Efficacy of Medium Versus Low Dose Ultraviolet A1 in the Treatment of Childhood Localized Scleroderma (Morphea)

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ABSTRACT

The purpose of this study was to evaluate the effectiveness of medium versus low dose ultraviolet A1 in the treatment of childhood localized scleroderma (morphea). Thirty patients with localized scleroderma (LS) referred by dermatologist were participated in this study. Their age ranged from 6 to 13 years. Patients were classified into two groups of equal number; group (1) received UVA1 (340-400 nm) phototherapy at a medium dose of 40 J/cm2 while group (2) received UVA1 (340-400 nm) phototherapy at a low dose of 20 J/cm2 for three times a week for 10 weeks. Skin thickness, echogenicity and skin hardness were measured at the beginning and after 10 weeks of treatment. Results of this study revealed a highly significant differences between both groups, regarding skin thickness, echogenicity and skin hardness (P values < 0.05). On conclusion, medium dose UVA1 is more effective than low dose UVA1 in the treatment of childhood morphea.

Key words: *Localized scleroderma, morphea, ultraviolet A1, medium dose UVA1, low dose UVA1, ultrasonography, durometery, skin thickness, echogenicity, skin hardness.*

INTRODUCTION

Scleroderma is a broad term encompassing both localized and systemic sclerosis. Localized scleroderma (LS) is a cutaneous limited fibrosis that manifests as plaque morphea, generalized morphea, linear scleroderma, and deep morphea[15,33]. LS is the most common form of scleroderma in the pediatric age range. Systemic scleroderma (sclerosis) can manifest as either limited or diffuse disease which most commonly in adult age[2,8,41].

Localized scleroderma (LS) also known (morphea) denotes a spectrum of conditions characterized by circumscribed fibrotic areas involving different levels of the dermis, subcutis, and sometimes underlying soft tissue and bone. Although the clinical course of the disease is often benign, widespread lesions and disabling joint contractures may lead to significant complications. The pathogenesis of the different types of localized scleroderma is still unknown[3,23]. Numerous therapeutic agents have been reported to be effective in this disease spectrum, but controlled studies are rare[17,43].

Localized scleroderma (LS) or morphea is characterized by collagen accumulation and excessive sclerosis of the skin. The major complaints are tightness and itching and the disease is often complicated by contractures and cosmetic disfigurement. The underlying pathogenesis of morphea is not completely understood at this time, but ultimately results in an imbalance of collagen production and destruction[6].

Morphea, is a thickening and hardening of the skin and subcutaneous tissues. It includes specific conditions ranging from very small plaques only involving the skin to widespread disease causing functional and cosmetic deformities[39]. Morphea involves isolated patches of hardened skin and discriminates from systemic sclerosis by its supposed lack of internal organ involvement[42]. Morphea mainly involves women with a women: men ratio of 3:1. There is a higher frequency of family history of autoimmune diseases in patients with morphea[30]. Tests for autoantibodies associated with morphea have shown results in higher frequencies of anti-histone and anti-topoisomerase IIa antibodies[16].

Good outcome measures are required to determine whether a therapy is effective, both in routine clinical practice and in experimental clinical trials[12]. In disorders of skin thickening such as morphea and scleroderma, more commonly used outcome measures that use a subjective score based on palpated skin thickening are fraught with error. By contrast, measurements made by ultrasound have great promise as outcome measures that are quantitative, valid, reproducible, and responsive[34].

Ultrasound scanning is becoming an important diagnostic tool in dermatology. The major advantages of this technique are its non invasive, non-ionizing nature and its relatively low cost[10]. It shows great promise for the evaluation of localized scleroderma (LS). Disease-related structural changes, such as tissue thickening, atrophy, and architectural alterations, can be readily detected using ultrasound. High spatial resolution enables monitoring of changes in tissue thickness, echogencity over the course of disease and treatment[24].

Additionally, measurement of skin hardness by durometry may help improve the evaluation of therapeutic agents by providing greater intraobserver reliability than physical examination skin scoring[11,37]. Durometers measure skin hardness in patients with scleroderma on a continuous scale at each site, allowing for detection of smaller changes. Durometers are reliable, simple, accurate, scalable, demonstrate good sensitivity to change compared with traditional skin scoring, and reflect patients' self-assessments of their disease[1,7,27].

