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Topical Therapy of Vitiligo Using Sunlight Exposure with Lactic Acid Cream (10%) Versus Methoxsalene Solution

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ABSTRACT

Background: Vitiligo is a common autoimmune disease to which multiple therapies have been used. Lactic acid in different modes of preparation like 15% topical solution and 1% intralesional injection has been tried effectively in treatment of vitiligo. Objectives to test the efficacy of lactic acid cream10% with sunlight exposure in treatment of vitiligo, and to be compared with topical methoxsalene solution with sunlight exposure.

Materials and Methods: This is an interventional, therapeutic, single blinded, comparative study that was conducted in the Center of Dermatology, Medical City, Baghdad, Iraq, between April 2018 and June 2019. Patients with generalized and localized vitiligo were included. The diagnosis of vitiligo was based on clinical characteristic loss of skin pigmentation and supported by woods light examination. The demographic features were recorded. Physical examination was done to determine the site and number of patches per patient. The patients were divided into two groups: group A patients, were treated with lactic acid 10% cream followed by sunlight exposure. While in group B, the patients were treated with topical methoxsalene solution followed by sunlight exposure. All patients were assessed, and the surface area of each patch was measured before starting the treatment and every month for 3 months of treatment. The side effects were also recorded. A follow up visit after 3 months was done. A reduction rate in the surface area of vitiliginous patch was calculated.

Results: sixty patients, 41 (68.3%) females and 19 (31. 7%) males with a female to male ratio was 2.15:1. Their ages ranged between 3 – 42 years with mean± SD of 23.36±11.95 years. The disease duration ranged between 12-120 months. Total number of the lesions was 78 patches with a mean of 1.3 lesions per patient. No statistically significant differences were found between the two groups regarding demographic nor clinical features (P ≥ 0.05). In group A (lactic acid), 32 patients with 45 patches. The reduction rate in surfaces area of patches was increased at each visit. In the second visit, the reduction rate was (6.63%), the third visit, it was (17.45%). While in fourth and

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follow up visits the reduction rate was (30.22%) and (32.66%) respectively. The mean surface area of the lesions was decreased from 1.98±0.2cm2 to 1.23±0.1cm2 from the baseline visit to the last follow-up visit with P value<0.001 which was highly significant and the mean±SD of reduction rate was 32.66 ± 3.4 from the base line to the last follow-up visit. Group B(methoxsalene): 28 patients with 33 patches. The reduction rate was 13.12% in second visit while (16.32%) in the 3rd visit. In fourth and follow up visits, the reduction rate was (21.33%) and (20.78%) respectively. The mean surface area of the lesions was decreased from 4.63±0.9 cm 2 to 4.22±1.1 cm2 from the baseline visit to the last follow-up visit with P value 0.13 was not statistically significant.

Conclusion this study showed that lactic acid 10% cream in combination with sunlight exposure was statistically effective in treatment for vitiligo. Topical methoxsalene with sun light exposure was less effective than lactic acid and with more side effects.

Key Words Vitiligo, Lactic acid, methoxsalene, sun light, Sharquie, Iraq

INTRODUCTION

Vitiligo is a common autoimmune disease where many topical and systemic therapies have been used [1, 2.]

Lactic acid is an Alpha-hydroxy acid has been used since ancient times to induce rejuvenation of the skin by queen Cleopatra 69 B.C. [3] Alpha hydroxyl acids have been used in the last years as peeling agents but in low concentration.[4]

Sharquie has introduced lactic acid as mode of therapy for different skin diseases like alopecia areata, melasma and striae. [3, 5, 6]

Topical 15% lactic acid solution in combination with UVA has been used in vitiligo and the results showed clearly a statistically marked improvement (59.6%,P=0.002) when compared with lactic acid solution alone (52.4% p=0.003).[4] The theory behind this repigmentation is thought to be so called irritant theory which is similar to the inflammation induced by psoralen compound and ultraviolet light (UVL) through stimulation of keratinocytes to release inflammatory mediators such as basic fibroblast growth factor, interleukine-1, leukotriene C4 and E4, TGF-α(transforming growth factor alpha) and endothelin–1,3 thus stimulating proliferation of melanocytes and inducing repigmentation[7]. Most recently, intralesional lactic acid 1% solution was found to be more effective in therapy of vitiligo which is more effective than intralesional triamcinolone acetonide.[8] The objective of present work is to use 10% lactic acid cream in treatment of vitiligo as it is more easy to use and less irritant than solution neither associated with pain nor swelling and to be compared with topical methoxsalene both followed by sunlight exposure.

