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A Comparative Study for Efficacy of Khellin Ultra Violet A (KUVA) Versus Psoralen Ultra Violet A (PUVA) in the Treatment of Vitiligo

Conflict of interest: nothing to declare.
Authors' contribution: Ahmed Mohammed Radhi – conceptualization, data curation, investigation, methodology, project administration, resources, software, writing – original draft and writing – review & editing; Khalil Al-Hamdi – conceptualization, data curation, investigation, resources, software, supervision, writing – original draft and writing – review & editing.

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Abstract

Introduction. Vitiligo is a common disfiguring skin disease with unpredictable course and response to treatment modality. PUVA is a well-known modality of treatment but KUVA, to the best of our knowledge, was reported only in three previous research works, on a limited number of cases.
Purpose. The present work is a comparative therapeutic study designed to assess the efficacy, safety and tolerability of PUVA, with KUVA in the treatment of patient with vitiligo.
Materials and methods. A total of 100 patients with generalized vitiligo were enrolled in this study, randomly divided into two groups [50 patients for each]. The first group received PUVA therapy, the second group received KUVA therapy. Their ages ranged from 12–50 years (mean – 24.4±3.4 years). Photographing and eye examination and investigation was done every 6 months. The degree of re-pigmentation was evaluated by Vitiligo Area Severity Index (VASI) score.
Results. At the end of the study of 18 months a very good and excellent response was reported in 16 patients (32%) in PUVA group in comparison with 26 patients (52%) in KUVA group with statistically high significant difference (P=0.012). While there is no poor response in KUVA group, 1 patient (2%) in PUVA group have disappointing result according to VASI score, throughout the study. 48 patients (96%) have side effects in PUVA group while 14 patients (28%) reported in KUVA group.
Conclusion. KUVA appear to be better than PUVA as it induced earlier, better re-pigmentation.
Keywords: vitiligo, khellin ultra violet A, psoralen ultra violet A, vitiligo area severity index, pigmentation

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Сравнительное исследование эффективности комбинации хеллин – ультрафиолет А по сравнению с псорален – ультрафиолет А при лечении витилиго

Конфликт интересов: не заявлен.
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Резюме

Введение. Витилиго – распространенное обезображивающее заболевание кожи с непредсказуемым течением и реакцией на методы лечения. Псорален – ультрафиолет А (ПУВА) – это хорошо известный метод лечения, а хеллин – ультрафиолет А (ХУВА), по нашим данным, был описан только в трех предыдущих исследовательских работах по ограниченному числу случаев.
Цель. Оценить эффективность, безопасность и переносимость ПУВА с ХУВА при лечении пациентов с витилиго.
Материалы и методы. В этом исследовании приняли участие 100 пациентов с генерализованным витилиго, случайным образом разделенных на две группы (по 50 пациентов в каждой). Первая группа получала ПУВА-терапию, вторая группа – ХУВА-терапию. Их возраст варьировался от 12 до 50 лет (средний – 24,4±3,4 года). Фотографирование, осмотр глаз и исследование проводились каждые 6 месяцев. Степень репигментации оценивалась по индексу тяжести области витилиго (VASI).
Результаты. В конце исследования, которое продолжалось 18 месяцев, очень хороший ответ был зарегистрирован у 16 пациентов (32%) в группе ПУВА по сравнению с 26 пациентами (52%) в группе ХУВА со статистически высокой значимой разницей (P=0,012). У пациентов в группе ХУВА не зарегистрировано плохого ответа, в то время как у 1 пациента (2%) в группе ПУВА отмечен неутешительный результат по шкале VASI. В группе ПУВА побочные эффекты наблюдались у 48 пациентов (96%), в то время как в группе ХУВА – у 14 (28%).
Вывод. ХУВА, по-видимому, лучше, чем ПУВА, поскольку вызывал более раннюю, лучшую повторную пигментацию.
Ключевые слова: витилиго, хеллин – ультрафиолет А, псорален – ультрафиолет А, индекс тяжести области витилиго, пигментация

■ INTRODUCTION

The word vitiligo may be derived from the Greek vitellius, signifying a "calf's white patches" [1]. Vitiligo is an acquired pigmentary anomaly of the skin manifested by depigmented white patches surrounded by a normal or a hyperpigmented border.

