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Comparative results of non-segment vitiligo therapy with phototherapy combined with local application of cream containing complex of micro elements, antioxidants based on glauconite and activated siliceous water

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Relevance of the problem. Vitiligo is the most frequent pigmentation disorder that strongly affects the quality of life of patients. The prevalence of the disease is 0.5–1% worldwide, although it reaches up to 10% in various ethnic groups and populations [10]. The problem of vitiligo therapy does not lose its relevance, despite the wide variety of proposed methods. In order to stimulate melanogenesis medications such as copper, iron, placenta extract, dopegit, liposomal preparations with antioxidants, silymarin, melaginin, vitamin D, immunosuppressant's, simvastatin, ginko-biloba, and others were tested both systemically and locally, as well as in combination with physical methods (PUVA, phototherapy, in including infrared radiation, laser therapy), reflexology, oxygen-ozone therapy, PRP therapy, dermabrasion [1,2,3,6,9]. Generally recognized as the most effective therapy for vitiligo is NB-UVB therapy [6]. In particular, UVB rays stimulate the production of IL-1, IL-10, and TNF-alpha, suppress local and systemic immune responses via the synthesis of pyrimidine dimers in the DNA of skin cells, isomerization of urocaninic acid, thus inhibiting lymphoproliferation. One of the important effects of narrowband UV is considered to be stimulation of the release of regulators and inducers of melanogenesis, in other words fibroblast growth factor and endothelin -1 from keratinocytes [6,7], as well as an increase in vitamin D metabolites due to the induction of synthesis of cholecalciferol from dihydrocholesterol in the skin. The narrow-band UFO method is considered to be the safest and most effective. It can be used for unstable vitiligo, has no contraindications for people with hepatic diseases, but there are some drawbacks [9]. The method is contraindicated when taking certain medications (thiazide diuretics, tetracycline antibiotics, antidepressants), in cases of CVD, SLE, cutaneous porphyria, autoimmune bullous dermatosis. Of the side effects, the authors most often note itching, erythema, photoaging, xerosis, recurrence of herpes infection, carcinogenesis, as the absence of potentially active melanocytes increases the possible risk of malignant neoplasms of the skin. The positive effect of treatment is observed in 67% - 90% of cases, but it is difficult to achieve complete cure of vitiligo. The popular expression: "Vitiligo is a dermatosis with infinite possibilities, but without any promises" describes the success of vitiligo therapy in the best possible way.

To increase the effectiveness of vitiligo treatment combined therapy is used. In particular, GCS, immunosuppressant's, donors of growth factors, the effectiveness of which varies widely and remains a subject for discussion. In this regard, the objective of our work was to analyze the results of treatment of vitiligo with NB-UVB and excimer light, both in monotherapy and in combination with "Provitilin" cream.

Materials and methods. We examined 128 patients with non-segmental vitiligo aged 28.1±1.3 years old (66 men and 62 women). The disease duration was 42.6±3.6 months, while 52 (41%) people had the disease onset less than 1 year ago. Generalized vitiligo was observed in 92 (71.9%), mixed vitiligo in 8 (6.2%), acrofacial vitiligo in 24 (18.7%), and universal in 4 (3.1%) patients. Progressive (unstable) vitiligo was noted in 85 (66.4%), while stable vitiligo in 43 (33.6%) patients. The stage of progression of the disease was determined by the presence of the certain signs, providing differentiation of a stable disease from a progressive one. Signs of ongoing depigmentation include: 1) fuzzy borders of foci or the appearance of new spotty depigmented areas, 2) the Kebner phenomenon, 3) "trichrome" staining in foci, 4) signs of inflammation, hyperemia and itching in foci [7]. The severity of the disease (spread, degree of depigmentation + quality of life) was assessed according to M-VES scale proposed by us. In M-VES scale we propose to summarize the scores on 2 scales: VES [8] and QLAS for a full assessment of the severity of vitiligo.