Numerous treatment modalities, some with potentially hazardous side effects, are currently used for morphea (M) and systemic sclerosis (SS) with limited success[9]. The ultraviolet (UV) fraction of the solar spectrum is the most biologically active because it is almost completely absorbed by the skin. Today, different forms of UVA phototherapy are widely used and have subsequently developed into a treatment modality of importance within the field of dermatology and rheumatology at least as an adjunctive treatment and as a successful alternative in the treatment of skin manifestations of connective tissue diseases and related disorders[32].

Ultraviolet (UV) therapy has once more demonstrated its high value in the poor therapeutic armamentarium of sclerotic skin diseases. The introduction of psoralen and UVA in 1994 was recognized a cornerstone in the management of LS. However, disadvantages of psoralen and UVA such as possible gastrointestinal and carcinogenic effects have led to an intense search for LS[21]. Recent studies suggest that ultraviolet (UV) A1 phototherapy is an effective treatment for localized scleroderma (LS); however, the optimum UVA1 dose remains to be determined[40]. The purpose of study was to compare the effectiveness of medium versus low dose UVA1 in the treatment of childhood morphea.

PATIENTS AND METHODS

Subjects

This study was carried out on 30 patients (18 girls, 12 boys) with active localized scleroderma. They were recruited from the outpatient clinics of Dermatology, EL- Matria Teaching Hospital, Cairo, Egypt. Signed informed consent was obtained from each participant before enrollment in the study. The history and clinical examination were done for all patients and diagnosis of LS was made according to criteria proposed by American college of rheumatology for classification of scleroderma[31]. Features reported by clinicians as indicative of active disease included erythema, warmth, violaceous color, new lesion, expansion of lesion, and induration[25].

Reasons for exclusion were patients had a history of photosensitivity, skin malignancy, using potentially glucocorticoids, phototoxic or immunosuppressive medication, also participation in another clinical research study within the last 30 days. The criteria for entry into the treatment were; The patient's age ranged from 6 to 13 years. Elapsed time since the beginning of the LS disease was less than 3 years. Types of LS (morphea) included were plaque, generalized and mixed types. All subjects were participated in single blind, randomized, controlled trial. A complete history and physical exam, complete blood count, urinalysis and antinuclear antibody (ANA) were done for all patients. All laboratory testing was negative except ANA positivity was most frequent in mixed and generalized types.

A computerized random number list was generated and the subject allocation sequence was created from the list. Sclerotic plaques were assessed by ultrasound and the durometer at the baseline and after 10 weeks of treatment. Following the assessments, the patients were assigned into 2 groups of equal number. Group (1): received UVA1 (340-400 nm)

phototherapy at a medium dose of 40 J/cm^2 three times a week for 10 weeks. thirty phototherapy sessions resulted in a cumulative dose of 1200 J/cm^2 UVA1 while group (2) received UVA1 (340-400 nm) phototherapy at a low dose of 20 J/cm^2 three times a week for 10 weeks. thirty phototherapy sessions resulted in a cumulative dose of 600 J/cm^2 UVA1.

Ethical consideration

The experimental protocol was explained in details for each patient before the initial assessment and signed informed consent was obtained from each participant before enrollment in the study (from their families). The trial protocol was approved by the meeting of the department of surgery, faculty of physical therapy, Cairo university. There was no harm inflicted on the patients. On the contrary, all had benefited from the final results of the study.

Measurements

1- Ultrasonography Measurements:

Throughout this study, skin thickness and echogenisity were measured using a high-resolution ultrasound system dedicated to skin applications. A Derma Scan C Ver. 3 (Cortex Technology ApS, Hadsund, Denmark) was used. The system configuration for this study operated at 20 MHz and provided a resolution of 606130 mm (axial&lateral) with 8 mm penetration.

The system consists of a main unit accommodating the signal processing and computing components, a color monitor to display the two-dimensional recordings and a handheld B-scanning ultrasound probe. Transducer of the system was mounted in a water chamber. The chamber window was covered with a disposable plastic membrane. The size of the probe was 19X33 mm and the scan length 12.1 mm.

