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Original Article

A Double-Blinded Placebo Controlled Therapeutic Trial on Patients with Stable Non-Segmental Vitiligo Using A Specially Formulated Reducing Gel [Pseudo-Catalase] Enhanced by Narrow Band Ultraviolet B Exposure

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ABSTRACT

Background: Vitiligo is a skin disorder characterized by the loss of melanocyte cells, leading to depigmentation. Treatment options for Vitiligo encompass topical agents, systemic treatments, phototherapy, and surgical interventions. Some therapeutic approaches target the oxidative toxicity pathway, with pseudo-catalase enzyme treatment showing promise in this context.

Aim of the work: This study aims to assess the effectiveness and safety of a specially formulated reducing gel containing pseudo-catalase enzyme in conjunction with narrowband UVB therapy for stable non-segmental vitiligo.

Patients and Methods: In this double-blinded, placebo-controlled trial, 30 vitiligo patients were enrolled and randomly assigned to either the test gel group or the placebo gel group. Participants applied the assigned gel pre- and post-NBUVB treatment twice weekly for 24 weeks. Baseline and monthly assessments of Vitiligo Area Scoring Index [VASI] and photographic evaluations were conducted.

Results: The VASI scores of the test group exhibited a significant improvement [P value = 0.0001] compared to the placebo group [P value = 0.18] following treatment. Furthermore, post-treatment VASI scores were significantly lower in the test group compared to the placebo group.

Conclusion: The combination of pseudo-catalase reducing gel with NB-UVB therapy yields superior therapeutic benefits for stable non-segmental vitiligo in terms of repigmentation compared to NB-UVB therapy or placebo alone. These agents may enhance endogenous catalase activity through exogenous redox regulation, suggesting the need for further investigation.

Keywords: Vitiligo; Ultraviolet Therapy; Pigmentation Disorders.

INTRODUCTION

Depigmenting vitiligo is a skin disorder resulting from the complete destruction of melanocyte cells in the skin, caused by various factors, including genetic defects in melanocytes, prickle cells, and Langerhans cells in the epidermis, dysfunctional catalase enzyme in the blood, tissues, or both, external and internal stress factors, oxidative stress of melanocyte cells, cytotoxic cell death due to the accumulation of Reactive Oxygen Species [ROS] inside the cells and all epidermis, the autoimmune theory, the neurodegenerative theory, the metabolic theory with the synthesis of cholesterol in skin tissues, and the viral theory, which is not fully understood [1]. Its frequency varies from 0.5% to 4% worldwide and affects all ethnicities; however, it is more prevalent in individuals with autoimmune disorders and children whose parents have this condition [2].

Approximately 30–40% of the population with vitiligo has a family history of the disease [3]. Vitiligo has a devastating effect on patients' daily lives, particularly those with darker skin [4].

The loss of melanocytes, which generate melanin pigment in the skin, hair, mucous membranes, and retina, causes skin depigmentation [5]. This results in several white spots emerging on various regions of the skin [6]. The chemical substances produced by melanocytes in reaction to stress are known as reactive oxygen species [ROS]. They generate heightened oxidative stress indicators in the skin and blood, as well as a considerable depletion of antioxidative systems [7].

Furthermore, ROS may damage DNA, cause protein oxidation and fragmentation, and promote lipid peroxidation, all of which impede cellular function [8]. Treating vitiligo is challenging, with different treatment modalities being used. When more than 60–70% of the body's surface is affected by vitiligo, complete depigmentation becomes an optimal option. Phototherapy, including broad-band B [UVB], narrow-band [NB] UVB, Psoralen + UVA [PUVA], and targeted phototherapy utilizing light sources or excimer lasers, is used when vitiligo covers more than 60-70% of the body surface [9].

This work aimed to test the efficacy of a specially formulated gel containing reducing components [pseudo-catalase] activated by exposure to Narrow Band Ultra Violet B rays [NBUVB] in stable non-segmental vitiligo patients, compared to a placebo gel not containing the same chemical active ingredients, on the same patients.

