Research Article

Non Segmental Vitiligo in Children: Treatment with Narrow Band Ultraviolet B With and Without Topical 5 Fluorouracil on Ablated Lesions

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Abstract

Introduction: Vitiligo is a chronic idiopathic pigmentary disorder of the skin and hair, it is common in children below 12 years and its Management in children is difficult as therapeutic options are restricted when compared to that in adult patients. NB-UVB is an effective modality in the treatment of vitiligo with high success rates and low incidence of side effects and it is effective in childhood vitiligo. Skin ablation by mechanical dermabrasion with 5Fluorouracil (5FU) was introduced to treat vitiligo in 1983. This was modified replacing the mechanical dermabrasion by Erbium-YAG (ER:YAG) laser ablation and resulted in better prognosis in periungual vitiligo. **The Aim of the study:** Exploring the effect of the use of ER-YAG laser ablation plus application of topical 5FU on the outcome of short term NB-UVB phototherapy for children having non segmental vitiligo (NSV) and exploring safety of topical 5FU on this age group. **Patients and Methods:** The study was a left – right comparative study that included 22 children with non-segmental vitiligo (NSV), attending the Dermatology Outpatient Clinic of Minia University Hospital. This study included 22 child with a total of 22-paired symmetrical non segmental vitiligo lesions in different body parts and their ages ranging from 8-12 year. The treated sides were divided in to 2 groups: Group (A): included the 22 right sides of the body in the children that will subjected to ER-YAG laser plus 5FU before simultaneous NB-UVB therapy of both sides. Group (B) included the 22 left sides of the body in the same children that will subjected to NB-UVB phototherapy only. They were 9 (40.9%) females and 13 (59.1%) males with 22 paired vitiligo lesions in different body sites. Each pair was more or less symmetrical.They were collected during the period from March 2014 to April 2016. **Results:** The overall response to therapy was better using the combination therapy. (81.9%) of patients experienced a moderate to marked repigmentation response in the combination group compared with 0% of patients showed marked response and 13.6% showed moderate response in the mono-therapy group. In different body parts the response was significantly higher in lower limbs and feet but statistically insignificant in other body parts. Transient hyperpigmentation occurred in 3 cases and no koebnerization detected in any of the treated lesions. **Conclusion:** This study concluded that prior use of ER:YAG laser skin ablation, followed by 5FU application before NB-UVB phototherapy for non segmental vitiligo in children is a safe and tolerable technique that improves the outcome of short-term NB-UVB therapy and proved the safety of 5FU cream in this age group when applied to limited areas.

Key Words: Non Segmental Vitiligo, Children, Narrow Band Ultraviolet B, 5 Fluorouracil

Introduction

Vitiligo is an acquired, idiopathic disorder characterized by circumscribed depigmented macules. Functional melanocytes disappear from involved skin by a mechanism(s) that has not yet been precisely identified**.** Its incidence is 1–2% worldwide without sex or skin colour predilection[1]**.** Vitiligo can be extremely disfiguring, leading to significant peychologic morbidity. This is of particular concern for children and adolescents, as they are in their formative years and are developing their sense of self [2]**.** With the development of narrow band ultra violet B (NB-UVB), it was found that it offers a potential for the management of childhood vitiligo and was considered as an

effective and safe therapeutic option in adult patients with vitiligo that may significantly improve the quality of life. .Nevertheless, it requires more than one year for its completion and some patients may find this long duration of therapy inconvenient due to social and financial reasons[3]. Pharmacologically, 5 Fluorouracil (5FU) is an antimetabolite analogue of the naturally occurring pyrimidine uracil which is metabolized via the same metabolic pathways as uracil. It is supposed to induce repigmentation of vitiligo lesions by overstimulation of follicular melanocytes which migrate to the epidermis during epithelialization [4]. Application of 5FU after mechanical dermabrasion was introduced as a treatment for vitiligo by Tsuji and Hamada in 1983**.** Erbium-YAG (ER:YAG) laser with its controlled ablation, especially on irregular surfaces, was considered superior to mechanical dermab-rasion. Thus, a new technique using an ER:YAG laser instead of the mechanical dermabrasion together with 5FU application was used successfully for treating periungual vitiligo [5]**.**

Aim of the study

Exploring the effect of the use of ER-YAG laser ablation plus application of topical 5FU on the outcome of short term NB-UVB phototherapy for children having non segmental vitiligo (NSV) and exploring safety of topical 5FU on this age group.