PATIENTS AND METHODS

The study was an interventional, therapeutic, single blinded, comparative work that was conducted in the center of Dermatology, Medical City, between April 2018 and June 2019.Patients with localized and generalized vitiligo were included in the study. The diagnosis of vitiligo was based on clinical characteristic loss of skin pigmentation and Wood's lamp to confirm the diagnosis when it is needed. History was taken from each patient including age, gender, duration of vitiligo, family history of vitiligo, history of other medical illnesses. Physical examination was also performed for each patient including site, size, number of the patches. The patients were selected regardless of the activity of disease. The following groups were excluded from the study: patients had recently treated by other therapies in the last two months, pregnancy, lactation, history of photosensitivity and any dermatoses affected by UV light, and patients with resistant acrofacial and universal vitiligo, acral parts and

unreliable patients. Oral consent was taken from each patient before starting the trial and after a detailed explanation for the nature of the disease, its causes, prognosis method of treatment, follow up and the possible side effects. All patients photographed at each visit by a mobile GALAXY Note 4 Camera at the same place, distance, and good illumination. Ethical approval was granted by the Scientific Committee of the Scientific Council of Dermatology and Venereology Arab Board for Health Specializations. The patients were divided into two groups: group A patients were treated with lactic acid 10% cream topically to be applied for few minutes at mid-day once weekly followed by sunlight exposure for 5-10 minutes. Lactic acid 88% concentration (GAINLAND CHEMICAL COMPANY, UK) was mixed with aqua rosa to have a final concentration of 10%, PH 6.84 and was prepared according to the following formula: (concentration 1 X volume 1= concentration 2 X volume 2). While in group B, the patients were treated with topical methoxsalene solution prepared by using 8-methoxpsoralen 7.5 ml in 30 ml rectified spirit (METHOXSALENE 0.1% EX- MELADININE FAIBLE CLS pharma) to be applied for few minutes on lesion smoothly once weekly at midday followed by sunlight exposure for 5-10 minutes. Therapy response was assessed by the outline of each patch was drawn on graphic transparent paper with surface area measurement in centimeters. All patients were assessed before starting the treatment and every month for 3 months follow up visit after 3 months was done. Patients were evaluated clinically by looking for any changes in the size and repigmentation including follicular one by using graph papers. A reduction rate in the surface area of vitiliginous patch was calculated. The side effects were also evaluated and checked up regularly with regular photographic documentation in a good illumination and same place Termination of treatment was done if there is absence of improvement after 3month or due to poor tolerance to therapy caused by local or systemic side effects: like sever irritation, pain, erythema, itching and others.

Statistical Analysis: The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test (two tailed) was used to compare the continuous variables accordingly. Z-test was used to compare the categorical variables accordingly. A level of P – value less than 0.05 was considered significant.

RESULTS

Sixty patients with vitiligo were enrolled in this study and being evaluated during both treatment and follow-up period. They were 41 (68.3%) females and 19 (31. 7%) males with a female to male ratio was 2.15:1. Their ages ranged between 3 – 42 years. The disease duration ranged from 12-120 months. Total number of the lesions was 78 patches with a mean of 1.3 lesions per patient. Surface area of the lesions ranged from 0.5-16 cm2. Group (A): (lactic acid 10% cream): 32 patients with 45 patches (15 in male and 30 in females). Group (B): (topical methoxsalene solution): 28 patients with 33 patches (11 in males and 22 in females). No statistically significant differences ($P \geq 0.05$) were found between study groups regarding age, gender, disease duration, previous treatment, family history, nor sites involved as shown in table (3.1). Frequency of associated illnesses in study groups is shown in table (3.2). In group A the pattern of re-pigmentation of patches was peripheral in 18(56.2%) patients, perifollicular in 4(12.5%) patients, mixed in 9(28.1%) patients and 14(43.7%) patients with no response. In group B, the pattern of repigmentation was peripheral in 14(50%) patients, perifollicular in 3(10.7%) patients, mixed in 4(14.2%) patients and 12(42.8%) patients with no response. Table 3.3 and figure 3.1 shows the comparison between study groups in reduction rate of surface area of lesion at each visit. In lactic acid group, the reduction rate was increased at each visit. While, in methoxsalene group, the reduction rate