Mono-phototherapy was performed in 69 patients, including NB-UVB for 50 patients and excimer light in 19 patients. At the same time, all patients who received NB-UVB had unstable vitiligo, as a result of which they were also prescribed minipulsterapy [4]. Patients who received excimer light had stable vitiligo. In our study we also tested Provitilin cream applied locally. We applied mono-phototherapy in combination with the use of locally applied Provitilin cream. Totally 59 people received it, of which 35 patients had unstable vitiligo. They received NB-UVB+Provitilin, while 24 had stable vitiligo and had phototherapy with Excimer light+Provitilin.

NB-UVB phototherapy on NEOLUX Series 3 unit ("Daavlin" USA) was performed 3-5 times a week. Treatment was started by the definition of the minimum erythema dose or the dose was chosen according to the skin prototype, where with the 1st skin prototype treatment was started with a dose of 0,5 mJ/cm^2, with the 2nd, 3rd, and 4th prototypes with a dose of 0,1-0,2 mJ/cm^2, followed by an increase, in case of absence of erythema by 0.05 J/cm^2 depending on the reaction of the skin to UV. The cabin design ensures even distribution of UV rays (UVA, UVB 311 nm) over the entire surface of the body, with protection of eyes and genitals. Excilite μ 308nm excimer light unit (DEKA, Italy) was used to treat patients with vitiligo. The procedures were performed 3 times a week. Treatment was started after definition of the minimum photoerythemic dose (MPD) on the skin beyond the lesions. The result of irradiation was evaluated in 48 hours, after which the dose was either increased or maintained. When depigmented foci were located on the face, the initial dose was 0.03–0.05 J/cm^2, while on the trunk, upper and lower extremities 0,07–0,15 J/cm^2, and on the distal extremities and in the area of large joints (hands, feet, elbows, knees) 0,15–0,2 J/cm^2. The increase of a single dose depended on the dynamics of the process and the tolerability to treatment.

Local therapy included the application of cream "Provitilin", developed by RSSPMCDV and C on the basis of the natural mineral glauconite and silicon taken from the deposits in Uzbekistan. The composition of the cream Provitilin is as follows: lanolin, glauconite, activated siliceous water, silicon, vaseline, black cumin oil, zinc,

vitamin E and A. Glauconite is a clay mineral of alumosilicate class, characterized by a rich mineral composition due to which it has an absorption and cation-exchange property and the ability to selectively absorb cations and long-living radioisotopes. It also participates in oxidative processes, stimulates local immunity and helps to suppress the growth of opportunistic microorganisms on skin (Staphylococcus spp. E.coli, candida spp.). Enriched siliceous water (52 mg/l) and glauconite contain 9.6% of K2 O: 4.4 (potassium oxide), 3.5% of Na2 O: 0 (sodium oxide) 22.6% of Al2 O3 : 5.6 (aluminum oxide), 28.4% of Fe2 O3: 6.3 (iron oxide), 8.7A% of FeO: 0.8 (iron oxide), 4.7 % of MgO: 2.4 (magnesium oxide), and 53% of SiO2: 47.2 , as well as more than twenty trace elements (Pb, Mg, Sr, Cu, Zn, Se, J, Mn, Cd, Zn, Fe, Cs, and also REE elements La, Ce, Pr and Nd). The composition of trace elements, siliceous acid, vitamins A, E, selenium, zinc in the composition of Provitilin provides its effects such as moisturizing, antioxidant, anti-inflammatory, and regenerating. The drug improves metabolism and strengthens the local immunity of the skin, participates in the synthesis of melanin and repigmentation in lesions. It also preserves the barrier properties of skin (pH – 7,7). Method of application is to apply the cream Provitilin in a thin layer on the skin 2 times a day. The duration of application depended on the state of the process. If necessary, we used the cream Provitilin for a long time, up to 1 year.