There are a number of variables namely, race, age, sex, anatomical site, and time of the day may be relevant for the outcome of measurements of skin thickness. Measurements were made at the beginning and after 10 weeks of treatment. Measurements were made at each of five skin sites, over the dorsal aspect of the interarticular portion of the proximal phalanx of the right second finger (phalanx), over the area between the metacarpophalangeal joints II and III of the right hand (hand), over the dorsal aspect of the right forearm 3 cm proximal of the wrist (forearm), over the lateral aspect of the leg 12 cm proximal of the ankle joint (leg), and over the sternum 2 cm distal from the upper part of the manubrium (chest)[13,19]. All measurements were made before noon. When imaging, the transducer was positioned perpendicular to the skin to avoid obliquity and to prevent errors during determination of skin thickness. A thick layer of ultrasound gel is applied to improve near field visibility and avoid tissue compression, which would alter measurements of tissue thickness. An improvement occur after treatment if the thickness of skin decrease and echogenicity increase[22,24].

2- Durometer measurement:

Skin hardness was measured using handheld digital durometer (Rex Durometer Max Hand model 1700, type 0, without a foot attachment) with a calibrated gauge that registers linearly divided units on a scale from 0 to 100, that registers the relative degree of hardness. At the bottom of the durometer, there is a small, inferior indenter that is retractable and is responsible for the measurements registered on the gauge.

For measurements, the durometer was used at 25°C room temperature and rested by gravity against the skin; Between readings the durometer was reset to 0. Measurements were made at predetermined landmark sites at 9 locations, forearms, upper arms, abdomen, thighs, and legs. Measurements were made with the underlying muscles relaxed and the skin in a horizontal plane. Four consecutive durometry readings were taken at the same site and the results were averaged. and the average of each of these measurements was summed to give the total durometer score[27,37].

Durometer measurements are expressed in standardized durometer units (DU). Final hardness is defined as that recorded within 15 second of firm contact of the durometer with the skin without risk or discomfort. Durometer scores were recorded before and after 10 weeks of the treatment. Skin hardness may be affected by skin thickness as well as skin density, elasticity, and edema. Variability in durometer readings may result from not

allowing the entire weight of the durometer to bear down on the skin, not holding the durometer perpendicular to the plane of the skin site, or not positioning the skin horizontally. Durometers should be checked for malfunction and recalibration of the instrument is required. An improvement occur after treatment if the hardness of skin decrease[40].

Treatment Procedures

The UVA1 irradiation equipment was used to conduct this study and consisted of a Waldmann 7001 K cabin with Waldmann TL10 R low pressure lamps. (Waldmann, GmbH. Schwenningen, Germany). These lamps generate UVA1 wavelengths in the 340-400 nm range. In addition, infrared irradiation is emitted. However these infrared wavelengths are filtered out by an acrylic glass screen. The UVA1 irradiation levels are approximately 35 mW/cm^2 and are measured by a standard intrinsic UV meter. A dose of 20 J/cm^2 was achieved in approximately 10 minutes and 20 minutes to achieve 40 J/cm^2.

Group (1): received medium-dose (40 J/cm^2) UVA1. The frequency of therapy was three times a week for 10 weeks. thirty phototherapy sessions resulted in a cumulative dose of 1200 J/cm^2 UVA1. The starting dose was determined by Fitzpatrick skin type. Also the minimal erythematus dose (MED) (the dose of UV-A1 causing just perceptible erythema) will determined for every subject. Standard safety precautions, including the use of protective eyewear, were maintained. Group (2): received low dose (20 J/cm^2). The frequency of therapy was three times a week for 10 weeks. thirty phototherapy sessions resulted in a cumulative dose of 600 J/cm^2 UVA1.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Student t test was used to assess the difference between the studied parameters (thickness, echogencity and skin hardness) in two groups. Paired t test was used to analyze the thickness, echogencity and hardness of the skin within the group. Analysis was performed using SPSS/PC software (SPSS Inc., Chicago, IL, USA). All p values less than 0.05 were considered to be statistically significant.

RESULTS

Data concerning the patients' demographic and clinical characteristics included sex, age, positive family history, duration of disease, as well as initial skin thickness, echogenisity and skin hardness measurement have been collected at the beginning of the study. Follow up evaluation of skin thickness, echogenicity and skin hardness has been performed after 10 weeks of treatment.

