Evaluation of the Additional Effect of Vitix® Gel on Vitiligo Lesions in Patients Treated with Narrow-Band Ultraviolet-B Phototherapy

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Abstract. Vitiligo is a polygenic acquired skin disorder resulting from the destruction of melanocytes in epidermal cells. Conventional therapeutic options include covering agents, topical corticosteroids, topical immunomodulators, phototherapy with psolaren ultraviolet A (PUVA) and narrowband ultraviolet B (NBUVB). However, successful repigmentation with these modalities is expected only in half of the patients. This study aimed to compare the efficiency of topical Vitix® gel combined with NB-UVB versus NB-UVB alone in the treatment of vitiligo lesions. Thirty patients with vitiligo were enrolled in this study. All patients had relatively symmetrical lesions and received topical Vitix® gel in combination with NB-UVB on one side and NB-UVB alone on the other side. Data were analyzed using Wilcoxon and Mann-Whitney tests. Twenty-five patients completed the course of study (68% female, age: 32.3 ± 13.5 years). Five patients were excluded due to noncompliance to follow-up. The highest treatment response rate was observed in the upper limb's lesions. However, no statistical difference was observed in patients treated with Vitix® gel combined with NB-UVB versus NB-UVB alone after adjusting for age, sex and lesions' site ($p > 0.05$). Significant additional clinical repigmentation was not observed by adding Vitix® gel to NBUVB therapy in treatment of vitiligo lesions.

Keywords: NB-UVB; Treatment; Vitiligo; Vitix®.

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1 Introduction

Vitiligo is an acquired pigmentary cutaneous disorder resulting in symmetrical white patches with an otherwise normal appearance [1]. This cosmetically important and progressive disease affects 0.5–4% of the world's population with no gender and racial preferences [2].

Several not yet completely known pathogenic factors leading to the loss of functional melanocytes are responsible for this condition through biochemical, immunological, genetic, and oxidative mechanisms [3]. The oxidative stress theory emphasizes the increased levels of hydrogen peroxide (H_2O_2) and decreased amounts of pseudocatalase in the skin and blood cells of affected individuals [4, 5]. Moreover, reduction in epidermal H_2O_2 is associated with the cessation of the disease and more repigmentation [2, 6, 7].

Currently, narrowband ultraviolet B (NBUVB) is considered to be one of the best treatment options in vitiligo. NBUVB (wavelength of 311–313 nm) induces the proliferation and migration of follicular melanocytes via keratinocyte-associated growth factors [8, 9]. The antioxidant effect of a product containing Cucmis melo superoxide dismutase and catalase named Vitix® is thought to be beneficial in the treatment of vitiligo lesions. This study aimed to investigate the possible beneficial effect of Vitix® in combination with NBUVB in comparison with NBUVB alone in patients with vitiligo lesions.

Table 1 The association between type of treatment (NBUVB or NBUVB+ Vitix® gel) and repigmentation score during different months.

Month	Repigmentation Score	Treatment with NBUVB and Vitix® gel	Treatment with NBUVB	Wilcoxon test *p*-value
First Month	< 25%	25 (100)	10	0.432
	26–50%	0	0	
	51–75%	0	0	
	76–90%	0	0	
	91–100%	0	0	
Second Month	< 25%	20 (80)	20 (80)	0.386
	26–50%	5 (20)	5 (20)	
	51–75%	0	0	
	76–90%	0	0	
	91–100%	0	0	
Third Month	< 25%	15 (60)	16 (64)	0.167
	26–50%	8 (32)	5 (20)	
	51–75%	2 (8)	4 (16)	
	76–90%	0	0	
	91–100%	0	0	
Fourth Month	< 25%	10 (40)	10 (40)	0.456
	26–50%	9 (36)	8 (32)	
	51–75%	5 (20)	4 (16)	
	76–90%	1 (4)	3 (12)	
	91–100%	0	0	

2 Methods

2.1 Patients

This prospective, single-center trial study was approved by the institutional review board. Thirty patients with vitiligo lesions were enrolled in this study between January 2018 – January 2020 at the Department of Dermatology, Mashhad University of Medical Sciences. The inclusion criteria were as follows: patients older than 12 years, bilateral symmetrical lesions distributed on limbs, face or body involving more than 10% of the body surface. Subjects with a history of pregnancy, breastfeeding, immunosuppression, hypersensitivity to Vitix® gel, psychologic problems and any other contraindications for phototherapy were excluded from the study. Informed consent was obtained for all the subjects.