PATIENTS AND METHODS

Thirty participants took part in the study, all of whom had stable non-segmental vitiligo and had visited the Dermatological out-patients clinic at Al-Hussein University Hospital in Cairo between September 2021 and March 2022. The study included a three-month follow-up period lasting until June 2022. Patients were randomly assigned to receive either the test gel + NBUVB or the placebo gel + NBUVB.

The criteria for inclusion in the study are as follows: individuals aged 18-45 years of both sexes, with confirmed cases of stable non-segmental vitiligo, and having lesions for any duration.

The exclusion criteria for the study include the presence of any associated skin disease or systemic morbid disease [such as diabetes mellitus, dyslipidemia, thyroid diseases, hypertension, liver diseases, or kidney diseases], the use of any topical or systemic therapy within the last 3 months prior to entering the study, unstable vitiligo, and being pregnant or breast-feeding.

Ethical consideration: Informed written consent was obtained in accordance with the code of ethics for research work at Al-Azhar University. Each patient's testing and placebo gels were packaged and labeled in identical containers by a pharmacist, ensuring that patients, attending nurses, and the researcher were all blinded to the two gels until the conclusion of the study.

Data collection: Patients underwent the following procedures: a comprehensive history, including full personal, family history of vitiligo, and full medical history; a thorough clinical examination and estimation of the Vitiligo Area Scoring Index [VASI] before and after the conclusion of the study. VASI is a clinically-reported criterion for evaluating vitiligo. Additionally, investigations included daylight photography and photography under Wood's light for diagnosis confirmation, as well as laboratory work consisting of complete blood count [CBC], liver profile, lipid profile, thyroid hormone and antithyroid hormone antibodies, HBA1C blood test, and Vitamin D3 assessment.

Treatment protocols: The topical application of the test gel, referred to as VIT.T, involved applying a generous amount to the affected area and a large area of the surrounding skin. On the trunk, it was applied to the front side, and on the ventral aspects of the left arms and forearms, as well as on the frontal sides of the left thigh and leg.

The placebo gel, known as VIT.P, was applied to the backside of the trunk and the back side of the contralateral limbs. After gel application, all patients were exposed to NBUVB rays two hours later. The sessions were conducted in a scheduled manner, starting with the smallest Jule dose and gradually escalating to a maximum of 5 J/cm^2 dose, given twice weekly. Patients and attendees were instructed to wear eye protective goggles.

Follow up: The study period was around 6 months followed by 3 months follow up. Patients were examined at monthly intervals, photographs were obtained at the study's onset, on a monthly basis, and at its conclusion.

Statistical Analysis: All statistical analyses were performed using SPSS Descriptive statistics, including means, standard deviations [SD], frequencies, and percentages, were calculated to summarize the characteristics of the study participants. For comparative analyses, independent t-tests were employed to assess differences between two independent groups, while paired t-tests were used to evaluate changes within the same group before and after treatment. A p-value of <0.05 was considered statistically significant for all tests.

RESULTS

Regarding gender, females were the prevalent sex with 26 females 86.7% vs 4 males 13.3% [Table 1]. The mean age of patients was 30.03 years with no significant difference between males and females regarding age [Table 2].

The total number of lesions was 227 in the test group and 116 in the placebo group. Details of lesions site are shown in Table [3].

The VASI scores of the test group exhibited a significant improvement [P value=0.0001] compared to the placebo group [P value=0.18] following treatment [Table 4]. Furthermore, post-treatment VASI scores were significantly lower in the test group compared to the placebo group [Table 5].