Demographic characteristics of the patients.

As shown in table (1 and 2), there were no statistical significant differences (P>0.05) observed between both groups concerning general characteristics (age, sex, positive family history, duration of disease, as well as initial skin thickness, echogenisity and skin hardness measurement).

Table (1): Statistical analysis of the demographic characteristics of all patients for both groups (1 and 2).

	Group (1) (n=15)	Group (2) (n=15)	P-value
Age (years)	8.60±2.38	9.40±2.23	0.351*
Sex(female/male)	8/7	10/5	0.646*
Type of morphea (plaque:general: mixed)	7:5:3	6:4:5	0.534*
Positive family History	7/15(46%)	6/15(40%)	0.717*
Duration of disease (months)	18.53±9.1	18.13±9.78	0.909*
ANA positivity	9/15(60%)	11/15(73%)	0.446*

*Non significant

Table (2): Mean initial thickness, echogenicity and skin hardness of patients in both groups.

	Group (1) (n=15)	Group (2) (n=15)	P-value
Initial Thickness (mm)	X±SD	X±SD	
Phalanx	2.69±0.58	2.72±0.49	0.912*
Hand	2.30±0.35	2.40±0.39	0.467*
Forearm	2.24±0.52	2.24±0.51	0.425*
Leg	2.37±0.52	2.20±0.46	0.355*
Chest	2.29±0.48	2.25±0.41	0.809*
Initial echogenicity (pixels)			
Phalanx	17.80±3.94	18.53±2.33	0.541*
Hand	21.33±3.49	22.60±3.88	0.356*
Forearm	24.8±4.42	22.93±2.54	0.264*
Leg	25.53±4.45	24.00±4.14	0.337*
Chest	31.60±3.41	29.00±6.14	0.163*
Initial skin hardness (DU)	36.13±4.18	35.00±4.47	0.480*

X=mean, SD=Standard Deviation P-value=Probability level, *Non-Significant (P>0.05).

Results of group (1):

As shown in table (3) the mean value, standard deviation and P value of thickness, echogenicity and skin hardness pre and post treatment for group 1. The results showed significant differences pre and post treatment for group1 as P value <0.05.

Table (3): Mean thickness, echogenicity and skin hardness of patients pre and post treatment of group 1.

	Pre X±SD	Post X±SD	P-value
Thickness (mm)			
Phalanx	2.69±0.58	1.80±0.354	0.000*
Hand	2.30±0.35	1.58±0.20	0.000*
Forearm	2.24±0.52	1.58±0.24	0.000*
Leg	2.37±0.52	1.42±0.23	0.000*
Chest	2.29±0.48	1.48±0.22	0.000*
Echogenicity (pixels)			
Phalanx	17.80±3.94	26.23±5.70	0.000*
Hand	21.33±3.49	31.26±5.20	0.000*
forearm	24.80±4.42	34.54±3.54	0.000*
Leg	25.53±4.45	31.66±5.91	0.000*
Chest	31.60±3.41	42.33±3.58	0.000*
Skin hardness	36.13±4.18	23.86±4.42	0.000*

X=mean, SD=Standard Deviation P-value=Probability level *highly significant (P<0.05).

Results of group (2):

As shown in table (4) the mean value, standard deviation and P value of thickness, echogenicity and skin hardness pre and post treatment for group 2. The results showed significant differences pre and post treatment for group 2 as P value <0.05.

Table (4): Mean thickness, echogenicity and skin hardness of patients pre and post treatment of group 2.

	Pre X±SD	Post X±SD	P-value
Thickness (mm)			
Phalanx	2.72±0.49	2.35±0.39	0.000*
Hand	2.40±0.39	2.22±0.40	0.02*
Forearm	2.24±0.51	2.29 ±0.49	0.000*
Leg	2.20±0.46	2.13±0.45	0.000*
Chest	2.25±0.41	2.21±0.42	0.012*
Echogenicity (pixels)			
Phalanx	18.53±2.33	20.20±2.11	0.001*
Hand	22.60±3.88	24.53±3.66	0.000*
forearm	22.93±2.54	26.20±4.63	0.000*
Leg	24.00±4.14	25.46±3.85	0.002*
Chest	29.00±6.14	30.06±6.36	0.001*
Skin hardness	35.00±4.47	30.60±3.20	0.001*

X=mean, SD=Standard Deviation P-value=Probability level * significant (P<0.05).