The effectiveness of the therapy was assessed in 1 year of follow-up. The result was evaluated according to Kawakami recommendations 2011 [5], focusing on the regression of M-VES scores (our modification of VES scale), which, as we proved earlier, correlated with VES and QLAS.

In general, when evaluating the effectiveness of the therapy we followed the following gradation: combination of excellent and good results according to Kawakami is an effective treatment; combination of unsatisfactory results according to Kawakami and cases of vitiligo progression is a bad result; satisfactory results testify low effectiveness of the therapy.

Results. Assessment of the severity of vitiligo before treatment showed that the average M-VES score taking into account the quality of life, was 34,0±6,6 for generalized and 18,8±4,3 for acrofacial vitiligo. With universal vitiligo, the initial M-VES score was 28,3 ± 3,3, with mixed one was 12,5 ±1,3.

Assessment of the condition of patients after treatment showed that when using NB-UVB in 50 patients with unstable vitiligo stabilization was achieved in 46 cases (92%), 4 patients (8%) had vitiligo progression, in 34% and 32% of the cases excellent and good result was found one year after treatment. Two patients had no positive dynamics despite the treatment, and that was unsatisfactory result. With the progression of the disease we noted signs of scalloped and tricolor vitiligo, and increase in the lesion area, increase in the number of foci and increase of M-VES score in 3 patients. One patient had signs of Kebner phenomenon and a slight regression of M-VES. In all 4 cases there was a high resistance to therapy. In 2 patients with unsatisfactory result the repigmentation was insignificant, although it was observed around single hair follicles. There was reduction in the lesion area. However, the overall M-VES score regressed by

less than 10% due to high LV, which served the basis for stating unsatisfactory result (Table 1).

