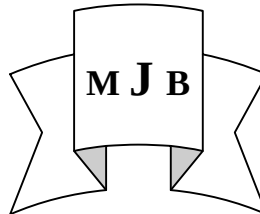


Treatment Recalcitrant Vitiligo with Narrow Band UVB

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Abstract

Background: Vitiligo is a common and chronic disease with a great impact on patients' quality of life. Phototherapy with narrowband ultraviolet B radiation is one modalities that are used increasingly for the management of the disease with variable results. In this study we review the efficacy, adverse effects, of narrowband ultraviolet B in the treatment of recalcitrant vitiligo in patients not responding to the topical and systemic steroid nor to topical or systemic psoralen.

Patients and methods: Twenty-two patients with vitiligo (whom not response to topical steroid or topical or systemic psoralen) were included in this study their ages ranged from 6 to 45 years with a mean of 26.733 years $\pm$ 8.11 SD, with vitiligo and Fitzpatrick's skin type II-IV from our outpatient clinic were included in the study. The duration of the disease was ranged from 1-17 years, with mean of 6.71 years $\pm$ 4.22 SD. All patients did not taken treatment for at least 3 months.

exclusion criteria were patients with a history of skin cancer or dysplastic naevus syndrome, photosensitivity or using photosensitizing medicine, psychiatric or epileptic disorders.

Before the study the surface area patches ranged between 4 cm² to 38 cm². The initial irradiation time was 36 seconds (200 mJ/cm²) then increase gradually with every visit by 9 second (50 mJ/cm²) if no any side effect was occur continue with increasing scale up to 3 minutes (1666 mJ/cm²) for five months (forty sessions). All patients were treated with narrow band UVB machine twice weekly (not consecutive days). No phototesting was done before the treatment.

Results: All twenty-two patients with vitiligo were completed this study. (10 males and 12 females).

The results of 22 patients treated with narrow band UVB machine twice weekly (not consecutive days) as follow. The mean size of patches before treatment were 16.61 $\pm$ 7.99 cm² after one month become 15.23 $\pm$ 7.27 cm², this size continued to decrease reaching to 12.96 $\pm$ 6.521 cm² by two months; at three months the size of lesions become 10.73 $\pm$ 5.841 cm², the size continued to decrease reaching to 9 $\pm$ 5.790cm² in the end of fourth month, while reaching to 8 $\pm$ 5.581cm² in the 5th month. The repigmentation grading was as follows after 20 weeks of treatment grade 0 were 2 patients (9.09%), grade I were 3 patients (13.63%), grade II were 5 patients (22.72%), grade III were 7 patients (31.81%), grade IV were 5 patients (22.27%). 54.54% of the patients showed more than 50% (grade III and grade IV) reduction in the size of vitiligenous area. P value was extremely significant (p=0.0003).

Conclusion: Treatment with narrow band UVB was relatively safe and effective in treatment of recalcitrant vitiligo and has no side effects except transient erythema.

Introduction

Definition:

Vitiligo is a specific, common, acquired disorder with a genetic

predisposition characterized by well-circumscribed milky-white macules devoid of identifiable melanocytes [1]. The word vitiligo may be derived from the Greek

vitellus , signifying a “ calf’s white patches “. [2]

Incidence

Vitiligo can start at any age but in 50% of patients it develops before the age of 20 years [2,3]. In Iraq, the mean age of onset is 17.9 years, and in 66% of patients it develops before age of 20 years and also has been found to be common among children [4].

The distribution between sexes is equal. vitiligo affects all races and it is stated that it occurs in 1% of the world population, [2,5]

Pathogenesis:

The pathogenesis of vitiligo is not well understood. Many theories have been implicated in the pathogenesis of the disease, and these include:-

I-The immune hypothesis:

This theory suggests an aberration of immune surveillance is destructive to melanocytes. Clinical support for the immune hypothesis include the presence of lymphocyte in the dermis of early lesions, the epidermotropism and Pautrier- like micro-abscesses [6].

Antityrosinase antibodies have been identified in patients with vitiligo and in 12% with autoimmune endocrine disease without vitiligo. Those with diffuse disease had a titer greater than those with focal disease. [7] The investigators suggest tyrosinase as the principle autoantigen of “auto-immune” vitiligo.

II- The neural hypothesis:-

This proposed by Chanco et al[8]. He theorized that from near by nerve ending a neurochemical mediator is melanocytotoxic.

Support for this hypothesis is derived from numerous clinical observations: namely the appearance of vitiligo in neurologically compromised skin, vitiligo sparing paralyzed limbs, vitiligo associated with viral encephalitis, and vitiligo with multiple sclerosis and Horner's syndrome.