Comparative analysis of the mean differences of skin thickness, echogenicity and skin hardness between both groups post-treatment.

Table (5) showed the mean differences of skin thickness, echogenicity and skin hardness between both groups post treatment. The results showed that there were highly statistically significant differences between both groups at the end of the study with P value <0.05.

Table (5): *Comparative analysis of the mean differences of skin thickness, echogenicity and skin hardness between both groups post-treatment.*

	Group1 X±SD	Group2 X±SD	P-value
Thickness (mm)			
Phalanx	1.80±0.354	2.35±0.39	0.000*
Hand	1.58±0.20	2.22±0.40	0.000*
Forearm	1.58±0.24	2.29 ±0.49	0.000*
Leg	1.42±0.23	2.13±0.45	0.000*
Chest	1.48±0.22	2.21±0.42	0.000*
Echogenicity (pixels)			
Phalanx	26.73±5.70	20.20±2.11	0.001*
Hand	31.26±5.20	24.53±3.66	0.000*
forearm	34.53±3.54	26.20±4.63	0.000*
Leg	31.66±5.91	25.46±3.85	0.002*
Chest	42.33±3.58	30.06±6.36	0.000*
Skin hardness	23.86±4.42	30.60±3.20	0.000*

X=mean, SD=Standard Deviation P-value=Probability level *highly significant (P<0.05).

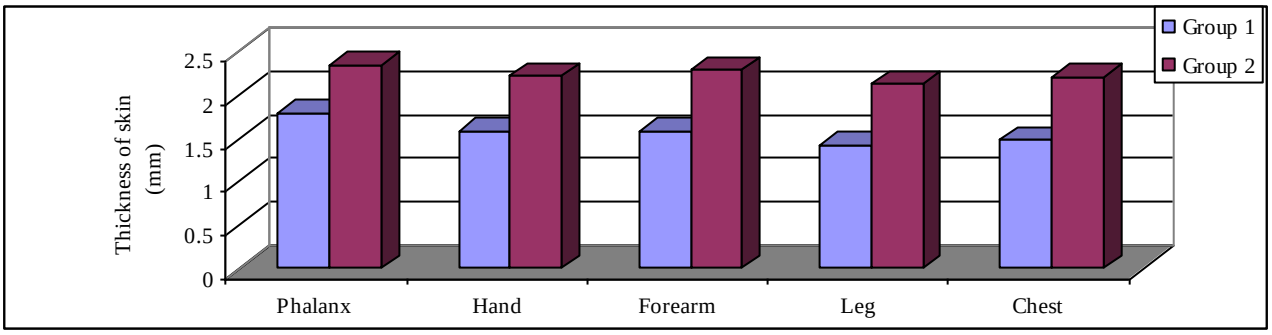

Fig. (1): *Comparative analysis of the mean differences of skin thickness between both groups post-treatment.*

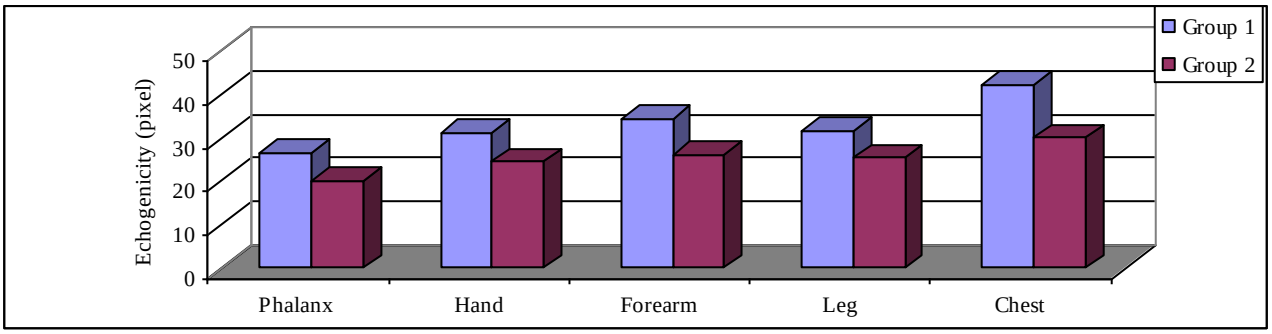

Fig. (2): *Comparative analysis of the mean differences of echogenicity between both groups post-treatment.*

