

Long-term Follow-up and Correlated Factors of Vitiligo Following Autologous Epidermal Transplantation

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Autologous epidermal transplantation is an easy, safe, and effective option for the treatment of stable vitiligo. To evaluate the long-term outcome and correlated factors, 1 to 5 years of follow-up of 310 vitiligo patients treated with autologous epidermal transplantation was carried out by questionnaires, telephone calls, and clinical examinations. Some correlated factors including time, gender, age, location, Köbner phenomenon, and exposure to narrowband UVB (NB-UVB) have been considered and analyzed. Twenty-four recipient areas with 1266 sheets were observed and classified with 4 degrees (excellent, good, fair, and poor). Among them, 1099 sheets (86.81%) were classified with excellent to fair repigmentation (excellent repigmentation, 815 sheets [64.38%]). We also found hyperpigmentation in 76 patients (24.52%), and hypopigmentation in 66 patients (21.29%) on the transplanted areas. Köbner phenomenon could be observed in 25 patients (8.06%), which implies difficulty for normal repigmentation. Forty-two patients developed new lesions after the operation. The operation usually can get best results within 2 years and on areas with less movement such as the arm and leg. The treatment plus NB-UVB exposure are recommended for getting better repigmentation. Gender and age seem to have no relationship with the effect. After long-term follow-up, we concluded that autologous epidermal transplantation is an effective method for the treatment of vitiligo and the results can be mainly affected by the transplant location.

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Vitiligo is caused by disrupted epidermal melanization. Its etiology has been undetermined and its pathogenesis has been incompletely understood.¹ Various treatment options have resulted in varying degrees of success.² The treatment choice depends on the stability of the disease and the different anatomical locations affected.^{3,4} Autologous epidermal transplantation was first applied to vitiligo by Falabella⁵ in 1971. After 20 years it became widely used in depigmented diseases such as vitiligo, piebaldism, and halo nevi. It is a safe and effective method to treat vitiligo and the long-term effect is good, especially in localized segmental vitiligo with small lesions.⁶ Some problems are still unclear, such as whether the efficacy would be stable after the surgery and whether new lesions would develop after treatment. It is important to investigate the long-term results and factors that might affect the outcome of epidermal transplants. To form a basis for guidance in the selection of patients who will benefit most from this treatment, we have performed autologous epidermal transplantation in more than 1000 patients every year; we follow up on their therapeutic efficacy through questionnaires, telephone calls, and clinical examinations.

We report the efficacy of 310 patients with overall data who received autologous epidermal transplantation between August 2002 and January 2007. We evaluated the long-term effect and correlated factors such as transplantation time, gender, age, location, Köbner phenomenon, and exposure to narrowband UVB (NB-UVB) after transplant.

Materials and Methods

Patients—A total of 310 unrelated Han Chinese patients (161 males and 149 females) with stable vitiligo were recruited consecutively as outpatients at the Department of Dermatology, The Third People's Hospital of Hangzhou, China. The patients ranged in age from 6 to 68 years with a mean age (standard deviation [SD]) of 26.69 (11.71) years.

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There were 62 patients with vitiligo vulgaris, 123 patients with segmental vitiligo, 98 patients with focal vitiligo, and 27 patients with universal vitiligo. The duration of vitiligo ranged from 8 months to 20 years, with a mean (SD) of 6.25 (2.56) years. The characteristics of the patients are shown in Table 1. Patients with clinically stable lesions for at least 6 months were selected for treatment. The patients had been treated in the past with potent topical steroids and/or photochemotherapy for periods ranging from 8 months to 3 years with no significant response. None of the patients had any keloidal or bleeding tendencies.

Transplantation⁷ Methods and Evaluation Standard⁶—Seventy-five percent alcohol was used to sterilize the depigmented recipient areas and the donor areas. Suction cups were applied on the shaved inner aspect of the abdominal area over normal-looking skin as well as the lesions. Enough negative pressure (−300 mm Hg) was allowed for approximately 1 to 2 hours while the patient was sitting in a comfortable position until blisters evolved underneath the transparent cups. A small pair of scissors was then used to deroof the blister on a recipient glass slide and a nipper was used to grind until punctate hemorrhage occurred. The harvested layers consisted of only epithelium with no dermal components. Good homeostasis was ensured on the recipient dermabraded areas and the grafts were then applied smoothly, affirming direct contact between the graft and recipient site. Styptic plaster was applied smoothly on the grafts and then removed after 1 week. The sheets were applied to the recipient areas or abscission from the recipient areas. Narrowband UVB phototherapy

was initiated immediately after removing the final dressing. There were 2 to 3 sessions of UVB phototherapy weekly. The usual initial dose of UVB was 0.4 J/cm² for Fitzpatrick skin type III and 0.5 J/cm² for Fitzpatrick skin type IV. The subsequent treatment dose was increased by 20% every session until moderate asymptomatic erythema was observed. The patients received the therapy twice weekly for 1 or 2 months. The outcome was assessed by questionnaires, telephone follow-up, and clinical examinations 3 months later.

Repigmentation was graded as excellent with 95% to 100% pigmentation of the treated area, good with 65% to 94%, fair with 25% to 64%, and poor with 0% to 24%.⁶

Statistical Analysis—The Kruskal-Wallis test was used to examine the relationship between the percentage of repigmentation and another variable. We used the χ^2 test to analyze the difference between the 2 groups. The level of $P < .05$ was accepted as statistically significant.