III- The self-destruct hypothesis:-

Theorizes that certain tyrosine analogues and intermediates (dopa, dopachrome, 5, 6 DHI) in melanin synthesis are known to be toxic to melanocytes. Melanocyte appears to have intrinsic protective mechanism that eliminates toxic melanin precursors. Disruption of this labile mechanism could permit accumulation of indoles and free radicals which are destructed to melanocytes [9].

Clinical Features:-

The depigmentation process passes through two stages of pigment loss:

Stage I (early lesions) appears as a light whitish brown color and this may stay for months before it changes into a milky white color the so called stage II (late lesions) [2,5]. Many clinical types of vitiligo are found, but the following types represent the most characteristic patterns of vitiligo, namely, generalized (type A). segmental (type B) [2] .

Many modalities of treatment are found as:

Topical therapy:-

Topical 8- methoxypsoralens [10] ,topical steroid [11]

,fluorouracil [12] ,topical coal Tar [13] and other treatments.

Systemic therapy:-

Psoralen-UVA, [14] ,systemic Puvasol [2] ,systemic Steroids [15]

Patients and Methods

This opened clinical trial study was for a period extended from January 2010 to April 2011.

Twenty-two patients with vitiligo (whom not response to topical steroid or topical or systemic psoralen) were included in this study their ages ranged from 6 to 45 years with a mean of 26.733 years ± 8.11 SD, with vitiligo and Fitzpatrick's skin type II-IV from our outpatient clinic were included in the study, after written informed consent had been obtained. The duration of the disease is range from 1-17 years, with mean of 6.71 years ± 4.22 SD. All patients did not taken treatment for at least 3 months.

exclusion criteria were patients with a history of skin cancer or dysplastic naevus syndrome, photosensitivity or using photosensitizing medicine, psychiatric or epileptic disorders. Before the study the surface area patches ranged between 4 cm² to 38 cm².

All patients were treated with narrow band UVB machine twice weekly (not consecutive days). The patients before taken the dose of radiation should taken a good bath in their house and putting a thin film of emollients (Vaseline), to reduce the corneal layer of skin (remove the scales), so both procedures will increase UVB penetrations. Then

the patients enter the machine room. Total body was exposed except male genitalia and nipples, which were shielded in all cases with cloth and sunscreen . No phototesting was done before the treatment.

The initial irradiation time was 36 seconds (200 mJ/cm²) then increase gradually with every visit by 9 second (50 mJ/cm²) if no any side effect was occur continue with increasing scale up to 3 mint (1666 mJ/cm²) for five months (forty sessions).

If side effects develop deals as follow:

1- If patients develop light pink, mild burn will continued on same time exposure not increase in previous session.

2- If patients develop significant erythema (burn) then we skip two sessions and reduce the time to previous session and 10% of the dose increase in subsequent sessions .

3- if the patients develop significant erythema, edema, blister then stop the treatment till the complete recovery, then decrease exposure dose to the half, and 10% of the dose increase in subsequent sessions .

Follow up: Assessment of response to treatment

❖ The response to treatment was assessed every two weeks for five months. The outline of the lesion was drawn on a transparent paper. In the first visit and each month of treatment.

❖ The surface area of the lesion was calculated using graphic paper. Every four weeks interval, the reduction in size of the lesion

was recorded on the same transparent paper.

- ❖ The percentage of reduction in surface area was calculated.
- ❖ The patients were followed up for 3 months after the last sessions.

Table 1 Grading of repigmentation

Grades	% of response
Grade 0	no response
Grade I	Repigmentation of less than 25% of the patch
Grade II	Repigmentation of the patch from 25% - 49%
Grade III	Repigmentation of the patch from 50- 74%
Grade IV	Repigmentation more than 75% to complete pigmentation

Statistical analysis

All data coded and computerized using SPSS 7.5 (Statistic package for social science).

All data arranged and tabulated in number, percentage, mean and standard deviation.

Response to treatment was measured by using paired and unpaired t-test, chi-square test and analysis of variance (A NOVA) test. $P < 0.05$ was considered as level of significance.

Results

All twenty-two patients with vitiligo were complete this study. 6 to 45 years with a mean of 26.733 years ± 8.11 SD. (10 males and 12 females). The result of previous treatment as follow:-

The side effects were also recorded.

The responses of therapy were evaluated according to the flowing scale: (Table.1)

Twelve patients were treated with topical and systemic steroid.

Seven patients were treated with topical PUVA-Sol.