Table [1]: Sex distribution

Gender	Male	Female
Number pf patients	4	26
Percentage	13.3	86.7

Table [2]: Age distribution

	Total age	Male	Female	P value
Mean	30.03	30.75	29.92	0.44
± SD	10.76	5.17	5.17	
Minimum age	18	22	18	
Maximum age	45	35	45	

Table [3]: Total number of lesions in both test and placebo areas

Site of lesions	Test	Placebo
Face	50	0
Neck	14	0
Breast	50	0
Abdomen	15	0
Upper limb	36	34
Lower limb	62	58
Back	0	24
Mean size	3.239643 cm	2.099 cm
Total Number of lesions	227	116

Table [4]: VASI score before and after the treatment

Test effect			
VASI score	**Before treatment**	**After treatment**	**P value**
Mean	2.18	1.17	0.0001
± SD	1.07	0.83	
Placebo Effect			
VASI score	Before treatment	After treatment	P value
Mean	1.97	1.69	0.18
± SD	0.67	0.64	

Table [5]: Comparing the VASI score of the test and the placebo gel at the end of the study

	Test gel	Placebo gel	P value
Mean	1.17	1.97	0.009
± SD	1.07	0.67	

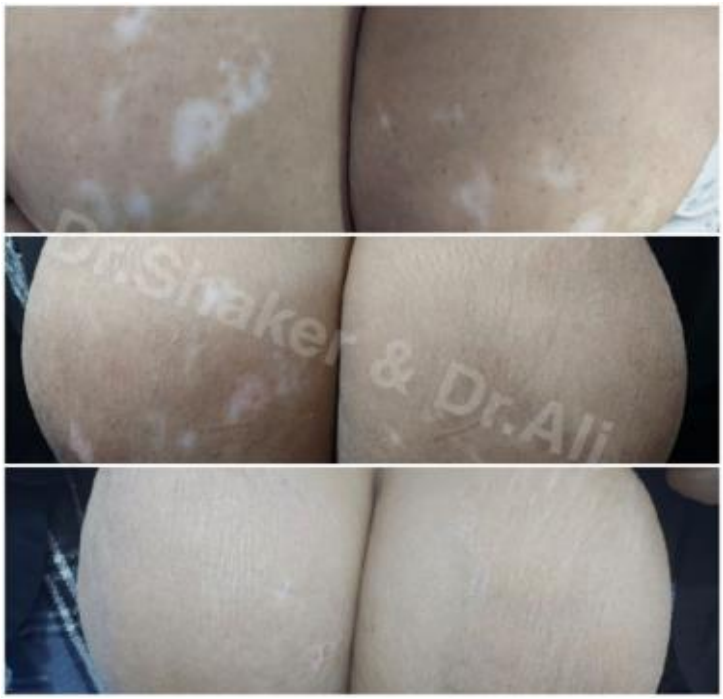

Figure [1]: Female patient 37 years old, vitiligo for 7 years, both breasts skin was affected. She received 24 sessions of NBUVB + antioxidant cream over a period of 3 months-excellent result

Figure [2]: Female patient, 39 years old, multiple face lesions, day light and wood's light photos [photos before treatment]