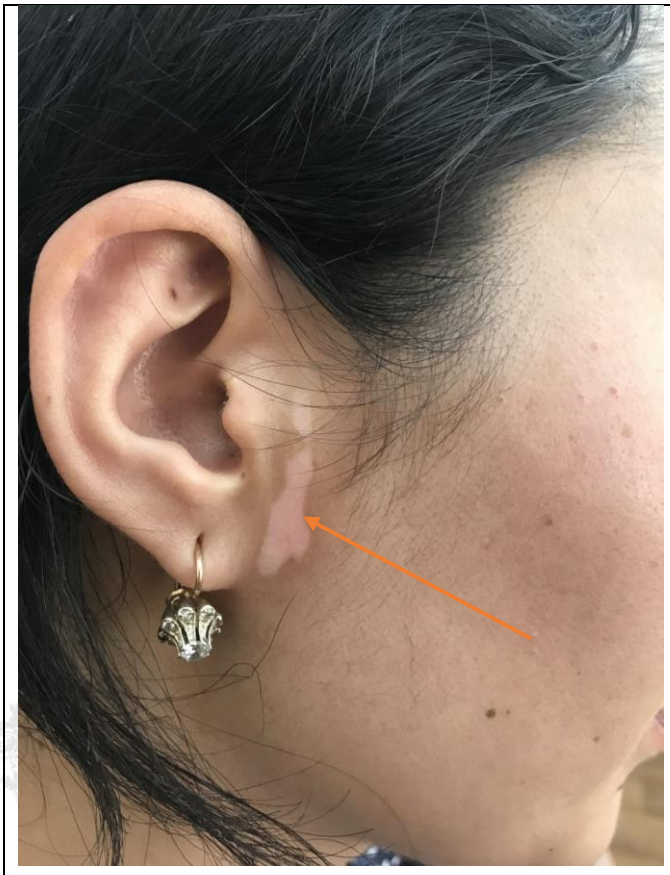
Table 1

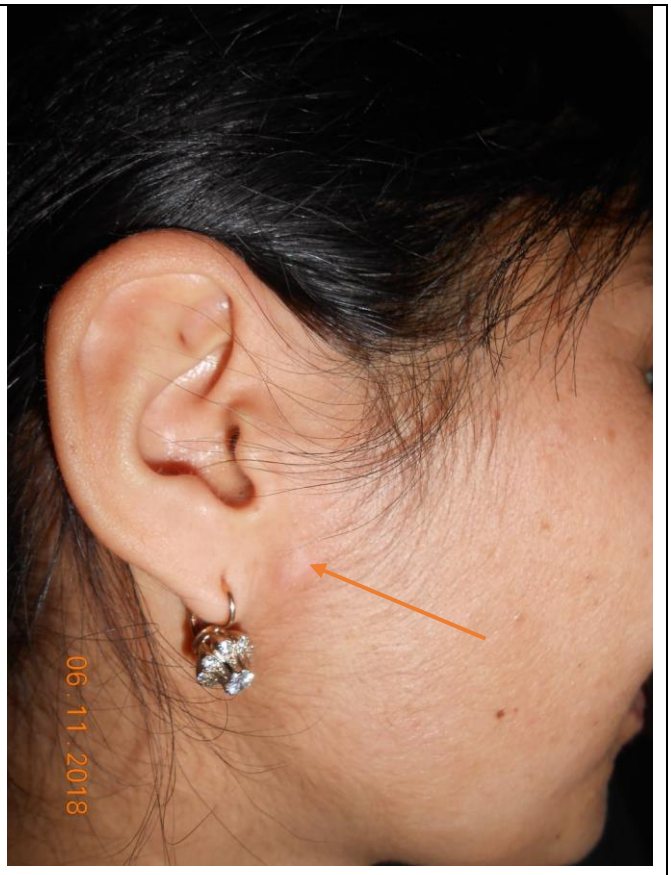
Assessment of vitiligo mono wave phototherapy result

Therapy result in one year	Criterion – decrease of M-VES score (%)	NB-UVB		Excimer light	
		n=50	%	n=19	%
Excellent	50%	17	34.0	10**	52.6
Good	25-50%	16	32.0	7	36.8
Satisfactory	10-25%	11	22.0	2**	10.5
Non-satisfactory	0-10%	2	4.0	0**	0.0
Deterioration	Signs of unstable vitiligo and/or increase/no dynamics in M-VES score	4*	6.0	0**	0.0
TOTAL		50	100	19	100

**- *statistically significant in comparison with NB-UVB with p<0,05.*

The results of mono-phototherapy showed that excimer light gave the best effect with excellent and good results noted in 52,6% and 36,8% of the cases, respectively, which we associated with the initially stable course of vitiligo, as well as with the mechanism of action of excimer light with 308nm wavelength. The high efficiency of excimer light is explained by its inducing effect on apoptosis of cytotoxic CD8+ T-lymphocytes. In lesions excimer light suppresses activity of T-lymphocytes, stops inflammation, and activates peripheral and perifollicular melanocytes, which provides skin repigmentation and suppression of melanocyte death. The authors consider the following advantages of excimer light: early response to therapy, possibility of using high doses in initial therapy, low risk of side effects, short duration of treatment when the effect is achieved in 30-60 procedures, compared with UFOs, which requires up to 200 irradiations [1]. Overall effectiveness of excimer light according to various authors account for 75% of complete repigmentation [8]. After excimer light therapy we managed to achieve almost complete repigmentation of foci and improvement of the quality of life of the patients (Fig.1).





Before treatment M-VES=18,6	After treatment M-VES =4,4

Fig.1 Excellent result of treatment with excimer light.

The addition of Provitilin cream to phototherapy made it possible to improve the results of treatment, since we did not detect any deterioration in the condition in any case. At the same time, the number of good and excellent results was 22.9% and 51.4% in the subgroup that received NB-UVB+Provitilin, and 41.7% and 50.0% in the subgroup that received Excimer light+ Provitilin (Table 2).

Table 2.

