the Rt half vs only salicylic acid 30% on the Lt half.

All patients received six sessions with 2 week intervals and followed up for 3 months. The results of group B revealed combination peeling therapy on Rt side improved the mean Michelsons acne severity score (MAS) as it was 20.0 before treatment. After treatment, it decreased to 6.4 with a highly significant difference ( $P = 0.001$ ). When comparing between both sides at the end of the study, a significant difference ( $P = 0.006$ ) was detected in favor of the Rt side, the study concluded that combination peels are safe, effective, and superior to a single peel in the treatment of mild to moderate acne vulgaris<sup>(19)</sup>. In other study by Bae et al.<sup>(17)</sup> comparing salicylic acid peels versus jessner's solution for acne vulgaris the study revealed that Inflammatory and noninflammatory acne lesion counts decreased in proportion to the duration of treatment. The count of inflammatory acne lesions was matched between salicylic acid and Jessner's solution peels, although count of noninflammatory acne lesions, sites treated with salicylic acid showed statistically significant improvement ( $p = 0.04$ ), whereas those treated with Jessner's solution did not. The authors explained that by the effect of salicylic acid is mainly due to the lipophilic activity and strong comedolytic effect. Because the initial event in comedo formation is excessive keratinization in the midportion of the follicular canal, lipophilicity, which is required for penetrating the milieu of the sebaceous unit, is important for comedolysis<sup>(20,21)</sup>. Therefore, higher concentrations of salicylic acid in salicylic acid peels (30%) than in Jessner's solution peels (14%) may be responsible for the superiority of salicylic acid peels in managing noninflammatory acne lesions<sup>(17)</sup>. Lee and Kim<sup>(22)</sup> also demonstrated that both inflammatory and non-inflammatory acne lesions were effectively reduced by salicylic acid peel. The majority of their cases (77.1%) showed moderate or good improvement. Also incomparingbetween 30% glycolic acid and 30% salicylic acid peels in the treatment of mild to moderately severe facial acne vulgaris<sup>(23)</sup>. The results revealed significant decrease in acne lesions with salicylic acid peels.

Regarding safety in our study treatment agents were tolerated well by the patients. Hyperpigmentation was the most frequent side effects reported in 5 patients while Postpeel burning and stinging sensation with erythema were observed in 4 patients and dryness of skin was observed in only one patient of study population. There was no significant difference between both groups as regards side effects. Which indicates great tolerability of peeling agents in accordance with other previous studies used salicylic acid<sup>(16)</sup>that showed both the peeling agents were tolerated very well in all the patients of the two groups and also reported that both the peels did not produce any serious side effects<sup>(17)</sup>. Furthermore, it has been reported that peeling agents were well tolerated by all patients on both sides of the face and no patients have been forced to drop out of the study<sup>(19)</sup>. In their study burning sensation, erythema, and exfoliation were the most frequent side effects.

In the current study, there were no statistically significant differences among both studied groups as regarding age, sex, and risk factors for acne. These results came in agreement with Saitta et al.<sup>(24)</sup> who revealed that acne can be present in all age groups, but it was most prevalent in adolescence. Over 90% of male and 80% of female have experienced acne by the age of 21 years. Similar results were reported<sup>(25)</sup> as the mean age in group A was 20.4 years and in group B was 20.5 years. In our study sex distribution was almost equal in both groups but female predominance was obvious as the majority of cases 75% was females this came in agreement with Collier et al.<sup>(26)</sup> who reported that acne was more frequent in women than men also been reported that female predominance 65% versus male 35%<sup>(23,25)</sup>, which coincide with most of other studies<sup>(27-29)</sup>. However Shishira et al.<sup>(30)</sup>observed more number of males than females in their study.

In our trial 49% of study population were associated with psychological stress which showed no statistically significant difference between both groups. Stress is an important factor of flaring up of acne during stressful situations as examinations, during financial constraints and during family disputes were reported by earlier researchers<sup>(31,32)</sup>.

Acne vulgaris is a multifactorial disease with periodic flares. Many triggers and aggravating agents have been implicated in disease flares. In the current study we found no significant differences between both groups regarding all investigated risk factors as positive family history, dairy product consumption, fast food consumption, daily makeup usage, regular exercise and special diet habits. Dairy product and fast-food consumption were the most prevalent 80% and 77 % of the whole study population respectively. This was supported by Kwon et al. and Cermanet al.<sup>(33,34)</sup>whodemonstrated that a low glycaemic load (GL) diet had beneficial effects in the treatment of acne. Large prospective cohort studies on 4273 teenage boys and 6094 teenage girls in the United States revealed a positive correlation between milk consumption and acne. There was a strong association between intake of skim milk and acne in boys<sup>(35-37)</sup>.

## V. CONCLUSION

From this study could be concluded that using of salicylic acid 25% as a topical chemical peeling alone and in combination with systemic Azithromycin plus, Zinc sulphate and Benzoyl peroxide gel are safe, effective, and superior to a single peel in the treatment of mild to moderate acne vulgaris in addition to reduce the side effets that revealed in pereviouse studies, that used higher concentrations of salicylic acid. This study also indicated that combination treatment of mild to moderate acne vulgaris lesions by systemic Azithromycin plus

chemical peeling by topical 25 % salicylic acid, Zinc sulphate and Benzoyl peroxide gel is more efficient than topical 25 % salicylic acid alone and both treatment protocols are comparable in respect to safety and tolerability.

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