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Comparative Study Of Puva Therapy Vs Narrow Band Therapy In The Treatment Of Vitiligo.

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ABSTRACT

Phototherapy is the most commonly used modality in the treatment of vitiligo. Oral PUVA is the classical treatment and the NB-UVB is a recently introduced form excluding the shorter erythemogenic wavelengths. This study was designed to compare the effects of PUVA and NB-UVB clinically and immuno-pathologically in managing non-segmental vitiligo. Thirty vitiligo patients were divided randomly into two groups and treated either by oral PUVA or by narrow-band UVB for 4 months, and evaluation was done clinically and immuno-pathologically. One patient in the PUVA group (3.3%) failed to respond to therapy while 29 patients (93.3%) improved including all NB-UVB cases. Excellent repigmentation was achieved in 6.7% of the PUVA group and 66.6% in the NB-UVB group; good repigmentation was achieved in 60% of PUVA and 20% in NB-UVB while 26.7% in PUVA and 13.3% in NB-UVB showed mild repigmentation. The color matching was excellent in all NB-UVB patients. Recurrence and activation of vitiligo were demonstrated in some NB-UVB cases and were less in PUVA-treated cases. Microscopic examination revealed the persistence of dermal lymphohistiocytic infiltrate and the interface changes in biopsies from vitiliginous lesions treated with NB-UVB more than with PUVA. NB-UVB provides significantly better results than oral PUVA in managing non-segmental vitiligo. Although NB-UVB therapy has a rapid effect, the observation of recurrences and development of new lesions of vitiligo was less significant with PUVA. It was also observed that PUVA has a better immuno-modulatory effect on vitiligo than NB-UVB and may give a better response over a longer period.

Keywords: PUVA, Vitiligo, NB-UVB.

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INTRODUCTION

Vitiligo is an acquired pigmentary disorder characterized by the loss of melanocytes from the skin and the subsequent development of depigmented patches of variable sizes, which may enlarge and coalesce to form extensive areas of leukoderma [1]. Treatment modalities aim to stimulate melanocyte proliferation or interfere with inflammatory factors affecting melanocyte structure or function; however, no single treatment method is consistently effective, with relatively few side effects [2]. Ultraviolet irradiation is among the many possible approaches and is divided into ultraviolet A (UVA) (320 - 400 nm), ultra-violet B (UVB) (290 - 320 nm), and ultraviolet C (UVC) (200 - 290 nm) [3]. PUVA (psoralen followed by irradiation with UVA) has been a well-established management of non-segmental vitiligo since the last century [4]. Nar-row-band UV-B therapy was introduced recently as a new light therapy that emits a concentrated UVB source of 311 nm and has been shown to have a profound therapeutic efficacy for the treatment of skin conditions including vitiligo [5].