Sometimes surrounded by red rim (inflammatory vitiligo) [2]. Nine topographical types of vitiligo have been described [Morphology qualitative studies the shape, texture and distribution of materials at a surface, whereas topography focuses on the quantitative dimensional measurement of features on a surface], according to the extent and distribution of the involved areas [3–5].

Vitiligo can begin at any age, but in 50% of cases it develops before the age of 20 years. The condition is gradually progressive, sometimes extending rapidly over a period of several months and then remaining quiescent for many years. Hypomelanotic macules are usually first noted on the sun exposed areas of skin, on the face or on the dorsa of hands. These areas are prone to sunburn. Rarely, itching in the absence of sunburn may occur. Damage to the 'normal' skin frequently results in an area of depigmentation – an isomorphic or Koebner phenomenon. The amelanotic macules in vitiligo are found particularly in areas that are normally hyperpigmented, for example the face, axillae, groins, areolae and genitalia. Areas subjected to repeated friction and trauma are also likely to be affected, for example the dorsa of hands, feet, elbows, knees and ankles. The distribution of the lesions is usually symmetrical, although sometimes it is unilateral and may have a dermatomal arrangement. Rarely, there is complete vitiligo, although a few pigmented areas always remain. The pigment loss may be partial or complete, or both may occur in the same areas (trichrome vitiligo). The macules or patches of vitiligo have a convex outline, increase irregularly in size and fuse with neighboring lesions to form complex patterns. The hairs in the patches frequently remain normally pigmented, but in older lesions the hairs too are often depigmented. The margins of the lesions may become hyperpigmented. The main symptom is the cosmetic disability, although some patients present because of sunburn in the depigmented areas [6].

Spontaneous repigmentation is noted in about 10–20% of patients, most frequently in sun-exposed areas. It is usually seen in younger patients, the repigmentation being quite trivial and mainly perifollicular. In addition to premature greyness of the hair, uveitis also rarely occurs [7]. Careful examination of the ocular fundus may show abnormalities [8]. The goal of treatment is to restore melanocytes to the skin. Therapy involves stimulating melanocytes within the hair follicle to proliferate and migrate back into depigmented skin. Depigmented skin is devoid of melanocytes in the epidermis. Melanotic melanocytes in the bulb and infundibulum of the hair follicle are absent in vitiliginous skin. The distribution, age of onset and hyperpigmented border will suggest the diagnosis. Examination with the Wood's light in a dark room accentuates the hypopigmented areas and is useful for examining patients with light complexions. The axillae, anus, and genitalia should be carefully examined. These areas are frequently involved but often clinically non apparent without the Wood's light. Vitiligo may be a predictor of metastases in melanoma patients, and a Wood's light examination may show early subtle changes in these patients [9].

Psoralen plus ultraviolet A (PUVA) photochemotherapy is the photochemical interaction between a psoralen medication and ultraviolet A (UVA) (320–400 nm) radiation, which has a beneficial therapeutic effect in psoriasis, along with over 30 other skin diseases. The term was originally used for oral methoxsalen (8-MOP) photochemotherapy, but is now loosely used to describe other routes of administration, such as topical and bath PUVA, as well as the use of other psoralen compounds.

Khellin and UVA have been reported to be as effective as PUVA in the treatment of vitiligo. KUVA reportedly does not lead to the phototoxic erythema seen with PUVA. This

advantage permits the patient to use KUVA at home, with daily regime, with natural sun light, safe with fair skin. Also, the photodynamic properties of khellin and visnagin in their photoreaction with DNA have been studied and khellin does not induce detectable DNA mutations.

The present work is a comparative therapeutic study designed to assess the efficacy of PUVA, with KUVA in the treatment of patients with vitiligo.

■ MATERIALS AND METHODS

Study design and setting

A comparative therapeutic study designed to assess the efficacy and tolerability of oral KUVA in the treatment of vitiligo in comparison with oral PUVA in the terms of the degree of re-pigmentation (Vitiligo Area Severity Index (VASI)), duration of treatment, total UVA dose and side effects in Iraqi patient. This study was conducted in Basrah teaching hospital during the period from October 20 2018 to April 30 2022.