2.2 Study Lesions and Intervention

Symmetrically or near-symmetrically distributed pairs of vitiligo lesions were selected in 30 patients for assessment. The patient's body was divided into two halves along the sagittal plane, with the lesions on one side were treated with Vitix® gel combined with NBUVB versus the other side treated with NBUVB alone. The phototherapy device (Waldmann UV 1000 L, Medizintechnik, Schwenningen, Germany) was used to administer the NBUVB treatment. The Vitix® gel was applied 15–30 min before receiving NBUVB phototherapy which was administered 3 times per week on nonconsecutive days for 4 months [10]. Treatment response was visually evaluated monthly by an experienced dermatologist with more than 4 years of experience in treating vitiligo lesions, who was blinded as to which side of the body was applied by the Vitix® gel. Serial photographs were also taken monthly. Repigmentation rate was evaluated using Investigator's Global Assessment (IGA), which is classified into 5 categories as suggested in former studies [11]: 5 (excellent with 91–100% repigmentation rate), 4 (very good with 76–90% repigmentation rate), 3 (good with 51–75% repigmentation rate), 2 (fair with 26–50% repigmentation rate), and 1 (poor with less than 25% repigmentation rate).

2.3 Statistical Analysis

Data were analyzed using SPSS software (version 15.0; SPSS, Inc., Chicago, IL, USA). The normally distributed data were presented as mean ± SD. Wilcoxon and Mann-Whitney tests were used to compare the treatment response score between two treatment groups and

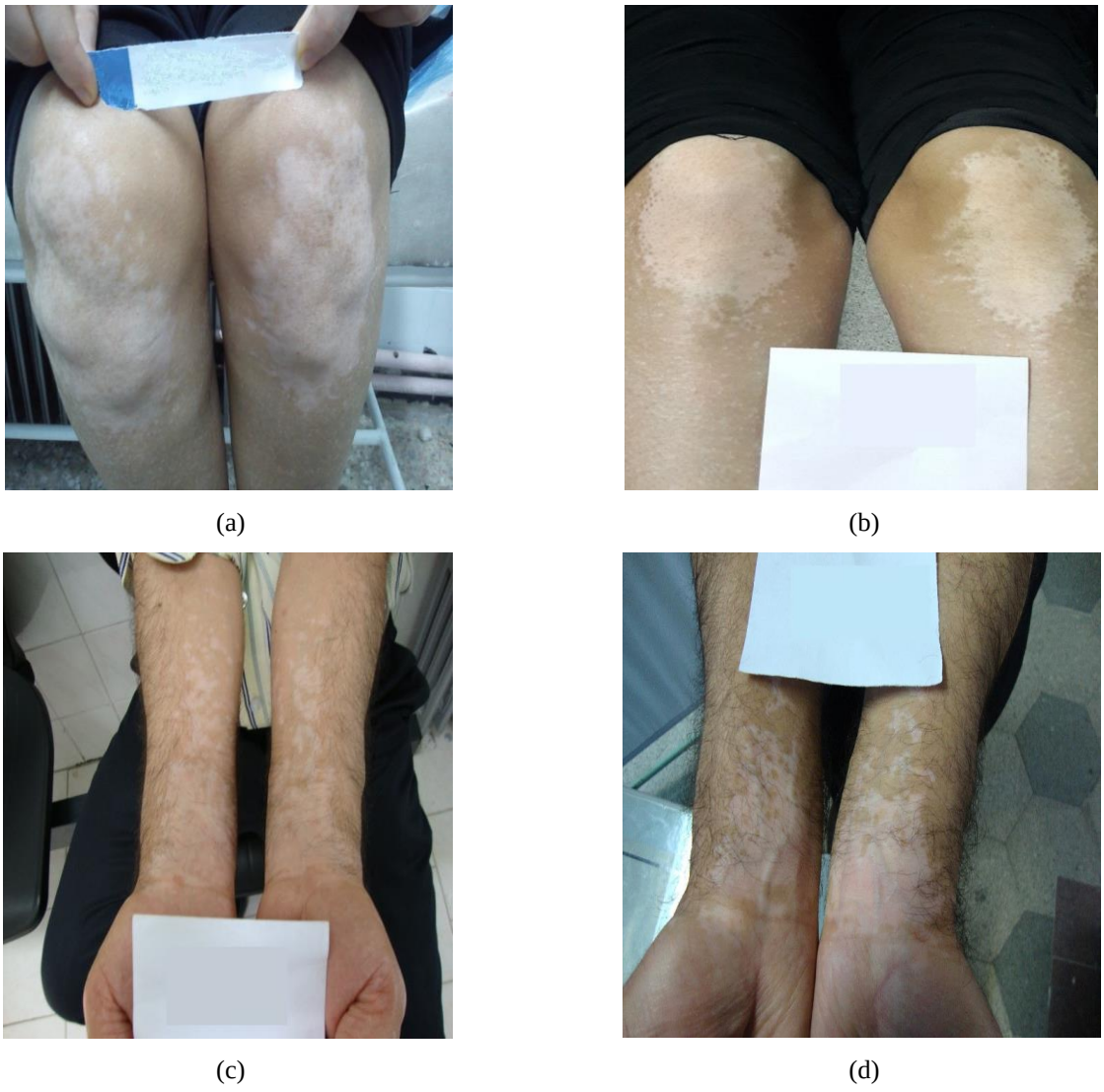
different time intervals. A p-value less than 0.05 was considered statistically significant.