Five patients treated with systemic psoralen and ultraviolet A light.

The type of vitiligo of these patients as follow:-

Fifteen patients were with generalized vitiligo.

Five patients were with acrofacial vitiligo.

Two patients with segmental type.

The therapeutic results in treatment were as follow:-

The results of 22 patients treated with narrow band UVB machine twice weekly (not consecutive days) were show in table (2).

The mean size of patches before treatment were 16.61 ± 7.99 cm² after one month became 15.23 ± 7.27 cm², this size continued to decrease reaching to 12.96 ± 6.521 cm² by two months; at three months the size of lesions became 10.73 ± 5.841 cm², the size continued to decrease reaching to 9 ± 5.790 cm² at the end of fourth month, while reaching to 8 ± 5.581 cm² in the 5th month. The repigmentation grading was as follows after 20 weeks of treatment grade 0 were 2 patients (9.09 %), grade I were 3 patients (13.63 %), grade II were 5 patients (22.72 %), grade III were 7 patients (31.81%), grade IV were 5 patients (22.27 %) as shown in figure (1).

The number of sessions were 40, but three patients with grade IV get complete recovery with only 22, 28, 32 sessions respectively and not need complete to forty sessions, the mean number of exposures were 38.27 ± 4.71 SD.

The distribution of the lesions were found on the head,

Table 2 Response to narrow band UVB treatment with four weeks interval

	No.	Mean size of patches (cm ²)	SD
Before	22	16.61	7.99
4 weeks	22	15.23	7.27
8 weeks	22	12.96	6.521
12 weeks	22	10.73	5.841
16 weeks	22	9	5.79
20 weeks	22	8	5.581

neck, trunk, limbs. Most of the responded (get more than 50% reduction in the size of affected area (significant improvement)) sites are found in the face, neck, trunk, arms and thigh, while most of the non responded (less than 25% reduction in the size of the affected area (non significant improvement)) sites were in the hands and feet, except two patients with symmetrical vitiligo of the dorsum of their hands get more than 75% reduction in their patches of vitiligo. One of patients with segmental type vitiligo get significant improvement, and other not.

Treatment with narrow band UVB was relatively safe and has no side effects except transient erythema. 54.54% of the patients showed more than 50% (grade III and grade IV) reduction in the size of vitiliginous area. P value was extremely significant ($p=0.0003$) table(3).

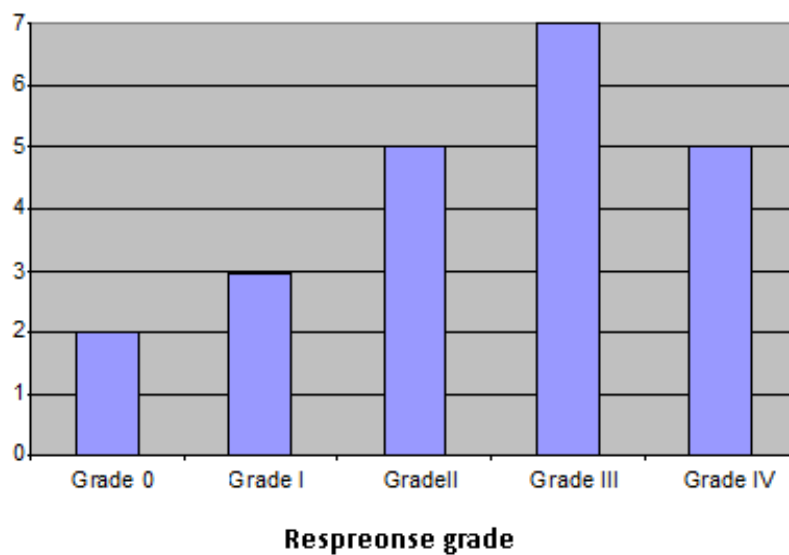


Figure 1 Response to narrow band UVB at the end of 5th month



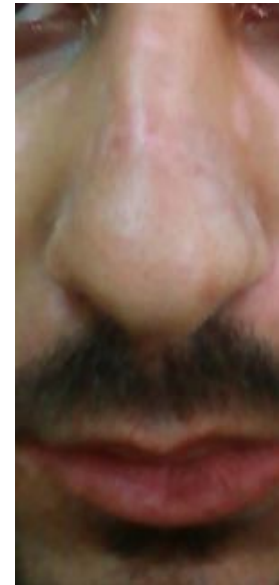
Before



**after 22 sessions
(stop treatment)**

Table 3 Comparison response to narrow band UVB before treatment and after the end of treatment

	No.	Mean size of patches (cm ²)	SD	P value
Before treatment	22	16.61	± 7.99	
After 20weeks	22	8	± 5.83	0.0003

**Before****after 18 sessions
(still on treatment)****Discussion**

Vitiligo is a common dermatological disease encountered in daily practice and many modalities of therapy have been used for its treatment like phototherapy, photo-chemotherapy, immune modulators, steroids, surgical procedures and cosmetics. Each has its advantages and limitations [1].