Patients and Methods

The study was a left – right comparative study that included 22 children with non-segmental vitiligo (NSV), attending the Dermatology Outpatient Clinic of Minia University Hospital. They were collected during the period from March 2014 to April 2016. The study was approved by the ethical committee of the Faculty of Medicine, Minia University. A written consent was obtained from the legal guardian of each patient after explaining the procedure and the possible effects and side effects . This study included 22 child with a total of 22-paired symmetrical non segmental vitiligo lesions in different body parts and their ages ranging from 8-12 year. The treated sides were divided in to 2 groups: Group (A): included the 22 right sides of the body in the children that will subjected to ER-YAG laser plus 5FU before simultaneous NB-UVB therapy of both sides. Group (B) included the 22 left sides of the body in the same children that will subjected to NB-UVB phototherapy only. NBUVB was continued for a maximum period of 4 months ,the outcome was then evaluated both qualitatively and quantitatively. Routine investigations were done to all children before and after using 5FU cream to detect its safety in this age group. Patients on lines of topical treatments for vitiligo other than NB-UVB were instructed to stop this treatments at least two weeks before the start of the therapy. Patients on NB-UVB phototherapy continued their sessions. However, the sessions were stopped for about one week on the side of laser therapy until re-epithelization took place then they were resumed. Patients of stable lesions regardless of overall disease activity or lesions with white hairs were not excluded from the study. Inclusion criteria: Age ranging from 8-12 years, symmetrical NSV lesions on the two sides of the body. Exclusion criteria: any child with associated chronic diseases such as diabetes, cardiac, hepatic and renal diseases, patients with lesions exclusively on the Face, patients with segmental vitiligo ,uncooperative child or guardian. The duration of this study was about 4 months and evaluation of response was done after 2, 3 and 4 months then follow up was done monthly for 3 months after the end of therapy. The evaluation of the response after the first month was very difficult even with Wood's light because of the presence of an erythematous hue after the ER:YAG session. The quantitative response to therapy (repigmen-tation in %) was evaluated subjectively by two investigators simultaneously and the evaluation was done each time by the same investigators. The qualitative response was subdivided into mild, moderate and marked according to the quantitative response, mild (1% to 25%), moderate (26% to 75%) and marked (more than 75%) repigmentation.

Results

The study included 22 children with NSV attending the Dermatology Outpatient Clinic of Minia University Hospital. They were 9(40.9%) females and 13(59.1%) males with 22 paired vitiligo lesions in different body sites. Each pair was more or less symmetrical. The age of the patients ranged between 8 and 12 years with a mean and SD of 9.95±1.64 years. The duration of the disease ranged from 1 to 24 months,

with a mean ± SD of 8.77±6.01 months. A positive family history of vitiligo was present in 3 out of 22 patients (10%) (Table 1). After 2 months, 8 patients (36.4%) in group A achieved a marked response, with no response (0%) in group B. The overall qualitative and quantitative response to therapy after 2 months in the two groups was statistically significant as shown in table (3).The number of patients with marked response was increased to 9 patients (40.9%) after 3 months in group A compared to none (0%) in group B, The overall qualitative and quantitative response to therapy after 3months in the two groups was statistically significant as shown in table (4). At the end of the therapy (after 4 months) 10 (45.5%) patients showed marked response in group A, while in group B, no patients showed marked response. The difference between the two groups in their marked response was statistically significant after 4months (p value < 0.001). The overall qualitative and quantitative response were significantly higher in group A than in group B, (p value > 0.001) as shown in table (5). Table (6) showed that investigations before and after therapy were within the normal ranges with no significant difference detected between the two groups .

Table (1): Clinical data of studied vitiligo patients.

Character	N=22	
	N	%
Sex		
Male	13	59.1%
Female	9	40.9%
Family history		
+ve	3	13.6%
-ve	19	86.4%
Resident		
Rural	11	50%
Urban	11	50%
	Mean ± SD	**Range**
Age (years)	9.95 ± 1.64	8 – 12
Duration of disease (months)	8.77 ± 6.01	1 - 24

Table (2): Number of vitiligo lesions according to their site

Site of lesions	Number of lesions	%
Upper limbs	2	9.09%
Hands& fingers	2	9.09%
Lower limbs	11	50%
Feet	5	22.7%
Trunk	2	9.09%
Total	22	100%

Table (3): Comparison between the studied groups as regards the overall qualitative and quantitative response after 2 months.