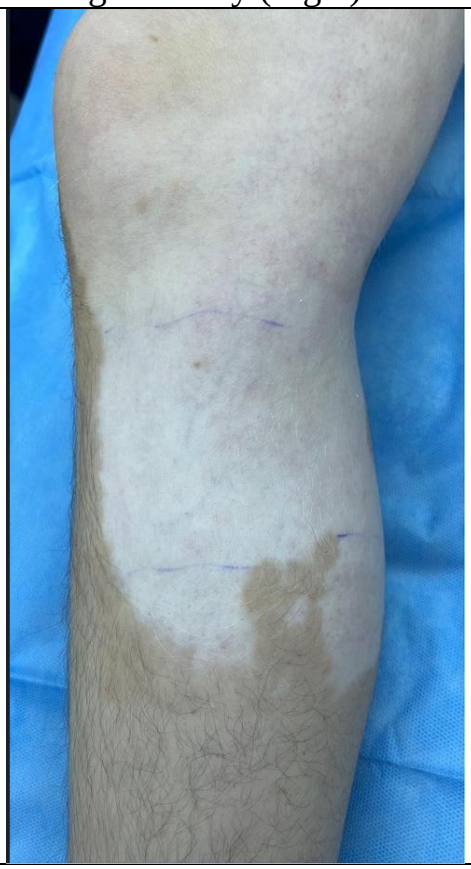
Results of vitiligo combined therapy

Therapy result in one year	Decrease of M-VES score (%)	NB-UVB+ Provitilin, n=35		Excimer light +Provitilin, n=24	
		n	%	n	%
Excellent	50%	18	51.4	12	50.0
Good	25-50%	8	22.9	10*	41.7
Satisfactory	10-25%	7	20.0	2*	8.3

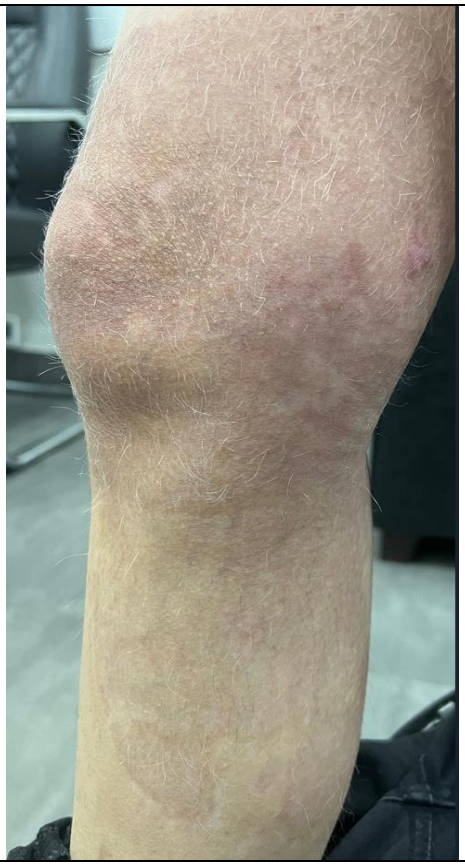
Non-satisfactory	0-10%	2	5.7	0*	0.0
Deterioration	Signs of unstable vitiligo and/or increase/without dynamics M-VES score	0	0,0	0	0.0
TOTAL		35	100	24	100.0

**- statistically significant in comparison with NB-UVB +Provitilin with p<0,05.*

In NB-UVB+ Provitilin subgroup there was no progression of vitiligo. There we managed to achieve stabilization in 100% of the cases. At the same time, in 2 patients with unstable vitiligo the result was unsatisfactory because the repigmentation was insignificant and regression of lesion area was partial, while the quality of life of these patients was equal to 15-17 according to QLAS. Excellent result in the Excimer light subgroup+ Provitilin was characterized by almost complete repigmentation of lesions. Good result in NB-UVB+ Provitilin subgroup was characterized by stabilization of vitiligo, repigmentation, reduction of the lesion area and complete elimination of some foci, while regression of M-VES score was observed in 25-50%, and the quality of life improved significantly (Fig.2).