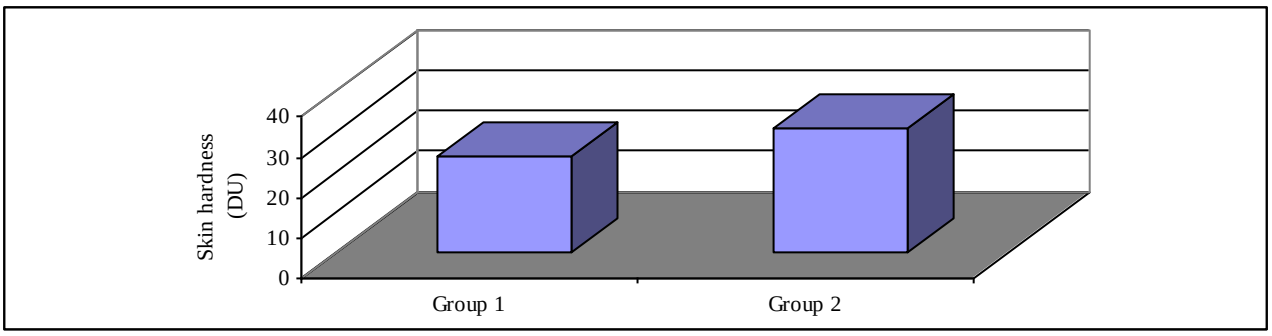

Fig. (3): *Comparative analysis of the mean differences of skin hardness between both groups post-treatment.*

DISCUSSION

Localized scleroderma (LS) is the most common form of scleroderma in the pediatric age range. For both systemic sclerosis and LS, there is an initial inflammatory phase followed by the replacement of normal tissue structures by abnormal collagen[29]. Although scleroderma refers to hardening of the skin, pediatric LS often affects deeper tissue, including muscle, bone, and some internal organs[14]. Because active disease can persist for years, growing children are at risk for major morbidity including joint contractures, limb length discrepancy, and facial atrophy[20,26].

Various therapies for morphea have been used with limited success, including ones with potentially hazardous side effects. Recent studies suggest that ultraviolet UVA1 phototherapy is an effective treatment for localized scleroderma (LS); however, the optimum UVA1 dose remains to be determined[4].

This study was conducted to compare the effectiveness of medium dose versus low dose UVA1 in childhood morphea. Patients were divided into two groups of equal number, group 1: received medium dose (40 J/cm^2) UVA1, while group 2: received Low-dose (20 J/cm2) UVA1. The frequency of treatment was three times a week for 10 weeks.

Results of study showed that there was significant difference for both groups post treatment as regard to the thickness, echogenicity and skin hardness, this confirm the effectiveness of UVA1 for the treatment of morphea whatever the dose. The effectiveness of UVA1 may attributed to facilitation of the induction of interstitial collagenase enzyme that prevent the accumulation of collagen which is the main pathology of LS or morphea.

The results of this study were in agreement with Kreuter; 2006[21] who reported that there are three main pathways are considered to contribute to the development of LS: disturbance of collagen metabolism, autoimmune activity, and vascular alteration. UVA exhibits its effects in all of these 3 directions by up-regulation of specific messenger RNA of matrix metalloproteinase, depletion of skin – infiltrating T cells and proinflammatory cytokines (IL-1, IL-6), induction of a shift of the balance between proto-oncogenes and tumor suppressor genes toward the induction of apoptosis, and modulation of endothelial regulation⁄ transformation. Also they stated that UVA1 wave lengths penetrate deeper into the skin than do UVA2 and UVB wave lengths and therefore, might be able to initiate more collagenase activity.

Breuckmann et al., 2001[4] reported that a shift of the balance between protooncogenes (e.g., bcl-2) and tumor suppressor genes (e.g., p53) towards the induction of apoptosis seems to be one of the major effects of UVA1 irradiation.