METHODS

This study was conducted on 30 vitiligo patients attending the outpatient clinic of the Dermatology & Venereology Department, Nandha Medical College and Hospital, Erode Tamil Nadu, India in the year December 2023. These patients were divided randomly into two groups: 15 patients were treated by PUVA and 15 patients were treated by NB-UVB. Vitiligo patients included in the study had non-segmental vitiligo in generalized or localized forms. Exclusion criteria enclosed: patients receiving treatment in the last 2 months, patients with light-sensitive or aggravated dermatoses, patients with or giving a history of skin tumors, and patients with aphakia or cataracts. PUVA treatment group also excluded children, pregnant or lactating female patients, and patients with abnormal liver or renal functions. All patients were subjected to full history taking including, general clinical examination including abdominal, chest, cardiac, ophthalmological, and ENT examination, dermatological examination including the type and extent of vitiligo, and complete routine laboratory investigations, including complete blood picture and liver and kidney function tests. Repeated laboratory tests were performed every two months after starting treatment in patients who were treated by PUVA. In the PUVA group, the patient ingested 8-MOP at a dose of 0.4 mg/kg of body weight/session on a full stomach 1 and a half hours before UVA exposure. The UVA cabinet used was a UV compact irradiation cabinet COSMEDICO Medizintechnik, GP-42, Germany. Patients received 2 PUVA sessions/week. The starting dose was 2 J/cm^2, which is a common starting dose for patients with similar skin types [6] and a 25% dose increment was provided every next session [7] guided by the patient's response till asymptomatic erythema was observed. Erythema reading for PUVA- treated patients was performed at 72 hours after UVA irradiation [6]. The last previous reading was utilized as the therapeutic dose throughout the 4 months of therapy. 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. In the NB-UVB group, patients received 2 NB-UVB sessions/per week. The starting dose was 0.574 J/cm^2, which is the starting dose of skin type IV, according to manufacturer instructions, and a 25% dose increment was done every next session guided by the patient's response, till asymptomatic erythema was observed. Erythema reading for NB-UVB treated patients was performed 24 hours after UVB irradiation [8], the previous dose was utilized as the therapeutic dose throughout the 4 months of therapy. NB-UVB phototherapy cabinet used was COS- MEDICO Medizintechnik, GH-8 ST, Germany, containing fluorescent TL-01 (100 W) tubes as the source of irradiation. Every patient was photographed before the start of treatment and then repeatedly every two months throughout PUVA and NB-UVB treatment. Skin biopsies were harvested from each patient before PUVA and NB-UVB therapy (1 biopsy from the center of the vitiliginous area) and after 4 months of PUVA and NB-UVB therapy (2 biopsies; one from the non-responding areas and the other biopsy from the pigmented areas). Three-and-a-half-millimeter punch skin biopsies were used to obtain all samples after Mepivacaine HCL 3% local anesthesia. Biopsies were fixed in 10% formalin embedded in paraffin blocks and sectioned by microtome into 5 μm thick sections. The resulting sections were mounted on glass slides and subjected to histopathological examination using Hematoxyline-Eosin, Fontana Masson, and immunohistochemical staining using melanoma antigen recognized by T-lymphocyte (MART-1), CD3, CD20 and CD68.MART-1 antibody (1:100, Neomarker, Fremont, CA 94539, USA) recognizes an 18 KD molecular weight MART-1 antigen which is present in the endoplasmic re-reticulum of melanocytes. It has been found to localize to melanosomes suggesting a role in melanosomes biogenesis and it is useful for biological studies on melanocytes and melanoma cells as well as for the development and monitoring of immunotherapy for the patients with melanoma [9]. CD3 marker (1:200, Dako, code No./M 7254) is a Pan-T lymphocyte marker. It recognizes CD3 antigen which

is a pan-T cell antigen, composed of 5 invariable polypeptide chains. CD20 marker (1:400, Da- ko, code No./M 0755) is a pan-B lymphocyte marker. It recognizes the CD20 antigen which is present in the B lymphocyte. CD68 marker (1:300, Neo markers Fremont, CA, Lot: 397P601A) recognizes CD68 antigen which is present in the cytoplasm of histiocytes. This marker is important for identifying histiocytes in tissue sections. After 2 and 4 months of therapy, we evaluated the patients subjectively into improvement or failure. The patients who showed improvement were evaluated objectively by using an instrument called a planimeter. The im- proved patients were divided into three groups; the excellent group of patients when improvement ranged between 70% - 100%, the good repigmentation group of patients when improvement ranged between 40% & 70%, and the mild repigmentation group of patients when improved- ment is less than 40%. A planimeter is a measuring instrument used to measure the area of an irregular plane figure on a map or photograph. A pointer on the planimeter is used to trace around the boundary of the shape. This induces a movement in another part of the instrument and a reading of this is used to establish the area of the figure. The resulting data were analyzed with SPSS statistical package version 12.0 (SPSS Inc., Chicago) for Windows (Microsoft Corporation, Redmond). Data were expressed as mean ± standard deviation. Comparison between groups of data was done by independent samples (unpaired) t-test or ANOVA (between 2 or more groups). Comparison between baseline data and after treatment was done by paired t-test. The difference between compared groups was expressed as probability of value (p value). The difference was considered significant if $p < 0.05$.