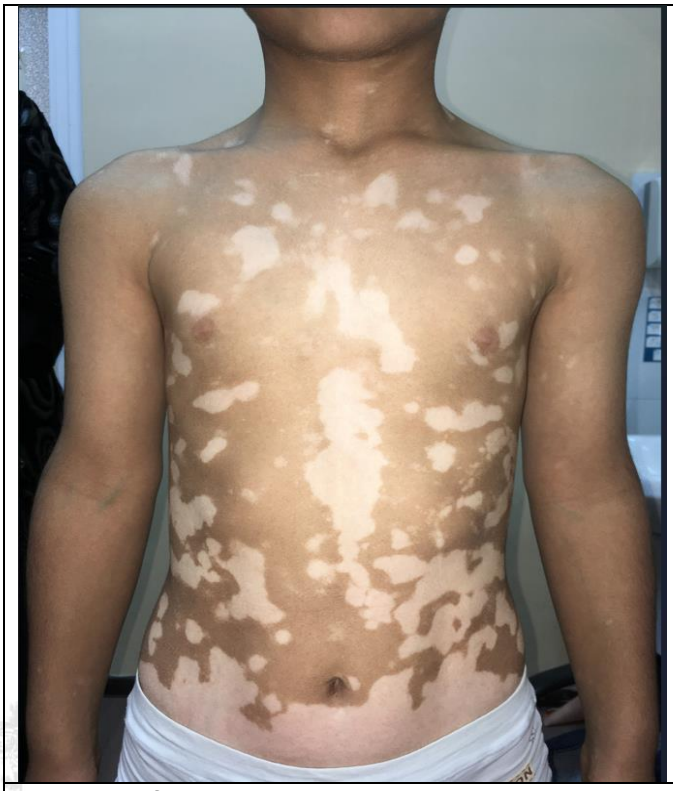


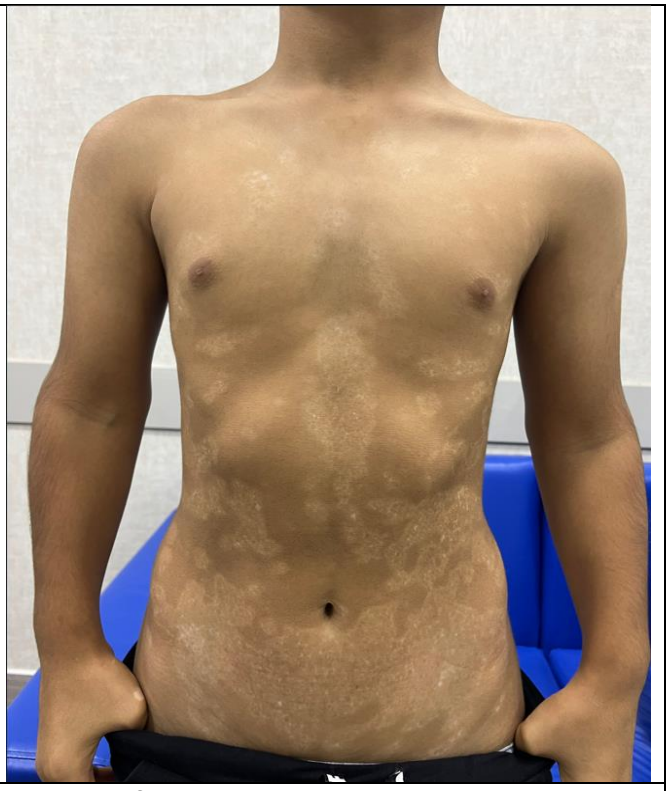
Before treatment M-VES=14,5



After treatment M-VES=2,2

Excellent result in the subgroup Excimer light +Provitilin





Before treatment M-VES=18,3	After treatment M-VES=10,2
Good treatment outcome in the subgroup NB-UVB+ Provitilin.	

Figure 2. Results of vitiligo combined therapy.