3 Results

Overall, 25 out of 30 patients fulfilled the exam criteria [17 (68%) female, age 32.3 ± 13.5]. Five (16.7%) patients dropped out of the study due to non-compliance for follow-up. The response to NBUVB phototherapy alone and in combination with Vitix® gel did not achieve a statistically significant difference during the different courses of treatment ($p > 0.05$). More details are presented in Table 1. No significant correlation was found between gender, the involved sites and percentage of repigmentation in lesions receiving NBUVB phototherapy and Vitix® gel ($p > 0.05$). At the end of the first month, all patients were classified as score 1 according to the repigmentation classification mentioned above. This score was seen in 78%, 62% and 40% of the individuals in the 2nd, 3rd and 4th months of treatment, respectively. Score 4 (76–90% repigmentation) was only achieved in 8% of the cases at the end of the 4th month following the treatment.

However, we observed a statistically higher response rate in the 3rd ($p = 0.014$) and 4th ($p = 0.028$) months of therapy in all lesions. The response in depigmented patches of the upper extremities was superior to the lesions of lower extremities ($p < 0.05$).

Comparison of repigmentation scores between the 1st and 4th months of the treatment showed a significant therapeutic response in lesions treated in either group ($p = 0.001$). No patients experienced any complications during the course of treatment. Fig. 1 demonstrates pigmentation changes following NBUVB phototherapy with/without Vitix® gel in two patients.



(a) (b)

(c) (d)

Fig. 1 (a) Patient one who received NBUVB and Vitix® gel on the left lower extrimity and NBUVB alone on the right lower extrimity. (b) Patient one after 4 months of treatment. (c) Patient two who received NBUVB and Vitix® gel on the right side and NBUVB alone on the left side. (d) Patient two after 4 months of treatment. No significant improvement was observed between right and left sides after 4 months of treatment. Significant improvement was seen in both patients between 1st and 4th months of treatment.

4 Discussion

Oxidative stress is one of the main mechanisms suggested in the pathogenesis of vitiligo. The level of H_2O_2 which increases both in plasma and skin lesions of the affected individuals is the principal culprit of melanocyte destruction in this theory [12, 13]. Furthermore, reduction of epidermal H_2O_2 might play a role in the repigmentation process in 95% of cases [2, 6, 7]. Catalase converts H_2O_2 to water and oxygen. The lower activity of catalase in leukocytes and melanocytes of vitiligo patients has been reported previously [2, 12, 14, 15]. Lower catalase activity may be associated with H_2O_2 accumulation that may further inhibit catalase activity, destroying melanocytes. Superoxide dismutase (SOD) which induces the conversion of superoxide anions to oxygen and hydrogen peroxide protects cells from the toxic effects of free radicals [16]. There are different reports of SOD activity in patients with vitiligo ranging from normal to higher levels in several studies [17–19]. Therefore, anti-oxidation-based therapies like a formulation containing Cucumis melo superoxide dismutase and catalase (Vitix®) applied with NBUVB might have the potential of inducing repigmentation through enhancement in H_2O_2 catalysis and its subsequent removal from the epidermis [20].