Clinical assessment of cases and data collection

A total of 100 vitiligo patients were enrolled in this study, female to male ratio is 2.85, divided into two groups (50 patients for each). The first group received PUVA therapy, the second group received KUVA therapy. Odd and Even Number was followed for patient enrolment in specific group (first patient, group I, second patient, group II, and so on), were odd to PUVA group and even to KUVA group to avoid bias. Their ages ranged from 12–50 years (mean = 24.4 years, ±SD 3.4 years), each patient included in this study was informed that he or she is a part of scientific study, and informed council were signed in addition ethical approval was obtained from the scientific committee of Arab board dermatology and venereology. The UV cabinet Waldmann 7002 (UV lamps (UVA) 42 × PUVA 120 W), was used for therapy plan.

All patients were interviewed, full clinical history was taken then patient was examined regarding distribution of vitiligo in addition general examination of abdomen, chest, cardiac and ophthalmological exam were also done to exclude any systemic disease. Woods light exam was also done to confirm diagnosis in doubtful cases. A complete routine laboratory investigation obtained, including complete blood picture, liver and kidney function tests. Repeated laboratory tests were performed six, twelve, eighteen months after starting treatment for all the patients, to exclude any abnormality especially liver function test (SGOT, SGPT, LDH, Alk. Phosph).

Drugs

In PUVA group, the patient is given 8-MOP at a dose of 0.4-0.6 mg/kg of body weight/session on a full stomach 1 and half hour before UVA exposure. While in KUVA group, the patients were given Khellin at a dose of 100 mg 1 and a half hour before UVA exposure. We use Shifa company 25 mg tab. Patients received 2 UVA sessions/wk. The starting dose was 0.5–1 J/cm^2, dose increment depending on the photo-type and degree of the preceding erythema (Minimum Erythemal Dose (MED) is a minimal dosage of UVA that produce just perceptible redness 72hr after exposure). Therapy was applied as long as the re-pigmentation process continued and was interrupted if there was no evidence of new re-pigmentation in treated vitiligo affected skin lesion after 25–30 session.

Some of the patients had to interrupt the therapeutic course for a certain period of time (minimum 2 week to maximum 1 month) because of school or college. These interruptions did not lead to reversal of mean as long as the therapy induced re-pigmentation in any of the patients. Patients were instructed to wear protective goggles during UVA exposure and sunglasses for 12 hours after the session. The genital area was shielded in all cases.

Follow up

Monthly follow up were performed during for 18 months to assess clinical response of vitiligo (repigmentation), satisfaction, and report any side effects. Every patient was in the first visit photographed [we use Samsung digital camera (K zoom), 20 mega pixels], and VASI scored. Photography and VASI scoring were repeated every six months throughout UVA treatment, or at any time of obvious response appeared. Then response was evaluated as poor, mild, moderate, good, very good, excellent, according to response to treated by VASI Score.

Data Analysis

All data was provided to computer using Statistical Package of Social Sign program [SPSS version 20] for windows [IBM Corporation, NY, USA]. Chi-square test were used to see whether there is any significant association between specific therapy (psoralin and khellin) with response, side effect, gender, age, duration of disease, family history, time of treatment, LFT, cataract among the study patients. P value less than 0.05 was accepted as the level of statistical significance.

■ RESULTS

One hundred patients with wide spread vitiligo who completed the study period were enrolled in this study, their ages ranged from 12 to 50 years (24.42±10.075 years); the mean duration of the disease was 4.7±4.768 years. Ten male patients (20%) in PUVA group (Figures 1 and 2), in comparison 16 patients (32%) in KUVA group (Figures 3 and 4) and it is obvious Table 1 revealed that there is no any statistically difference between the two groups (P=0.127). Regarding age, and family history of both groups, there was, also, no significance difference between the groups (P=0.125, 0.318 respectively).