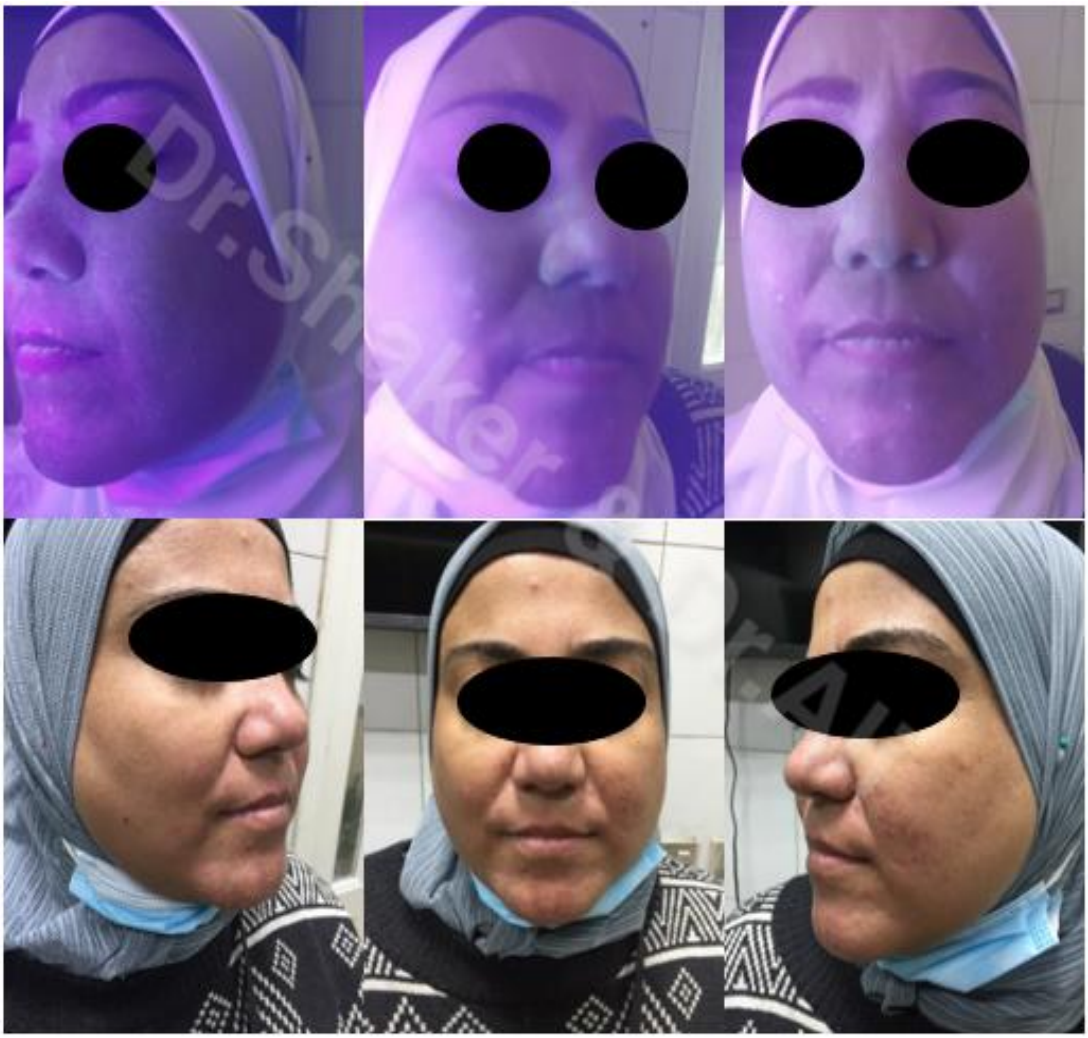

Figure [3]: Same patient shows complete cure after 5 weeks treatment [10 sessions NBUVB+ test gel]

Figure [4]: Male patient,28 years old, Focal lesion on the gluteal area right side, shows complete cure after 7 weeks [14 sessions] NBUVB+ test gel

Figure [5]: Female patient, 28 years old, vitiligo for 20 years, photos show marked improvement [no complete cure] after receiving treatment for 10 weeks [20 NBUVB sessions+ test gel]. [patient disappeared after this stage of treatment