was increased until the fourth visit, then it decreased at follow up visit. In the second visit, the reduction rate was significantly higher in methoxsalene group than that in lactic acid group (13.12% versus 6.63%, P= 0.001). No statistically significant difference in reduction rate between study groups in the third visit (17.45% in lactic acid group versus 16.32% in methoxsalene group, P= 0.098). In fourth and follow up visits, the reduction rate was significantly higher in lactic acid group than that in methoxsalene group (30.22% versus 21.33%, P= 0.001; and 32.66% versus 20.78%, P= 0.001 respectively). In group A, the mean surface area of the lesions was decreased from 1.98±0.2 cm 2 to 1.23±0.1cm2 from the baseline visit to the last follow-up visit with P value<0.001 which was highly significant and reduction rate mean± SD of 32.66 ± 3.4 from the base line to the last follow-up visit. While in group B, the surface area of the lesions was decreased from 4.63±0.9 cm 2 to 4.22±1.1 cm2 from the baseline visit to the last follow-up visit with P value 0.13 was not statistically significant and reduction rate mean± SD of 20.78±3.1 from the baseline visit to the last follow-up visit. Table 3.4 shows the comparison between study groups in side effects. Incidence of erythema, itching, and burning was significantly higher in methoxsalene group than that in lactic acid group (P < 0.05).

Table 3.1 Demographic and clinical features of patients in both groups.

General Characteristics	Study Group		P- Value
	Lactic acid Mean ± SD	methoxsalene Mean ± SD	
Age (Years)	25.62 ± 11.0	20.17 ± 12.2	**0.074**
Gender	**n (%)**	**n (%)**	
Male	12 (37.5)	7 (25.0)	**0.406**
Female	20 (62.5)	21 (75.0)	
Duration of disease (months)	42.7 ± 33.4	27.8 ± 27.7	**0.067**
Previous treatment			
Yes	24 (75.0)	20 (71.4)	**0.754**
No	8 (25.0)	8 (28.6)	
Family history of vitiligo	9 (28.1)	11 (39.3)	**0.362**
Distribution			
Localized	21 (65.6)	13 (46.4)	**0.134**
Generalized	11 (34.4)	15 (53.6)	
Site			
Face	5 (15.6)	0 (0)	**0.028**
Neck	0 (0)	2 (7.1)	**0.124**
Trunk	8 (25.0)	7 (25.0)	**1.0**
Upper extremities	14 (43.8)	10 (35.7)	**0.526**
Lower extremities	18 (56.3)	14 (50.0)	**0.628**

Table 3.2 Frequency of associated illnesses in study groups.

Variable	Study Group		P - Value
	Lactic acid (%) n= 32	methoxsalene (%) n= 28	
Psychological conditions	19 (59.4)	15 (53.6)	**0.652**
Thyroid disease	1 (5.3)	1 (3.6)	**0.92**
Psoriasis	1 (5.3)	0 (0)	**0.347**
Atopic dermatitis	3 (9.4)	1 (3.6)	**0.368**
Insulin dependent DM	1 (5.3)	1 (3.6)	**0.92**
Non-insulin dependent DM	1 (5.3)	3 (10.7)	**0.238**
Connective tissue disease	1 (5.3)	1 (3.6)	**0.92**

Table 3.3 Comparison between study groups in reduction rate of lesion at each visit.

Visits	Rate of reduction (%)		P- Value
	Lactic acid Group Mean ± SD	Methoxsalene Group Mean ± SD	
Baseline	0	0	**-**
2nd Visit	6.63 ± 2.1	13.12 ± 3.3	**0.001**
3rd Visit	17.45 ± 2.5	16.32 ± 2.7	**0.098**
4th Visit	30.22 ± 3.1	21.33 ± 2.8	**0.001**
Follow up visit	32.66 ± 3.4	20.78 ± 3.1	**0.001**