To date, little is known about the mechanism of action of NB-UVB in vitiligo. Melanocytes could be recruited from the outer root sheath of the hair follicle to repigment vitiliginous skin through the action of phototherapy. Recovery from vitiligo is initiated by the activation and proliferation of these melanocytes, followed by the upward migration to the nearby

epidermis, accounting for the perifollicular pigmentation islands, and by subsequent downward migration to the hair matrices to produce melanin. [16,17,18]

There are evidences suggesting that focal adhesion kinase (FAK) plays a crucial role in transducing a variety of signals that modulate cell adhesion and cell migration. Increased expression of phosphorylated FAK (p125FAK) may indirectly modulate cytoskeletal proteins necessary for cell migration. The matrix metalloproteinases (MPPs) are a family of enzymes involved in the degradation of extracellular matrix components such as collagen, gelatine and fibronectin. Expression of MMPs is markedly increased in situations involving active tissue remodeling and cell migration [19]. Both keratinocytes and fibroblasts release putative melanocytes growth factors. Melanocytes proliferation is controlled by different classes of mitogens: leukotriene (LT) C4 and D4, endothelin-1 (ET-1) and tyrosine kinase growth factors basic fibroblast growth factor (bFGF), stem cell factor, hepatocyte growth factor (HGF), melanotropin, epidermal growth factor, and platelet-derived growth factor.

Certain study demonstrated that NB-UVB radiation stimulates the release of bFGF and ET-1 from keratinocytes, which induce melanocyte proliferation. In addition, NB-UVB irradiation stimulating the expression of p125FAK in melanocytes and inducing the expression of MMP2 in

melanocyte supernatants may enhance melanocyte migration.[17]

Treatment with narrow band UVB was relatively safe and has no side effects except transient erythema. 54.54% of the patients with recalcitrant vitiligo showed more than 50% reduction in the area of vitiligo.

The distribution of the lesion was found in the head, neck, trunk, limbs. Most of the responded (get more than 50% reduction in the size of affected area) sites are found in the face, neck, trunk, arms and thigh, while most of the non responded (less than 25% reduction in the size of the affected area) site were in the hands and feet except two patients with symmetrical vitiligo of the dorsum of their hands get more than 75% reduction in their patches of vitiligo.

The result of our study was more better than previous study [20] in 2003 in which the Asians patients with recalcitrant vitiligo treated with narrow band UVB. The differences points between two studies were as follow: -

1- Asian study showed 42% of those patients get improvement more than 50% of the affected surface while in our study the percentage of patients with improvement of more than 50% was 54.54%.

2- The number of treatment sessions range from 36-175 in previous Asian study, while in our study the treatment session were much less ranged from 22-40 sessions.

3- Also previous study demonstrated that no patients with

vitiligo of the hands and feet get acceptable improvement compared with our study where two patients with recalcitrant vitiligo get complete improvement .

The explanation of this variations were as follow:

1- we thought that some patients noncomplained and not taken the treatment as right as the doctor says specially for topical and systemic psoralen and for this reason considered as a recalcitrant patients.

2- This study demonstrated that there was some mistake in the way of given topical and systemic psoralen i.e. some doctors given psoralen to the patients and told them to expose to sun at (12 PM- 1 PM), during this time relatively the UVB very high compared with UVA (2), so most of patients will develop sever skin burn and finally the patients will stop the treatment.

As we know the most important site for patient need to be treated is the face and the most difficult site to treat is around the eyes because thin skin and easily irritated during treatment in addition the risk of using topical potent steroid for long time increase risk of eye disease (cataract and glaucoma). Our study demonstrated that most of the responder patients had lesions on the face with out any side effect. Also our study demonstrated that narrow band UVB was also effective in the most resistant type (segmental vitiligo).

Conclusion

Narrow band UVB is a safe and effective treatment for recalcitrant vitiligo without any side effect apart from transient erythema.

Recommendations

1- Its important to make the narrow band device available in all hospitals.

2- Like the response of recalcitrant vitiligo we thought that the response of classical generalized vitiligo is a more better than recalcitrant type.

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