RESULTS

The present study was conducted on 27 female patients (90%) and 3 male patients (10%). The age of these patients at the time of examination ranged from 7 to 52 years old. The duration of the disease before phototherapy ranged from 2 months to 8 years. A positive family history of vitiligo was present in 5 (16.6%). Regarding skin Fitzpatrick types; 2 patients (6.6%) were skin type III, 20 patients (66.7%) were skin type IV, and 8 patients (26.7%) were skin type V. In PUVA-treated patients, 13 female patients (86.7%) and 2 male patients (13.3%) were included. The age of these patients at the time of examination ranged from 21 to 52 years, with a mean of 29.8 (±12.09) years. The duration of the disease before PUVA ranged from 2 months to 8 years, with a mean of 37.73 months ± 29 SD. A positive family history of vitiligo was present in 4 patients (26.7%). The erythemogenic dose ranged from 4.883 to 7.629 J/cm^2 and the therapeutic dose of PUVA ranged from 3.906 to 6.104 J/ cm^2. As regards skin type, 1 patient (6.7%) was skin type III, 11 patients (73.3%) were skin type IV and 3 patients (20%) were skin type V (Table 1).

Table 1: Data of the patients included in each group.

Items	PUVA	NB-UVB
Age of patients at the start of treatment	21 to 52 yrs The mean of 29.8 ± 12.09	7 to 45 yrs The mean of 16.2 ± 11.02
Sex	13 females (86.7%) and 2 males (13.3%)	14 females (93.3%) and 1 male (6.7%)
Family history	4 patients (26.7%)	1 patient (6.7%)
Skin type	Type III: 1 (6.7%) Type IV: 11 (73.3%) Type V: 3 (20%)	Type III: 1 (6.7%) Type IV: 9 (60%) Type V: 5 (33.3%)
Duration of vitiligo before treatment	2 ms to 8 yrs The mean of 37.73 ± 29	2 ms to 8 yrs The mean of 30.53 ± 26.27
The therapeutic dose	3.906 to 6.104 J/cm^2	1.402 to 2.737 J/cm^2

Table 2: Percentage of improvement after 2 and 4 months.

Percentage of improvement	NB-UVB	PUVA	p-value*
Range Percentage of	12 - 90	6 - 37	
improvement Mean ± SD after 2 months p-value	45.4 ± 21.57 -	17.13 ± 10.08 -	0.0005 -
Range	23 - 98	10 - 70	

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Table 3: Degree of repigmentation after treatment.

Degree of repigmentation	PUVA group N = 14	NB-UVB group N = 15
Excellent repigmentation	1 patient (6.7%)	10 patients (66.7%)
Good repigmentation	9 patients (60%)	3 patients (20%)
Mild repigmentation	4 patients (26.7%)	2 patients (13.3%)

Histopathological Findings

Before treatment, a microscopic examination of the involved skin in vitiligo showed no basal melanization in 22 (73.3%) of the 30 biopsies while 8 (26.7%) showed basal melanization. With the Fontana- Masson stain, a similar ratio of basal pigmentation was demonstrated. Hyperkeratosis was present in 12 biopsies (40%). Interface changes and epidermal vacuolization were found in 4 biopsies (13.3%), all were included in the PUVA group of patients. Dermal infiltrates composed mainly of mononuclear cells (Lympho-histiocytic); seven biopsies (46.7%) in PUVA group and 7 biopsies (46.7%) in NB-UVB group showed sparse infiltrate, 7 biopsies (46.7%) in PUVA group and 5 biopsies (33.3%) in NB-UVB group showed moderate infiltrate, and 1 biopsy (6.7%) in PUVA group.

Table 4: Side effects were reported in the study groups.

NB-UVB group N = 15	PUVA group N = 15	Side effects
3 patients (20%)	4 patients (26.7%)	Pruritus
1 patient (6.7%)	0 (0%)	Photo dermatitis
0 (0%)	7 patients (46.7%)	Nausea
0 (0%)	1 patient (6.7%)	Elevation in the liver enzymes
3 patients (20%)	1 patient (6.7%)	Recurrence at the same site of treatment
4 patients (26.7%)	1 patient (6.7%)	New lesions in other sites

Table 5: Histopathological findings in the center of the vitiliginous lesions before treatment.