2 months	Group A (n=22)	Group B (n=22)	P value
(1)Quantitative response (%)			
Range	(0-95)	(0-0)	**< 0.001***
Mean ± SD	60.22±27.41	0±0	
Median	70	0	
(2)Qualitative response	**N%**	**N%**	
Marked	8(36.4%)	0(0%)	**< 0.001***
Moderate	10(45.5%)	0(0%)	
Mild	2(9.1%)	0(0%)	
No response	2(9.1%)	22(100%)	

- (1)Mann Whitney test for non-parametric quantitative data between the two groups
- (2)Fisher Exact test for qualitative data between the two groups
- *: Significant difference at p value < 0.05

Table (4): Comparison between the studied groups as regards the overall qualitative and quantitative response after 3 months.

3 months	Group A (N=22)	Group B (N=22)	P value
(1)Quantitative response %			
Range	(0-95)	(0-45)	**< 0.001***
Mean ± SD	63.41±28.63	4.77±11.69	
Median	70	0	
(2)Qualitative response	**N%**	**N%**	
Marked	9(40.9%)	0(0%)	**< 0.001***
Moderate	9(40.9%)	1(4.5%)	
Mild	2(9.1%)	3(13.6%)	
No response	2(9.1%)	18(81.8%)	

- (1)Mann Whitney test for non-parametric quantitative data between the two groups
- (2)Fisher Exact test for qualitative data between the two groups
- *: Significant difference at p value < 0.05

Table (5): Comparison between the studied groups as regards the overall qualitative and quantitative response at the end of the therapy

4 months	Group A (n=22)	Group B (n=22)	P value
(1)Quantitative response %			
Range	(0-100)	(0-75)	**< 0.001***
Mean ± SD	67.04±30.53	11.36±21.54	
Median	70	0	
(2)Qualitative response	**N%**	**N%**	
Marked	10(45.5%)	0(0%)	**< 0.001***
Moderate	8(36.4%)	3(13.6%)	
Mild	2(9.1%)	6(27.3%)	
No response	2(9.1%)	13(59.1%)	