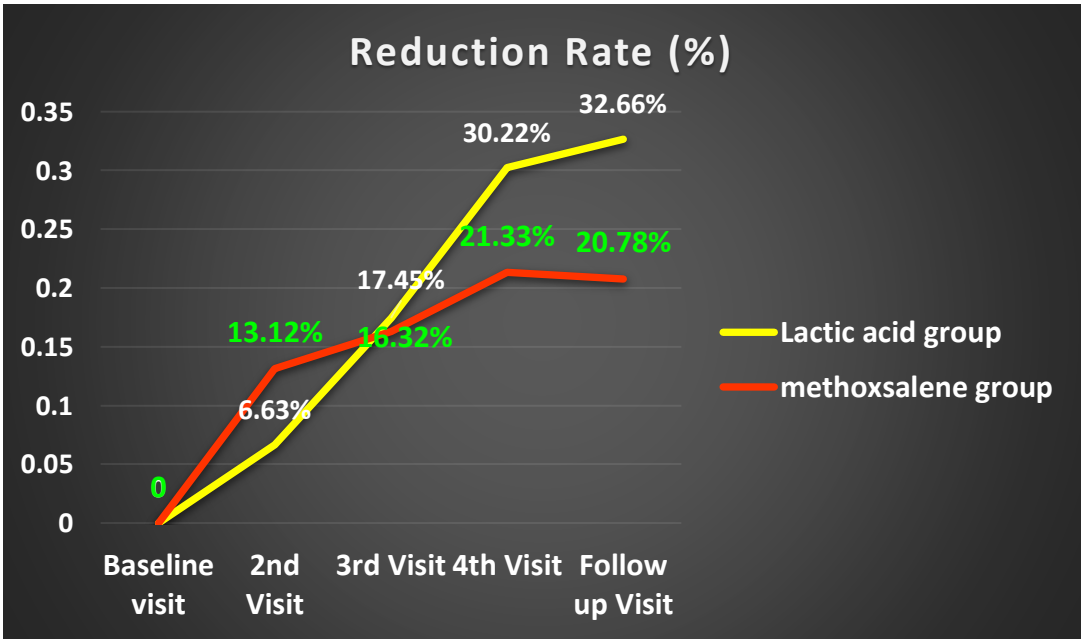

Figure 3.1 Reduction rate of lesion at each visit in study groups.

Table 3.4 Comparison between study groups in side effects.

Side effects	Study Group		P - Value
	Lactic acid (%) n= 32	Methoxsalene (%) n= 28	
Erythema	6 (18.8)	14 (50.0)	**0.01**
Itching	3 (9.4)	16 (57.1)	**0.001**
Burning	0 (0)	4 (14.3)	**0.027**

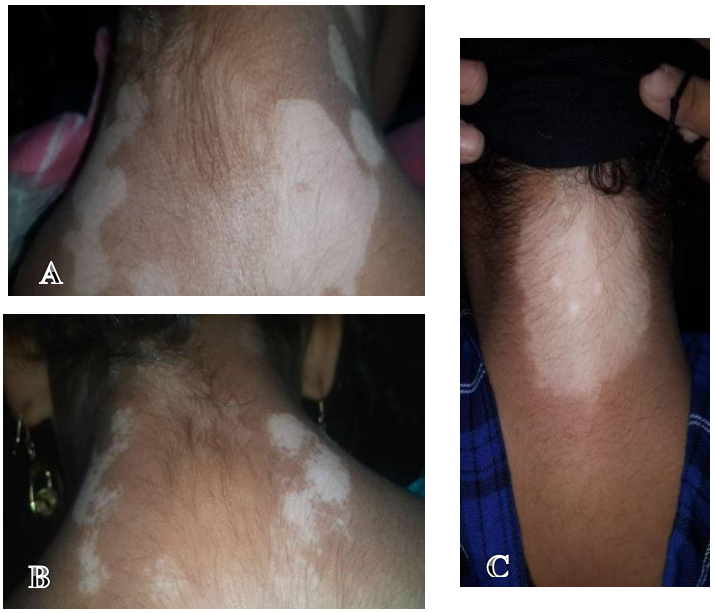

Figure 3.2 Methoxsalene group: ten years old female patient with vitiligo on the posterior aspect of neck (A) base line, visit (B) Repigmentation after 3rd session of treatment (C) after 3 months of follow-up.