Hyun, et al., 2006[18] mentioned that Transforming growth factor beta (TGF-beta) plays a central role in the pathogenesis of sclerotic skin diseases. Recently, special attention was contributed to a family of transcription factor proteins involved in TGF-beta signal transduction from cell surface to the nucleus, the so-called SMADs. Ultraviolet (UV) irradiation has been reported to alter TGF-beta/SMAD pathway in human skin. Also Scharffetter, et al., 1991[36] reported that Ultraviolet Al (UVA1; 340-400 nm) radiation

is associated with induction of collagenase in fibroblasts of lesional skin.

The results of the study also showed that there were significant differences between both groups (medium and low dose group) as regard to thickness, echogenicity and skin hardness post-treatment. This may attributed to the cumulative dose of group 1 was double of the cumulative dose of group 2 (1200 J/cm^2 versus 600 J/cm^2) and the induction of collagenase enzyme is a dose dependant. So more activity of collagenase enzyme and improvement of disease in medium dose group was more than low dose.

These results were in agreement with Sator., et al., 2009[35] who concluded that medium-dose provides for better long-term results than low-dose UVA1 in LS as shown by ultrasound assessment but with clinical scoring, no significant difference between the two UVA1 dose regimens was detected, indicating that ultrasound measurement is a more sensitive method for quantifying treatment-induced skin changes in patients with LS.

Kreuter, et al., 2006[21] reported that Medium-dose UVA1 gives favorable results in a shorter period of time as compared to low-dose UVA1 therapy, where a minimum of 3 months exposure is needed to obtain clinical results.

Also Stege, et al., 1997[38] mentioned that The mechanism of action of UVA 1 on sclerotic skin is still not elucidated, although previous reports showed a dose-dependent up regulation of collagenase activity, which could be responsible for the softening of the skin.

Camacho; et al., 2001[5] stated that Medium-dose UVA1 therapy is effective in the treatment of localized morphea. Effectiveness is associated with an increase in the number of CD34+ dendritic cells in the dermis.

On conclusion, medium dose UVA1 is more effective than low dose UVA1 in the treatment of childhood morphea.

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الملخص العربي

كفاءة الجرعة المتوسطة مقارنة بالجرعة المنخفضة من الأشعة فوق البنفسجية ذات المدى الطويل (أ) في علاج تصلب الجلد عند الأطفال

يهدف هذا البحث إلي دراسة كفاءة الجرعة المتوسطة من الأشعة فوق البنفسجية ذات المدى الطويل (أ) مقارنة بالجرعة المنخفضة في علاج تصلب الجلد عند الأطفال . وقد أجريت هذه الدراسة علي ثلاثين مريضا تتراوح أعمارهم بين 6 إلي 13 سنة ممن يعانون من تصلب الجلد. وقد تم تقسيمهم عشوائيا إلي مجموعتين متساويتين في العدد . المجموعة الأولي (1) : تلقت جرعة متوسطة من الأشعة فوق البنفسجية ذات المدى الطويل (أ) (40 J/cm2) بواقع 3 جلسات أسبوعيا وذلك لمدة 10 أسابيع بينما المجموعة الثانية (2) : تلقت جرعة منخفضة من الأشعة فوق البنفسجية ذات المدى الطويل (أ) (20 J/cm2) بواقع 3 جلسات أسبوعيا وذلك لمدة 10 أسابيع أيضا. وقد تم قياس سمك وصدوية الجلد وأيضا صلابة الجلد قبل وبعد 10 أسابيع للمجموعتين. وقد أظهرت النتائج فروق ذات دلالة إحصائية بين المجموعتين بعد العلاج بالنسبة لسمك وصدوية الجلد وأيضا صلابة الجلد و يمكن أن نستخلص أن كفاءة الجرعة المتوسطة من الأشعة فوق البنفسجية ذات المدى الطويل (أ) أكبر مقارنة بالجرعة المنخفضة في علاج تصلب الجلد عند الأطفال .

الكلمات الدالة : الأشعة فوق البنفسجية ذات المدى الطويل (أ) ، الجرعة المتوسطة ، الجرعة المنخفضة ، تصلب الجلد عند الأطفال ، سمك الجلد ، صدوية الجلد ، صلابة الجلد ، دوبلر الموجات فوق الصوتية ، ديورومیتر .