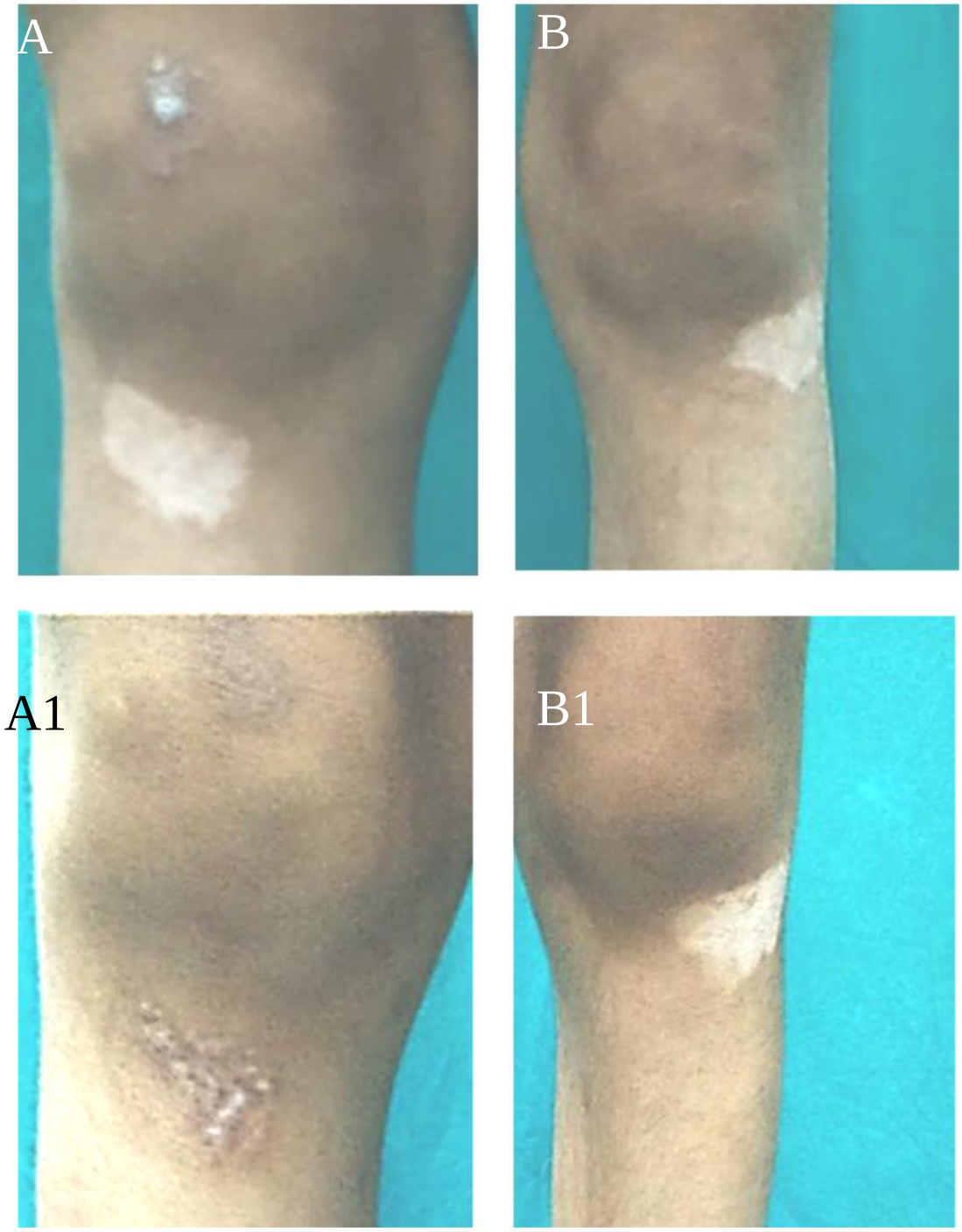

Fig. (1): Lower limb lesions before (A and B) and after (A1 and B1) therapy in groups A and B respectively showing marked response in group A and no response in group B.

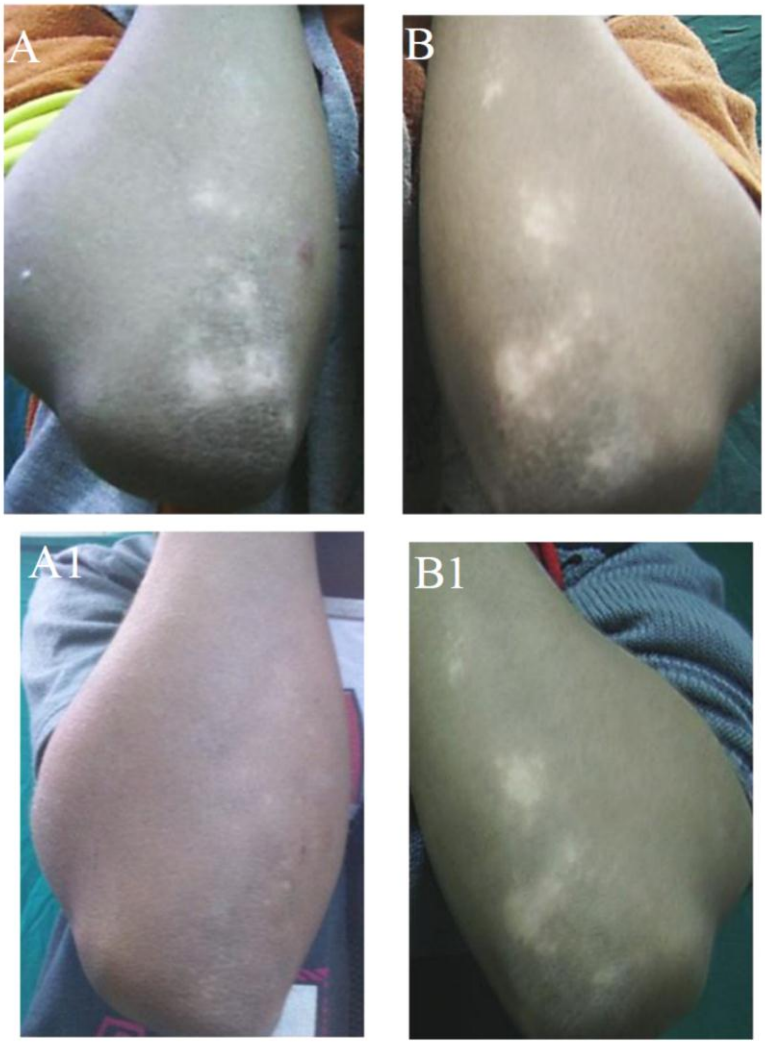

Fig. (2): upper limb lesions before (A and B) and after (A1 and B1) therapy in groups A and B respectively showing marked response in group A and no response in group B.