Table 1
Demography of patients

Variables		PUVA, n=50	KUVA, n=50
		No. (%)	
Gender	Male	10 (20)	16 (32)
	Female	40 (80)	34 (68)
Age	<20	15 (30)	25 (50)
	20–29	18 (36)	13 (26)
	30–39	11 (22)	8 (16)
	40–49	5 (10)	2 (4)
	≥50	1 (2)	2 (4)
Family History	No	43 (86)	47 (94)
	Positive	7 (14)	3 (6)

As shown in table 2 VASI score distribution for both PUVA and KUVA group at the beginning of the study was nearly similar with no statistically significant difference between two groups (P=0.135). We noticed that the sign of re-pigmentation in KUVA group was started after 2–4 week (4–8 sessions), while re-pigmentation was started after 4–8 week (8–16 sessions) in PUVA group.

Table 3 show each 6 months VASI score follow up, first 6 months revealed that good, very good, excellent response report in 11 patients (22%) in KUVA group, while there is no such response in PUVA group with statistically high significant difference (P=0.001). Second 6 months revealed no statistically significant difference. Third 6 months revealed that very good, excellent response report in 2 patients (4%) in KUVA group, while there is no such response in PUVA group with statistically high significant difference (P=0.027). Very good and excellent response was reported in 16 patients (32%) in PUVA group in comparison with 26 patients (52%) in KUVA group with statistically high significant difference (P=0.012) at the end of the study. While there is no poor response in KUVA group, 1 patient (2%) in PUVA group have disappointment result according to VASI score, throughout the study.

Table 2
VASI score throughout the study

VASI score		PUVA	KUVA	p-value
		No. (%)		
1st before the treatment	100% – complete depigmentation	11 (22)	12 (24)	0.135
	90% – specks of pigment present	28 (56)	20 (40)	
	75% – Depigment > Pigment area	7 (14)	16 (32)	
	50% – Depigment = Pigment area	4 (8)	2 (4)	
	25% – Pigment > Depigment area	–	–	
	10% – specks of depigmentation	–	–	
6 months	100% – complete depigmentation	–	–	0.019
	90% – specks of pigment present	8 (16)	3 (6)	
	75% – Depigment > Pigment area	31 (62)	20 (40)	
	50% – Depigment = Pigment area	7 (14)	16 (32)	
	25% – Pigment > Depigment area	4 (8)	10 (20)	
	10% – specks of depigmentation	0	1 (2)	
12 months	100% – complete depigmentation	–	–	0.016
	90% – specks of pigment present	1 (2)	–	
	75% – Depigment > Pigment area	22 (44)	16 (32)	
	50% – Depigment = Pigment area	20 (40)	11 (22)	
	25% – Pigment > Depigment area	6 (12)	15 (30)	
	10% – specks of depigmentation	1 (2)	6 (12)	
	0% – complete pigmentation	–	2 (4)	
18 months	100% – complete depigmentation	–	–	0.44
	90% – specks of pigment present	1 (2)	-	
	75% – Depigment > Pigment area	4 (8)	3 (6)	
	50% – Depigment = Pigment area	19 (38)	15 (30)	
	25% – Pigment > Depigment area	20 (40)	14 (28)	
	10% – specks of depigmentation	6 (12)	12 (24)	
	0% – complete pigmentation	–	6 (12)	

Table 3
VASI score follow up

Percentage achieved (Pigmentary Response)	First 6 months		Second 6 months		Third 6 months		At the end	
	PUVA	KUVA	PUVA	KUVA	PUVA	KUVA	PUVA	KUVA
	No. (%)							
0–19% Poor	36 (72)	17 (34)	32 (64)	32 (64)	19 (38)	31 (62)	1 (2)	0
20–39% Moderate	14 (28)	22 (44)	17 (34)	16 (32)	24 (48)	12 (24)	5 (10)	10 (20)
40–59% Good	0	4 (8)	1 (2)	2 (4)	7 (14)	5 (10)	28 (56)	14 (28)
60–79% Very Good	0	6 (12)	0	0	0	0	13 (26)	14 (28)
80% + Excellent	0	1 (2)	0	0	0	2 (4)	3 (6)	12 (24)
p-value	0.001		0.834		0.027		0.012	

Regarding sessions that KUVA group achieved to get these results range from 32–120 session (mean = 76), in comparison to 96–125 session (mean = 112) in PUVA group. Regarding the site of lesions as shown in table 4 truncal lesion responded better than the other site in both groups, where very good and excellent result were reported in 22%, 10% in KUVA and PUVA respectively.