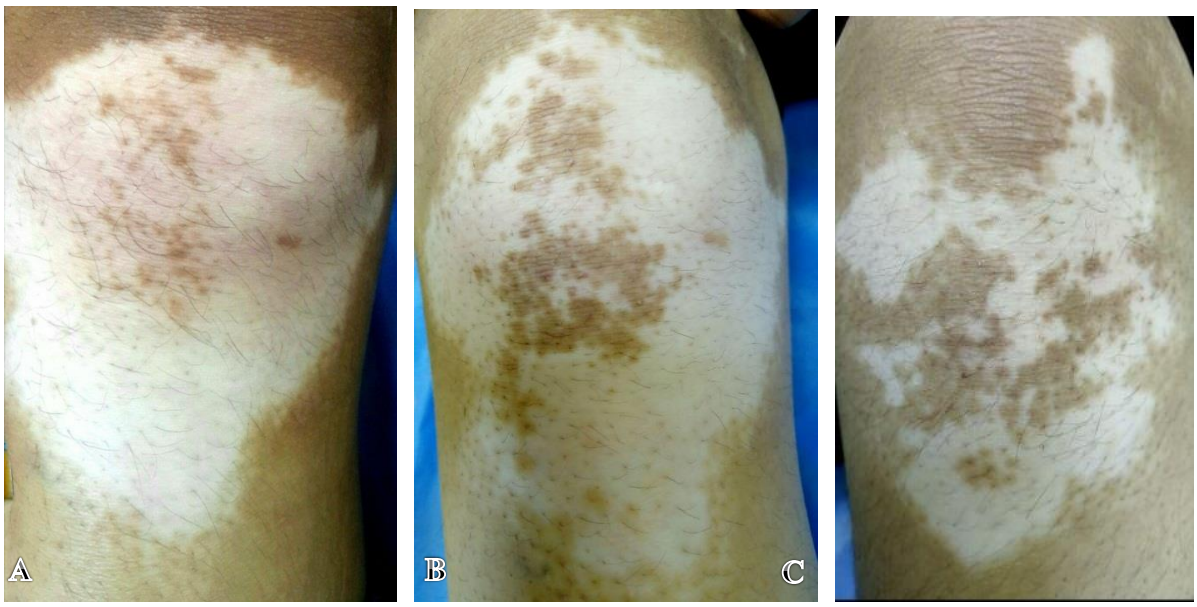

Figure 3.3 Lactic acid group: fourteen years old male with vitiligo on the knee. (A) Base line visit, (B)Repigmentation after 3rd session of treatment (C) after 3 months of follow-up.

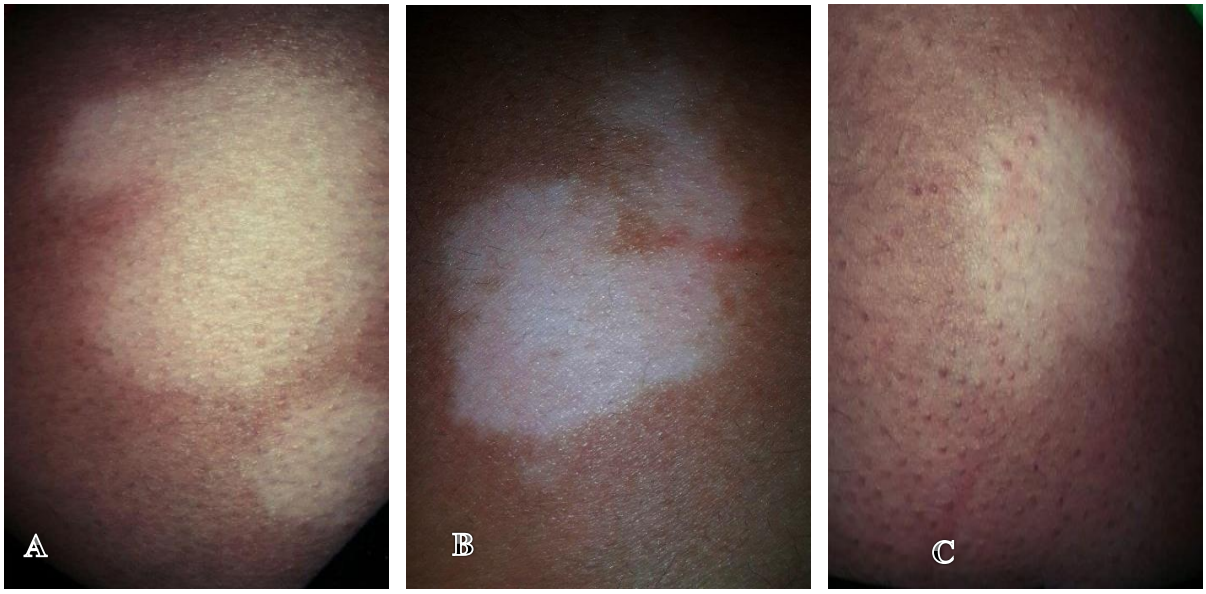

Figure 3.4 Methoxsalene group: thirty-two years old female patient with vitiligo on the inner aspect of the left thigh (A) base line visit, (B) Repigmantation after 3rd session of treatment (C) after 3 months of follow-up.