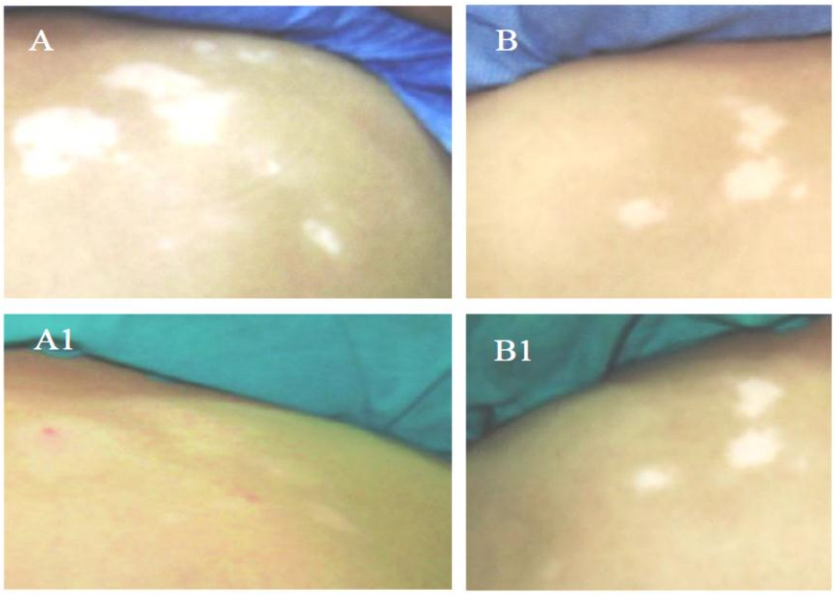

Fig. (3): Trunk lesions before (A and B) and after (A1 and B1) therapy in groups A and B respectively showing moderate response in group A and mild response in group B.

Table (6): Comparison between the investigations before and after therapy

	Before treatment	After treatment	P value
(1)Hb			
Range	(8.8-13.6)	(9.4-13.5)	0.373
Mean ± SD	11.27±1.44	11.45±1.27	
(1)WBC			
Range	(4.4-8.5)	(4.4-8.5)	0.324
Mean ± SD	6.76±1.33	6.86±1.16	
(1)RBC			
Range	(3.8-5.6)	(3.8-5.6)	0.690
Mean ± SD	4.84±0.57	4.81±0.53	
(1)Platelets			
Range	(215-425)	(210-465)	0.205
Mean ± SD	339.31±62.03	345.22±64.66	
(1)MCV			
Range	(82-100)	(83-100)	0.561
Mean ± SD	90.63±6.13	91±5.74	
(1)Urea			
Range	(11-34)	(13-36)	0.309
Mean ± SD	22.81±7.55	23.68±6.94	
(1)Creatinine			
Range	(0.6-1.5)	(0.7-1.5)	0.831
Mean ± SD	1.04±0.27	1.05±0.21	
(2)ALT			
Range	(5-46)	(4-44)	0.272
Mean ± SD	23.31±13.73	24.54±12.36	
(2)AST			
Range	(1-43)	(6-44)	0.379
Mean ± SD	18.18±13.42	18.86±11.72	
(1)T bilirubin			
Range	(0.3-1.2)	(0.3-1.2)	1
Mean ± SD	0.7±0.26	0.7±0.24	
(1)TPP			
Range	(5.6-8.4)	(5.7-8.3)	0.423
Mean ± SD	7.09±0.87	7.15±0.78	

- (1) Paired sample t test for parametric quantitative data.
- (2) Wilcoxon Signed Rank test for non-parametric quantitative data.
- *: Significant difference at p value < 0.05

Discussion

Vitiligo is an acquired disorder of skin pigmentation that is associated with tremendous psychological impact on the affected patients. It still remains a difficult disease to treat, although various non-surgical and surgical treatment modalities had been used . Vitiligo usually presents itself in childhood or young adults. Approximately half to one third of them develop this condition by 20 years of age and around 25% of them before 8 years with a mean age of onset varying between 4 and 5 years, and not all treatment modalities could be used in children[6].