Generally, efficacy of the therapy in NB-UVB+Provitilin was equal to 74,3%, while in Excimer light +Provitilin subgroup it was 91,7% (Fig.3).

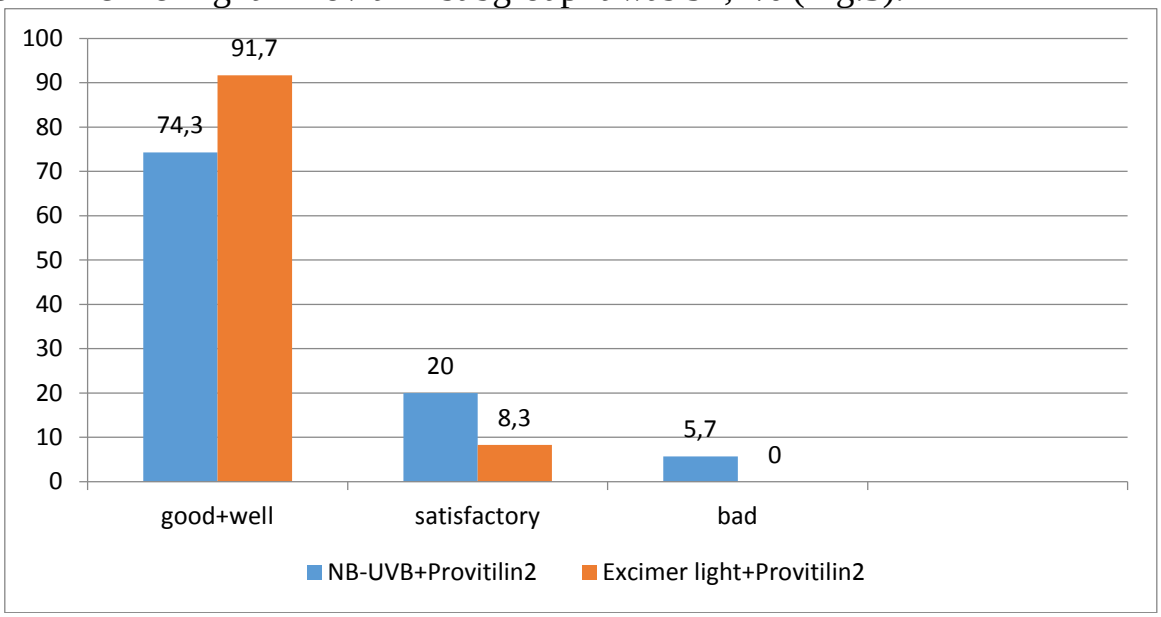


Figure 3. Efficacy of mono-phototherapy combined with Provitilin.

From these data it can be seen that addition of Provitilin improved the results of mono-phototherapy from 72% to 81,4%, helped to achieve complete stabilization of vitiligo in 100% of cases, and reduced the number of bad results from 9% to 3,4%, i.e. 3 times. At the same time, the efficiency of excimer light in combination with Provitilin was significantly higher than NB-UVB ($p<0.05$), amounting to 91,7% versus 74,3%.

Our results clearly demonstrate that local exposure to Provitilin containing trace elements and siliceous compounds contributes to the effectiveness of phototherapy, possibly due to exposure to zinc and selenium containing enzymes of SOD and heme-containing catalase.

CONCLUSIONS

1. The overall effectiveness of mono-phototherapy was the best when using excimer light in 89,5%, with NB-UVB in 66%; poor treatment results were observed in 12% of the cases with NB-UVB.

2. The addition of Provitilin provided improvement of the results of monophototherapy from 72% to 81,4%, helped to achieve complete stabilization of vitiligo in 100% of cases, and to reduce the number of bad results from 12% to 3,4%, i.e. 4 times.

3. The effectiveness of excimer light is significantly greater than NB-UVB ($p<0,05$), amounting to 91,7% in combination with Provitilin therapy, versus 74,3% for NB-UVB+Provitilin.

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