In this study, we aimed to evaluate the added effect of topical Vitix® gel in depigmented patches of vitiligo patients who were simultaneously under treatment with NBUVB phototherapy. Another topical product containing pseudocatalase and calcium in combination with NBUVB was investigated in 33 patients with vitiligo in the Schullreuter study which showed excellent results of full repigmentation in 90% of the face and hand lesions [6]. Kostovic who treated the affected patients with Vitix® gel (twice daily) and NBUVB phototherapy (3 times a week) observed more than 50% repigmentation in 57.9% of the patients [21]. The difference might be due to the applying protocol of the product which was only used on the days that patients received phototherapy and also because of the shorter study period. The study by Sanclemente et al. suggested that topical catalase/superoxide dismutase may be as effective as topical betamethasone 0.05% [22]. A statistically significant difference could not be found in Yuksel study investigating the use of NBUVB alone or combined with Vitix® gel [23]. The efficacy of Vitix® gel in the removal of reactive oxygen spices was assessed by Schullreuter and Rokos *in vivo* and *in vitro* conditions. They reported no pseudocatalase capacity for this preparation [20]. Moreover, in Patel's study, a topical pseudocatalase mousse with a different formulation did not show any significant effect on the vitiligo lesions [24].

This study was subject to some limitations. Not dividing patients into two groups helped us to remove the individual differences, and therefore, there was the same pathogenesis of melanocytic loss in the lesions. However, we faced certain limitations. The patients may have applied the gel on the lesions of both sides of their body to achieve a remission much sooner. Furthermore, the duration of the disease course was not the same in our cases and this might have interfered with the effect of antioxidant treatment as the best results are usually obtained in recent vitiligo lesions.

5 Conclusion

In the current single-center trial, no significant clinical improvement was observed when Vitix® gel was applied in NBUVB in comparison with NBUVB alone. However, our study once again emphasized the high success rate of NBUVB in treatment of vitiligo, while the use of antioxidant products like Vitix® gel remains a controversial issue in the treatment of vitiligo.

Disclosures

The authors declare no competing interests.

Acknowledgments

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References

1. D. J. Gawkrodger, A. D. Ormerod, L. Shaw, I. Mauri-Sole, M. E. Whitton, M. J. Watts, A. V. Anstey, J. Ingham, and K. Young, "Guideline for the diagnosis and management of vitiligo," British Journal of Dermatology 159(5), 1051–1076 (2008).
2. K. U. Schallreuter, J. Moore, J. M.Wood, W. D. Beazley, D. C. Gaze, D. J.Tobin, H. S. Marshall, A. Panske, E. Panzig, and N. A. Hibberts, "In vivo and in vitro evidence for hydrogen peroxide (H_2O_2) accumulation in the epidermis of patients with vitiligo and its successful removal by a UVB-activated pseudocatalase," Journal of Investigative Dermatology Symposium Proceedings 4(1), 91–96 (1999).
3. K. U. Schallreuter, L. R. Paus, P. Bahadoran, M. Picardo, A. Slominski, Y. E. Elassiuty, E. H. Kemp, C. Giachino, J. D. Liu, R. M. Luiten, and T. Lambe, "Vitiligo pathogenesis: autoimmune disease, genetic defect, excessive reactive oxygen species, calcium imbalance, or what else?" Experimental Dermatology 17(2), 139–140 (2008).
4. V. Maresca, M. Roccella, F. Roccella, E. Camera, G. D. Porto, S. Passi, P. Grammatico, and M. Picardo, "Increased sensitivity to peroxidative agents as a possible pathogenic factor of melanocyte damage in vitiligo," Journal of Investigative Dermatology 109(3), 310–313 (1997).