There have been several reports introducing ablative laser-assisted trans-epidermal delivery of topical medicine in the treatment of Vitiligo[7]. Many studies reported the effects of CO_2 laser or Er: YAG laser ablation followed by application of many topical agents combined with narrow band ultraviolet B (NB-UVB)

phototherapy for treating non-segmental Vitiligo. However, ablation of the entire epidermis compromised the skin healing process. Fractional laser do not ablate the entire epidermis and thereafter leave intact skin between coagulated necrotic columns. This characteristic facilitates the skin healing process. Recently, fractional CO_2 laser was reported to be used in the treatment of refractory vitiligo followed by NB-UVB or sun exposure [8]. Er: YAG laser was introduced as a gentler alternative to the CO_2 laser. Under proper parameter setting, the Er: YAG laser could create less residual thermal damage and faster healing [9] . Anbar et al., (2008) [10] in their study used the same technique in adults and concluded that the prior use of ER: YAG laser skin ablation, followed by 5FUapplication before NB-UVB phototherapy for vitiligo is a safe and tolerable technique that improves the outcome of short-term NB-UVB therapy and is expected to increase patient compliance. In the present study we used the same technique but the only difference was the age group being used in children not in adults.

In a study by Abd El-Samad and Shaaban, (2012) [1] multiple sessions of intra-dermal 5FU in 60 adult vitiligo patients which were also shown to improve NB-UVB efficacy, with 48% of subjects achieving > 75% repigmentation compared to 7% of subjects treated with NB-UVB alone. They concluded that intradermal 5FU injection in combination with NB-UVB shortens the duration of NB-UVB therapy and improves the outcome and repigmentation. This was in agreement with the present work, but the intradermal injection allows for the entrance of large doses of 5FU for long duration, which could be considered a disadvantage especially for a child. Moreover, the side effects of the intradermal injection such as pain, burning sensation, hyper pigmentation, atrophy and erosions at the border of the lesion were reported which makes it less preferable than the topical 5FU which principally has less side effects. Topical application of 5FU for two days on dermabraded or laser ablated skin results in an inflammatory reaction with erythema, erosion, and crustation[11]. Accordingly, 5FU is considered an inflammatory agent that can strongly inhibit wound epithelialization and delay wound healing, which gives a chance for melanocytes to proliferate. 5FU also has an antimitotic activity and inhibits agents or cells capable of destroying pigment cells. In addition, it has an immunomodulatory effect that can stabilize vitiligo. Hence, addition of an anti-inflammatory and immunosuppressive agent such as clobetasol to 5FU in the treatment of vitiligo will most likely have no beneficial effect asit could counteract the effect of 5FU. There are two main sources of repigmentation: the 1st is melanocytes from hair follicle (follicular repigmentation), and the 2nd is from the edge (marginal repigmentation)[12]. This results from two types of migration "vertical migration" towards the basal cell layer and "horizontal migration" towards the vitiligo border which results in perifollicular and marginal repigmentation patterns respectively. The response to therapy was affected by the anatomical site of the lesions.

Anbar et al., (2016) [13] reported better clinical results following application of 5FU to Er: YAG ablated skin of difficult to treat areas. However, in their study they depended on remote melanocytes through surgical intervention for repigmentation. They suggested that 5FU on the ablated skin induced an inflammatory reaction, which acted mechanically by opening the intercellular spaces and releasing inflammatory mediators, and acted immunologically through the sequestration of the inflammatory cells attacking the melanocytes to a higher level. Both mechanisms facilitate melanocyte migration from the punch grafts towards the achromic skin.

In our study, we depend on vertical migration of melanocytes (follicular repigmentation) and horizontal migration (marginal repigmentation) but we did not use remote melanocytes as we work on lesions of large size to some extent in areas with profuse hair and lesions of small size in areas devoid of hair. In order to depend on horizontal migration for repigmentation, the size of the lesion is a very important factor that should be taking in consideration [12]. Accordingly, it can be suggested that 5FU in the present study acted immunologically and mechanically to facilitate melanocytes' migrations from hair follicles and the margins of the lesions. All surgical techniques used in the treatment of Vitiligo recommended the stability of the disease to avoid Koebnerization. This was not applied to our technique and disease activity was not an exclusion criterion.

In the current study, no Koebnerization was detected in any of the treated lesions however hyperpigmentation was seen in 3 patients this is in accordance with the study of Sethi et al., (2007)[14] that reported the development of marked hyperpigmentation in the 5FU group, which is a known side effect of 5FU[15]. Normal investigations after using topical 5FU confirmed the safety of the use of this agent in children.

Conclusion

This study concluded that prior use of ER:YAG laser skin ablation, followed by 5FU application before NB-UVB phototherapy for non segmental vitiligo in children is a safe and tolerable technique that improves the outcome of short-term NB-UVB therapy and proved the safety of 5FU cream in this age group when applied to limited areas.

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