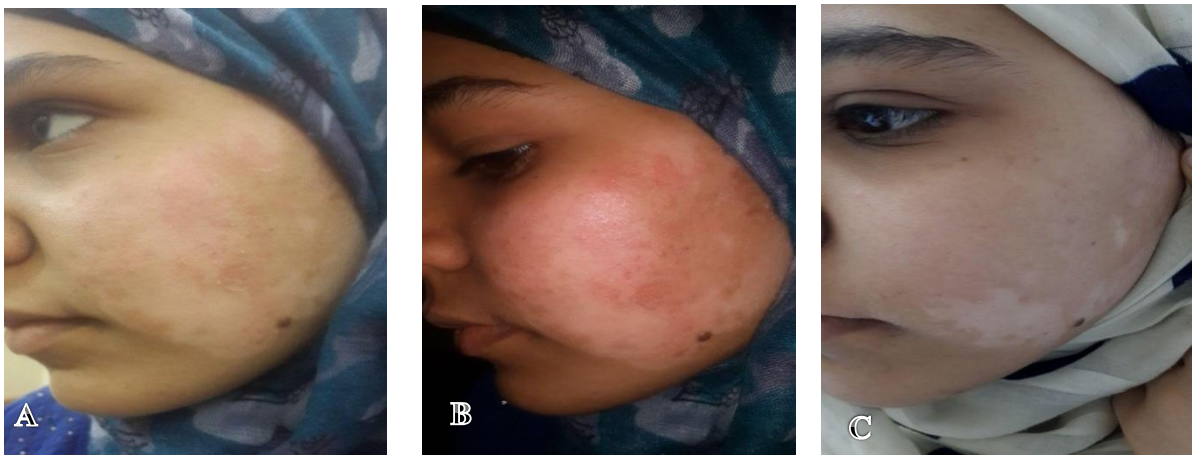

Figure 3.5 Lactic acid group: seventeen years old female patient with vitiligo on the face (A) base line visit, (B) Repigmantation after 3rd session of treatment (C) after 3 months of follow-up.

DISCUSSION:

Variable modes of therapy have been used for vitiligo, both topical and systemic. Topical therapy like psoralen, khellin, pseudo catalase and calcium in combination with short term UVB exposure, steroids, calcipotriol, immunomodulators as tacrolimus and pimecrolimus ointment, iodine tincture and topical lactic acid solution. [1, 2, 7, 9, - 12]. Systemic therapy like oral psoralens + UVA, PUVASOL (psoralens and sunlight), systemic steroids and vitamins C and E, each of these methods has its advantage and side effects. [13-16] Other studies showed significant improvement of treated patches with infrared radiation.[9] In well-stabilized localized segmental vitiligo, surgical therapies could be used by melanocytes transplant, where different modes have been used, but most recently since 2016, Sharquie et al invented new simple techniques for melanocyte transplant. The first one called direct transplant of melanocytes by dermabrasion technique gave 36.78% rate of pigmentation after 6 months. [17] The second one used needle

micrografting and gave repigmentation rate of 61.36% at four months. [17]

Psoralen compounds are old agents and remain the main standard therapy whether topical or systemic. It is most effective when combined with UV light therapy. [18] Topical methoxy psoralen solution has been used (0.07%) with sunlight, the repigmentation rate 55 % while, UVA alone result in repigmentation of 15.8 %. [2, 10, 19]

In comparison with intralesional solution, [8] lactic acid cream 10% was easier to apply once weekly with sunlight with no statistically significant side effects as compared with topical methoxsalene 0.1%. The result of this study was very encouraging as in lactic acid group, the reduction rate was increased at each visit. The reduction rate was statistically significantly higher in lactic acid group. The mean surface area of the lesions was decreased from 1.98±0.2 cm 2 to 1.23±0.1cm2 with P value<0.001 which was highly significant and reduction rate of mean 32.66 ± SD 3.4 from the base line to the last follow-up visit. The response was initially more rapid in methoxsalene group but with more side effects than lactic acid group.

The mechanism of action in both lactic acid and methoxsalene groups could be explained on basis of so called *Irritant theory* by stimulating keratinocytes to release inflammatory mediators such as basic fibroblast growth factor, interleukine-1, leukotriene C4 and E4, TGF-α(transforming growth factor alpha) and endothelin–1,3 thus stimulating proliferation of melanocytes and inducing repigmentation(7).

So, on conclusion, lactic acid 10% cream is new mode of therapy which is as effective as topical lactic acid 15%solution and intralesional lactic acid but as cream easier to be used with less side effects. In addition, lactic acid cream was more effective than topical methoxsalene.

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