Regarding the pattern of re-pigmentations, the study showed as in table 5, that among patients who achieved very good and excellent re-pigmentation, peri-follicular pattern was more than the other patterns, where it was reported in 22% in KUVA group and 10% in PUVA group.

Table 4
Sites to percent achieved in KUVA and PUVA

Site of lesions	KUVA Percent Achieved				p-value
	20–39% moderate	40–59% good	60–79% Very good	80% + excellent	
Face	1 (2)	4 (8)	1 (2)	1 (2)	0.516
Trunk	2 (4)	11 (22)	3 (6)	2 (4)	
Extremities	3 (6)	13 (26)	9 (18)	0	
	PUVA Percent Achieved				
Face	0	4 (8)	2 (4)	0	0.192
Trunk	3 (6)	6 (12)	5 (10)	6 (12)	
Extremities	7 (14)	4 (8)	7 (14)	6 (12)	

Table 5
Patterns to percent achieved in PUVA and KUVA

Type of re-pigmentation	PUVA Percent Achieved				p-value
	20–39% moderate	40–59% good	60–79% Very good	80%+ excellent	
Perifollicular	2 (4)	10 (20)	4 (8)	1 (2)	0.893
Diffuse	1 (2)	9 (18)	3 (6)	0 (0)	
Marginal	1 (2)	2 (4)	3 (6)	1 (2)	
Combined	2 (4)	7 (14)	3 (6)	1 (2)	
	KUVA Percent Achieved				
Perifollicular	4 (8)	7 (14)	5 (10)	6 (12)	0.78
Diffuse	4 (8)	4 (8)	4 (8)	4 (8)	
Marginal	1 (2)	1 (2)	0	0	
Combined	1 (2)	2 (4)	5 (10)	2 (4)	

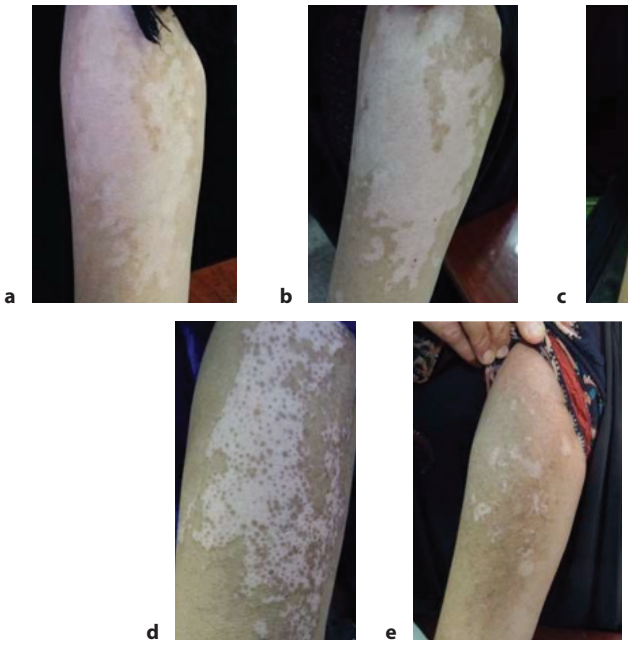

Fig. 1. 32-years-old female underwent PUVA: a) Before treatment (VASI=100%); b) 4 months after (VASI=90%); c) 6 months after (VASI=90%); d) 10 months after (VASI=50%); e) 14 months after (VASI=25%)