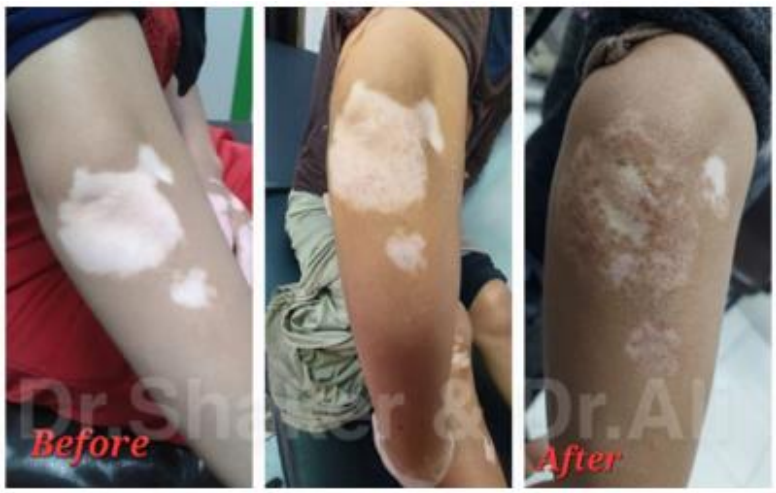

Figure [6]: Right elbow and forearm lesions, same patient, before, during and after treatment shows marked improvement

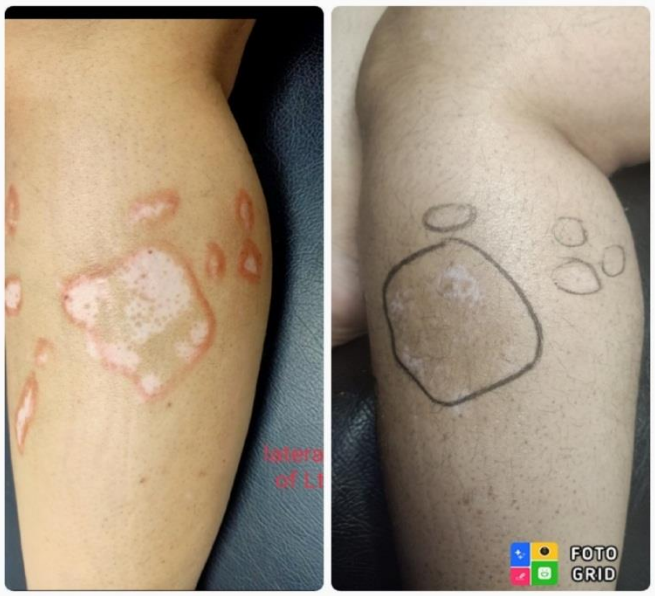

Figure [7]: Lateral side leg lesions-before and 2 months after treatment- 16 sessions NBUVB + testing gel [Excellent result]

DISCUSSION

Vitiligo is a skin condition that is notoriously challenging to treat [11]. Hydrogen peroxide [H2O2] is broken down into water and oxygen by the peroxisomal enzyme catalase, thus protecting cells against the extremely reactive free radicals formed from oxygen [12].

Gawkrodger [11] discovered that using a pseudo-catalase cream with Narrowband UVB [NBUVB] wasn't any more effective than using a placebo. **Bakis-Petsoglou *et al.*** [13] conducted a study with 32 patients. Pseudo-catalase was applied to the skin twice daily as a cream to the entire body, along with total body low dose narrow-band UVB radiation once or twice weekly. The clinical outcomes of this therapy resulted in a 95% reduction in the development of active vitiligo and repigmentation in 60-65% of treated individuals, regardless of illness duration. In terms of overall repigmentation, neither the pseudo-catalase cream nor the placebo cream group showed any discernible improvement over the other [P = 0.02]. The scientists attributed the statistically significant facial repigmentation in the pseudo-catalase and placebo groups, but not their hand repigmentation, to NBUVB.

No significant improvements in the lesion area were detected in a pilot, randomized, placebo-controlled experiment using topical pseudo-catalase/superoxide dismutase gel [14]. **Rahsepar *et al.*** [15] conducted research on 30 patients who were treated with Vitix® gel in combination with NBUVB on one side of the body and NBUVB alone on the other. During the varied periods of treatment, neither NBUVB phototherapy nor the addition of Vitix® [pseudo-catalase gel + superoxide dismutase gel] produced a statistically significant improvement over the control group [p > 0.05].