Histopathological changes		Vitiligo center		
		PUVA (n = 15)	NB-UVB (n = 15)	Total (n = 30)
Hyperkeratosis		7 biopsies (46.7%)	5 biopsies (33.3%)	12 biopsies (40%)
Basal melanization		5 biopsies (33.3%)	3 biopsies (20%)	8 biopsies (26.7%)
Interface changes		4 biopsies (26.7%)	0 (0%)	4 biopsies (13.3%)
Melanophages		7 biopsies (46.7%)	4 biopsies (26.7%)	11 biopsies (36.7%)
Eosinophils		1 biopsy (6.7%)	0 (0%)	1 biopsies (3.3%)
Lymphohistiocytic infiltrate	Sparse	7 biopsies (46.7%)	7 biopsies (46.7%)	14 biopsies (46.7)
	Moderate	7 biopsies (46.7%)	5 biopsies (33.3%)	12 biopsies (40%)
	Dense	1 biopsy (6.7%)	3 biopsies (20%)	4 biopsies (13.3%)

DISCUSSION

Phototherapy is one of the most commonly used treatments for vitiligo with appreciated success rates and low incidence of side effects. It is also highly recommended after surgical grafting treatments to guarantee success [10]. Oral PUVA is the combined use of a photosensitizing chemical compound and non-ionizing electromagnetic radiation, and this combination induces a beneficial result not produced by either alone [6]. NB-UVB is a more recent phototherapy modality that was developed to remove the shorter erythemogenic wavelengths and to use a concentrated UVB source of 311 nm. NB-UVB has been reported to be effective and safe in vitiligo [11]. In this study, we tried to have a clinical objective