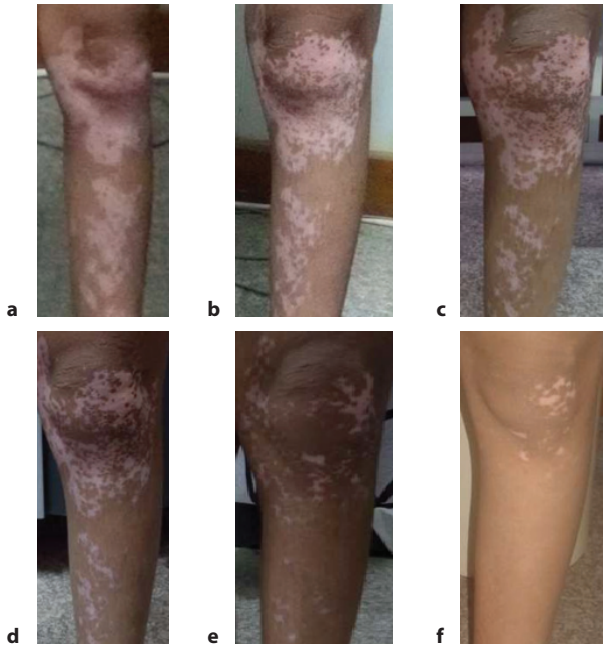

Fig. 2. 12-years-old female underwent PUVA: a) Before treatment (VASI=90%); b) 4 months after (VASI=75%); c) 8 months after (VASI=75%); d) 10 months after (VASI=50%); e) 12 months after (VASI=25%); f) 14 months after (VASI=10%)

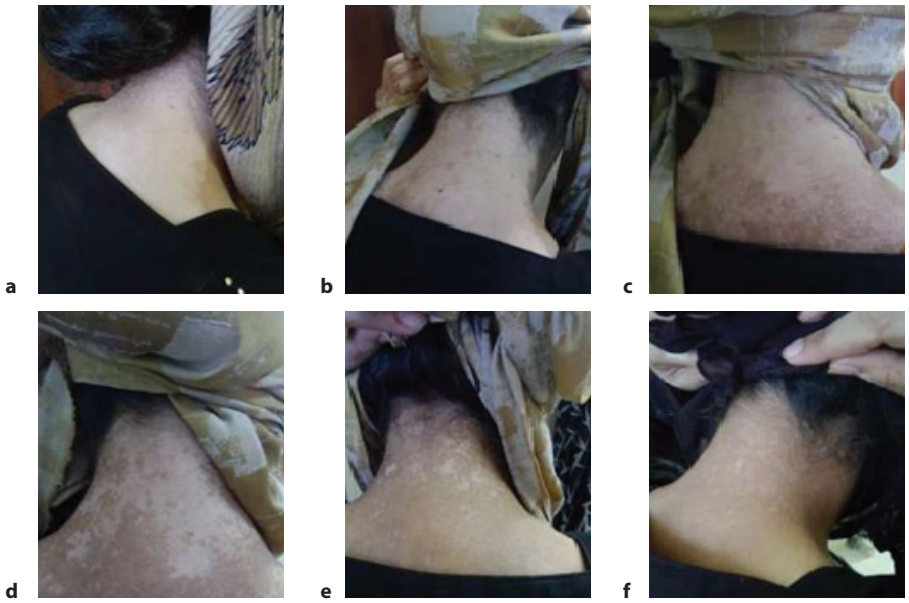

Fig. 3. 34-years-old female underwent KUVA: a) Before treatment (VASI=100%); b) 2 months after (VASI=90%); c) 3 months after (VASI=75%); d) 4 months after (VASI=50%); e) 6 months after (VASI=25%); f) 7 months after (VASI=10%)