Repigmentation of the face and dorsum of the hands was induced by a combination of topical pseudo-catalase/calcium and brief exposure to NB-UVB in a case study including 33 patients [16].

A prospective study of 59 individuals found that when Dead Sea climatotherapy was paired with topical pseudo-catalase, pigmentation was initiated faster in the treated skin within 10 to 16 days, compared to either of the two modalities alone [17]. **Casp *et al.*** [12] observed a full stop of vitiligo development in 70 patients: more than 75% repigmentation was identified in 66 individuals, with a disappointing response on the hands and feet. **Kostovi *et al.*** [18] reported more than 50% repigmentation in 57.9% of patients treated with Vitix® gel applied twice daily and NBUVB phototherapy administered three times per week.

In a study conducted by **Gawkrodger** [11], thirty-three patients were treated with a pseudo-catalase and calcium cream applied to all exposed areas of the body twice daily, followed by ultraviolet radiation therapy [UVB] twice weekly. The face and hand dorsum repigmented to 'Excellent' levels [range 4-27] in 90% of instances, although fingers and feet did not repigment. The

vulgaris type [20 patients: 'good-to-moderate response'] responded the best with 90%-100% repigmentation, followed by the localized vitiligo [5 cases]. In all cases, disease activity was halted. Additionally, a study conducted by **Akdeniz *et al.*** [19] involving the use of NB-UVB alone showed a statistically significant difference in percentage repigmentation [$P < 0.05$].

Our findings differ from those of two studies [13, 15], which observed that neither the pseudo-catalase cream nor the placebo cream coupled with NBUVB showed statistically significant results. Other studies [16, 17] demonstrated a quicker onset of pigmentation within 10 to 16 days. We noted the onset of repigmentation, especially on the face, after 5 weeks of therapy [10 sessions].

Casp *et al.* [12] found that more than 75% of patients experienced repigmentation, although the response on the hands and feet was unsatisfactory; therefore, our results are in line with theirs. Additionally, we concur with **Kostovi *et al.*** [18], who found more than 50% repigmentation in 57.9% of patients treated with Vitix® gel [a blend of pseudo-catalase and superoxide dismutase gel] and NBUVB phototherapy.

Both our results and those of **Gawkrodger** [11] agree that there was 'Excellent' repigmentation on the face and dorsal surface of the hands in 90% of patients, although fingers and feet did not repigment. **Cauhe *et al.*** [20] showed that the location of the vitiligo was an essential factor in determining the improvement from NB-UVB therapy in non-segmental vitiligo [NSV].

According to **Bae *et al.*** [22], the best response was observed on the face and neck, followed by the trunk, extremities, and finally the hands and feet. This observation aligns with the results of our study, in which we noted rapid improvement on the face, breast areas, and trunk compared to the effect on the skin of the hands and feet.

Lim *et al.* [22] demonstrated a repigmentation response in 33.26% of cases with non-segmental vitiligo undergoing NB-UVB monotherapy. This finding is relevant to our results, which indicated that the observed repigmentation with the placebo cream was likely due to the effect of NBUVB alone.

Dogra and Parsad [23] showed in a single case report from India that repigmentation was observed in less than 50% of lesions when using NB-UVB plus placebo. This finding is consistent with the VASI score results of repigmentation due to the placebo cream before and after treatment in our study, which were not statistically significant [$p = 0.182259$]; this suggests that the observed effects were likely due to NBUVB alone.

Our results contrast with those of **Naeini *et al.*** [14], who found no significant improvements in the lesion area after conducting a pilot, randomized, placebo-controlled experiment with topical pseudo-catalase/superoxide dismutase gel.

In conclusion, based on our findings, we conclude that the antioxidant pseudo-catalase gel mixture paired with NBUVB was an extremely effective therapy for vitiligo. In the treatment group, there were statistically significant variations in VASI values before and after treatment [P value = 0.00017].

Conflicts of interest: None.

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