evaluation of improvement after phototherapy by using a pla- nimeter to calculate the percentage of improvement and ca- categorize the resulting numbers into descriptive terms for overall evaluation. Clinical evaluation showed that only 1 patient (3.3%) failed to respond to therapy (PUVA group) while the re- remaining 29 patients (93.3%) demonstrated improvement ranging from excellent to mild repigmentation. The present study demonstrated that NB-UVB group patients showed statistically significantly better results than oral PUVA group patients. Similar success rates were observed in previous comparative studies demonstrating the superiority of NB-UVB to PUVA [7,12]. In our study, we also demonstrated a faster response to NB-UVB which provided considerable repigmentation (up to 90%) after only 2 months of therapy compared to mild improvement (up to 37%) in the PUVA group after the same period.Another dramatic finding was the difference in the color matching between the two modalities of treatment, which was excellent in all patients treated with NB-UVB while 42.8% of patients treated with oral PUVA showed darker unsightly repigmentation of the treated vitiligi- nous areas compared to the patient's unaffected skin. This hyperpigmentation has been reported previously too [7]. The predominance of perifollicular repigmentation as a main pattern of repigmentation after both modalities was clearly demonstrated. The starting doses of NB-UVB in previous studies varied considerably, ranging from 75 mJ/cm [13] to 740 mJ/cm [12], although these differences may reflect variations in calibration. Some studies used starting doses based on the minimum erythema dose [14]. In other reported studies, the starting dose was based on skin typing [15]. In the present study, the starting dose was 0.574 J/cm^2 based on patients' main skin type (type 4). The therapeutic dose ranged from 1.402 to 2.737 J/cm^2.The first exposure dose for PUVA-treated patients in previously reported studies was based on a minimal photo-toxic dose (MPD) to ensure a safe starting dose [16]. In other reported studies, the starting dose was based on skin typing [17]. In the present study, the starting dose was 2 J/cm^2 based on patients' main skin type. The therapeutic dose ranged between 3.906 and 6.104 J/cm^2. In other previously reported studies, the therapeutic dose did not exceed 5 J/cm^2 for PUVA and 2 J/cm^2 for NB-UVB [7]. The higher therapeutic doses utilized here may be correlated to the darker skin type and skin tolerance to radiation in our locality due to intensive sun exposure throughout the year. The PUVA patients were older than the NB-UVB patients due to the exclusion criteria used in selecting its patients. Age was not found to influence the outcome of vitiligo therapy with oral PUVA and NB-UVB in previous studies [18]. However, the presumption that the earlier the patient was treated, the better the response also exists [19] and we agree that the age factor cannot be denied when comparing results in vitiligo cases. Oral PUVA is not recommended for children younger than 12 years [4,6]. The phototoxic potential of psoralen is of great concern in children where avoidance of excessive sun exposure may be difficult to regulate, again, the risk of carcinogenesis and premature aging of the skin can- not be neglected in children with long-term use. On the other hand, NB-UVB has been reported to be effective and safe in childhood vitiligo [11]. In the present study, 8 (80%) out of 10 children developed more than 75% overall repigmentation after 4 months of NB-UVB therapy. Thus, higher success rates were observed with NB-UVB radiation therapy. NB-UVB therapy offers other advantages over oral PUVA therapy that make it preferable for most patients. In particular, PUVA therapy requires the use of eye protection after treatment sessions, cannot be used in pregnancy, is contraindicated in patients with hepatic im- impairment or who are taking warfarin or phenytoin, and requires the somewhat inconvenient prior administration of psoralen. Of greatest concern however, is the potential of PUVA to cause non-melanoma and melanoma skin cancer [20], although in our vitiligo patients, this was not detected at all for several years of UV therapy (data not shown), perhaps because of the skin type and genetic background in our locality. Nevertheless, it is important to mention that NB-UVB seems to be considerably safer than PUVA in the required number of treatment sessions as higher success rates can be achieved as early as 2 months of therapy. Although risks for cutaneous malignancies are reported with PUVA, however, to date there is insufficient data available to provide recommendations regarding a safe maximum narrow-band UVB dose. The general histological picture of vitiligo before treatment revealed the presence of hyperkeratosis in 40% of vitiligo skin biopsies. This finding was noticed in previous studies [21]. Hyperkeratosis declined after treatment, down to 12.5% of the non-responding areas and in 6.89% of the pigmented areas (with no significant difference between the 2 study groups). The presence of hyperkeratosis in a lower ratio after treatment may be due to the return of the epidermal turnover rate due to the stoppage of the keratinocyte degeneration and death process. Basal melanization was detected in vitiligo skin in 26.6%. Kim *et al.* (2008) found remaining melanocytes in 12% of vitiligo skin cases by using MART-1 stain. In the present study, using MART-1 antibody for immunohistochemical staining of melanocytes, MART-1 positive cells were found in the vitiligo skin in a higher percent- ages than in previous studies. After 4 months of photo-therapy treatment, basal melanization appeared in all biopsies of the pigmented areas and was present in 12.5% of the non-responding areas of the vitiliginous lesions after treatment. The present study demonstrated the presence of moderate to dense perivascular and perifollicular

lymphohistiocytic infiltrate in 53.3% of vitiliginous skin. Vitiligo is an unstable disease and its activity is usually unpredicted but related to immunological stimulation and subsequent destruction of new melanocytes. Detect- ing active cases after both modalities needed to be done in a further study to confirm the further advantage of a method over another, although we expect that PUVA will be superior in such cases due to its ability to reduce im- immunological inflammatory infiltrates with a subsequent clinical decline in disease activity and less development of new lesions as described previously in the results

CONCLUSION

NB-UVB treatment can provide statistically significantly better results than PUVA. Distinct advantages over PUVA include the lack of psoralen-related side-effects and precautions, a cosmetically better color match, and safety in children. Although NB-UVB therapy gives a more rapid effect than oral PUVA therapy, PUVA therapy was accompanied by significantly less recurrence and less development of new vitiligo lesions. The dermal infiltrates, composed mainly of T cells and Histiocytes, with the interface changes persisted after the NB-UVB repigmentation more than in the PUVA-treated areas. Thus, PUVA may provide a better immuno-modulatory effect on vitiligo than NB-UVB and may give bet- a ter response regarding the disease reactivation and recurrence. A combination of UVA and NB-UVB bulbs in the same treating cabinets may be recommended to obtain better treatment results.

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