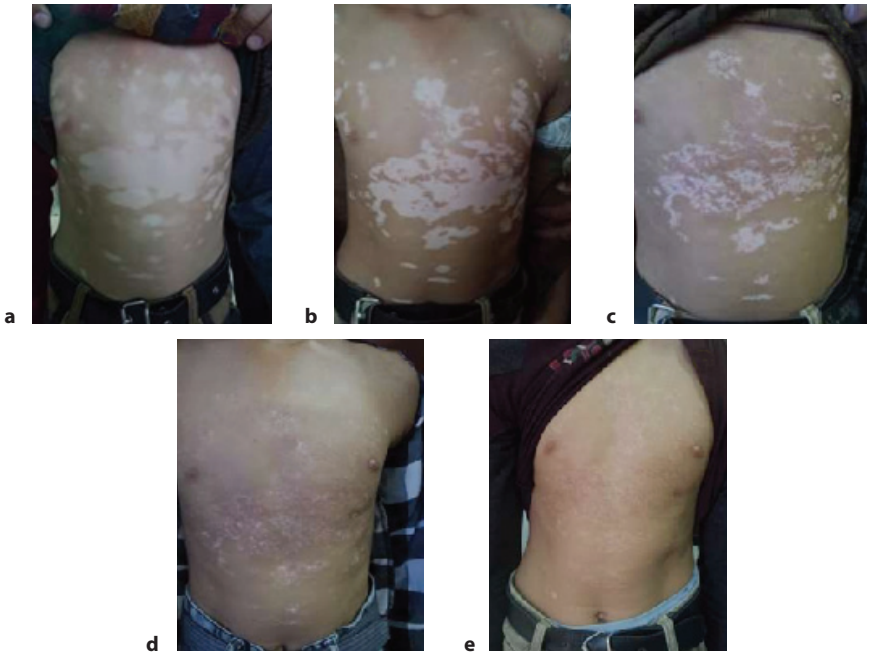

Fig. 4. 13-years-old boy underwent KUVA: a) Before treatment (VASI=100%); b) 4 months after (VASI=75%); c) 5 months after (VASI=50%); d) 6 months after (VASI=10%); e) 7 months after (VASI=0)

■ DISCUSSION

Vitiligo is a common disfiguring skin disease with unpredictable course and response to treatment modalities.

PUVA is a well-known modality of treatment [12, 13] but KUVA, to the best of our knowledge, was reported only in three previous research works, on a limited number of cases so that this study was designed to compare PUVA, with KUVA in the treatment of patient with vitiligo.

Regarding age, sex, family history finding of this study does not differ from that reported in literature [14].

The study showed that KUVA induce re-pigmentation earlier than those patients treated with PUVA, where signs of re-pigmentation was started within 2–4 weeks after the onset of treatment with KUVA. In comparison with 4–8 weeks in PUVA, the results from PUVA group are nearly similar or earlier than that reported [15].

The 3 previous studies that used KUVA did not mentioned the onset of re-pigmentation to compare our results with. But for PUVA therapy our result seems to be earlier than that reported in literature [16]. The difference in the response to PUVA group is probably attributed to the dose of psoralin were 0.6 mg/kg is used in the present work, while other studies used 0.4 mg/kg [17, 18].

At the end of the study very good and excellent result were reported in 32% of patient treated with PUVA in comparison with 52% among those treated with KUVA with statistically significant difference between two groups (P=0.012), On the other hand no patient treated with KUVA showed poor response, in contrast to 2% among those treated with PUVA. Which is clearly revealed that KUVA give better and earlier result than PUVA.

The overall result of the present work regarding KUVA therapy seems to be higher than the result of previous studies, that reported very good and excellent response were reported in range 39–41% [19–21]. The difference in response reported in our study is probably attributed to the longer period of treatment of patients that lasted to 18 months. While the follow up in the previous studies was 3–4 months only.

The study also showed that vitiliginous lesion of the trunk treated with both modalities re-pigmented earlier and better than the other sites such as face, and extremities. Although the percent of KUVA treated patient is higher than that of PUVA therapy. The previous studies did not mention the variation in the response of different site to treated modalities.

The trunk is responding better to treatment because of variation in the distribution of hair were trunk contains more hair than other parts. The result is probably differ from the well-known clinical observation that face respond earlier and better than the trunk which could be true for those patient treated by solar radiation rather than artificial UV light. As face is usually exposed to sun light more than covered part for both sexes.

■ CONCLUSION

KUVA appear to be more effective than PUVA by it induced earlier, and rapid re-pigmentation with less side effects with more patient satisfaction. A recommendation to use KUVA therapy as an effective treatment of vitiligo. Further studies with longer duration of follow up after cessation of drug to assess the rate of relapse among KUVA and PUVA treatment. KUVA can be used at home by the using solar radiation or artificial lights as it is safer with less phototoxic and other side effects.

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