5. S. Hasse, N. C. Gibbons, H. Rokos, L. K. Marles, and K. U. Schallreuter, "Perturbed 6-tetrahydrobiopterin recycling via decreased dihydropteridine reductase in vitiligo: more evidence for H2O2 stress," Journal of Investigative Dermatology 122(2), 307–313 (2004).
6. K. U. Schallreuter, J. M. Wood, K. R. Lemke, and C. Levenig, "Treatment of vitiligo with a topical application of pseudocatalase and calcium in combination with short-term UVB exposure: a case study on 33 patients," Dermatology 190(3), 223–229 (1995).
7. K. U. Schallreuter, J. Moore, S. Behrens-Williams, A. Panske, and M. Harari, "Rapid initiation of repigmentation in vitiligo with Dead Sea climatotherapy in combination with pseudocatalase (PC-KUS)," International Journal of Dermatology 41(8), 482–487 (2002).
8. W. Westerhof, L. Nieuweboer-Krobotova, "Treatment of vitiligo with UV-B radiation vs topical psoralen plus UV-A," Archives of Dermatology 133(12), 1525–1528 (1997).
9. M. L. Dell'Anna, A. Mastrofrancesco, R. Sala, M. Venturini, M. Ottaviani, A. P. Vidolin, G. Leone, P. G. Calzavara, W. Westerhof, and M. Picardo, "Antioxidants and narrow band-UVB in the treatment of vitiligo: a double-blind placebo controlled trial," Clinical and Experimental Dermatology 32(6), 631–636 (2007).
10. T. F. Mohammad, M. Al-Jamal, I. H. Hamzavi, J. E. Harris, G. Leone, R. Cabrera, H. W. Lim, A. G. Pandya, and S. M. Esmat, "The Vitiligo Working Group recommendations for narrowband ultraviolet B light phototherapy treatment of vitiligo," Journal of the American Academy of Dermatology 76(5), 879–888 (2017).
11. S. Singh, S. Khandpur, V. K. Sharma, and M. Ramam, "Comparison of efficacy and side-effect profile of oral PUVA vs. oral PUVA sol in the treatment of vitiligo: a 36-week prospective study," Journal of the European Academy of Dermatology and Venereology 27(11), 1344–1351 (2013).
12. O. Arican, E. B. Kurutas, "Oxidative stress in the blood of patients with active localized vitiligo," Acta Dermatovenerologica Alpina Panonica Et Adriatica 17(1), 12–16 (2008).
13. P. H. Proctor, E. S. Reynolds, "Free radicals and disease in man," Physiological Chemistry and Physics and Medical NMR 16(3), 175–195 (1984).
14. M. L. Dell'Anna, S. Urbanelli, A. Mastrofrancesco, E. Camera, P. Iacovelli, G. Leone, P. Manini, M. D'ischia, and M. Picardo, "Alterations of mitochondria in peripheral blood mononuclear cells of vitiligo patients," Pigment Cell Research 16(5), 553–559 (2003).
15. P. T. Pugliese, "The skin's antioxidant systems," Dermatology Nursing 10(6), 401–416 (1998).
16. N. Saha, M. A. Ahmed, A. I. Wasfi, and E. L. Munshid, "Distribution of serum proteins, red cell enzymes and haemoglobins in vitiligo," Human Heredity 32(1), 46–48 (1982).
17. M. L. Dell'Anna, V. Maresca, S. Briganti, E. Camera, M. Picardo, and M. Falchi, "Mitochondrial impairment in peripheral blood mononuclear cells during the active phase of vitiligo," Journal of Investigative Dermatology 117(4), 908–913 (2001).
18. E. Hazneci, A. B. Karabulut, C. Ozturk, K. Batcioglu, G. Dogan, S. Karaca, and M. Esrefoglu, "A comparative study of superoxide dismutase, catalase, and glutathione peroxidase activities and nitrate levels in vitiligo patients," International Journal of Dermatology 44(8), 636–640 (2005).
19. E. M. Shajil, S. Chatterjee, D. Agrawal, T. Bagchi, and R. Begum, "Vitiligo: pathomechanisms and genetic polymorphism of susceptible genes," Indian Journal of Experimental Biology 44(7), 526–539 (2006).
20. K. U. Schallreuter, H. Rokos, "Vitix®– a new treatment for vitiligo?" International Journal of Dermatology 44(11), 969–970 (2005).
21. K. Kostovic, Z. Pastar, A. Pasic, and R. Eeovic, "Treatment of vitiligo with narrow-band UVB and topical gel containing catalase and superoxide dismutase," Acta Dermatovenerologica Croatica 15(1), 10–14 (2007).
22. G. Sanclemente, J. J. Garcia, J. J. Zuleta, C. Diehl, C. Correa, and R. Falabella, "A double-blind, randomized trial of 0.05% betamethasone vs. topical catalase/dismutase superoxide in vitiligo," Journal of the European Academy of Dermatology and Venereology 22(11), 1359–1364 (2008).
23. E. P. Yuksel, F. Aydin, N. Senturk, T. Canturk, and A. Y. Turanli, "Comparison of the efficacy of narrow band ultraviolet B and narrow band ultraviolet B plus topical catalase-superoxide dismutase treatment in vitiligo patients," European Journal of Dermatology 19(4), 341–344 (2009).
24. D. C. Patel, A. V. Evans, and J. L. Hawk, "Topical pseudocatalase mousse and narrowband UVB phototherapy is not effective for vitiligo: an open, single-centre study," Clinical and Experimental Dermatology 27(8), 641–644 (2002).