Results

Effect Associated With Transplantation Time—Twenty-four recipient areas with 1266 sheets were observed and classified with 4 degrees (excellent, good, fair, poor). Among them, 815 sheets were classified as excellent repigmentation, 167 sheets as good repigmentation, 117 sheets as fair repigmentation, and 167 sheets as poor repigmentation. The total response rate for excellent to fair repigmentation was 86.81%. Results over 5 years are shown in Table 2. The response rate (including only excellent to fair responses) of 1 to 2 years was slightly higher than 2 to 5 years. The difference between them was

Table 1.

Characteristics of Patients Treated With Autologous Epidermal Transplantation

Leukoderma Type	No. of Patients		Age at Transplant, y	
	Men	Women	Range	Mean
Vitiligo vulgaris (scattered)	39	23	12–47	21.43
Segmental vitiligo	60	63	6–57	26.67
Focal vitiligo	46	52	7–68	23.45
Universal vitiligo	16	11	8–57	28.52

significant ($\chi^2=6.053$; $P=.014$). The effect decreased with time after transplantation.

Effect Associated With Gender and Age—Statistical analyses with the Kruskal-Wallis test in combination with graphical summaries showed a weak tendency toward better results in women (87.01%) than men (86.60%). However, this difference did not reach statistical significance ($P=.83$). We found that younger patients seemed to respond worse to the treatment, which may be attributed to the total number of sheets, which was far less in children than in adults (children, 161 [response rate, 83.23%]; adults, 1105 [response rate, 87.33%]).

Effect Associated With Localization—Twenty-four recipient areas with 1266 sheets were observed. To get larger groups and be able to handle the statistical comparison better, we pooled the 24 different locations into the following 8 groups: face, neck, hands and feet, trunk, arms and legs, waist and abdomen, scalp, and scrotum. The arms and legs group excluded the knee and elbow areas. We expected the anatomical locations within the pairs to be comparable when evaluating the outcome of treatments. When the Kruskal-Wallis test was used to compare the outcome of different locations, it was evident that the arms/legs and scalp groups had the highest outcome, while the face and waist/abdomen groups were generally the most difficult areas to repigment. The results are shown in Table 3.

The difference between the 8 groups was evident ($\chi^2=24.24$; $P=0.002$).

Hypopigmentation on Transplanted Area and Köbner Phenomenon on the Donor Site—Sixty-six patients had hypopigmentation wholly or partly in the transplanted area. Thirty-one patients did not show repigmentation when the styptic plaster was removed. One patient experienced hypopigmentation 15 days after surgery, 2 after 1 month, 7 after 2 months, and 25 after 6 months. Among the 66 patients, Köbner phenomenon occurred in 11 patients at the donor sites. There were 14 patients who had Köbner phenomenon out of 244 patients who successfully repigmented. The rate of Köbner phenomenon of hypopigmentation transplanted areas (16.67%) was higher than repigmentation transplanted areas (5.74%). A statistically significant difference ($\chi^2=8.369$; $P=.004$) regarding Köbner phenomenon was found between hypopigmented areas and repigmented areas, which showed that Köbner phenomenon occurred more easily in the hypopigmented areas.

Relationship Between Re-Depigmentation and New Lesions—Forty-two patients developed new lesions. Among them, 9 patients had both new lesions and hypopigmentation on the transplanted sites and 8 had new lesions on other sites. Twenty-five patients had new lesions on the transplanted sites. A significant correlation was found between the

Table 2.

Long-term Results Obtained With Autologous Epidermal Transplantation

Year	No. of Patients	Repigmentation of Sheets, ^a n				Total	Response Rate, % ^b
		Excellent	Good	Fair	Poor		
1	137	310	86	63	53	512	89.65
2	108	264	39	42	55	400	86.25
3	51	167	33	12	43	255	83.14
4	11	34	4	0	16	54	70.37
5	3	40	5	0	0	45	100
Total	310	815	167	117	167	1266	86.81

^aRepigmentation grading: excellent=95%–100%; good=65%–94%; fair=25%–64%; poor=0%–24%.

^bFor excellent to fair repigmentation.

hypopigmentation and new lesions on other sites ($\chi^2=15.34$; $P=.001$), which showed that the patients were temporarily stable.

Transplantation Plus NB-UVB Exposure—Seventy-seven patients received NB-UVB phototherapy after the surgery. They received 10 or more treatments, some of them being exposed more than 20 treatments. Repigmentation appeared in the white rim in 72 patients; of these patients, 27 received phototherapy. Statistical significance was found between exposure to NB-UVB and color expand ($\chi^2=8.052$; $P=.005$), which suggests that epidermal melanocytes or melanin activated by NB-UVB can migrate or transfer to hair follicles.

Side Effects—No scars or indurations were seen in any of the operated areas at follow-up. On the recipient site, hyperpigmentation was observed on transplanted areas in 76 patients (24.52%). Two patients had infection and 1 case had milium postoperatively. On the donor site, 34 patients had hyperpigmentation and Köbner phenomenon occurred in 25 patients.

Comment

Epidermal grafting was first applied to treat leukoderma by Falabella⁵ and has now become a widely used, effective surgical method in treating vitiligo and other depigmented diseases. We have performed autologous epidermal transplantation in patients with vitiligo since 1998. Many patients have experienced good effects, while others have not. In our study we found that the outcome of the surgery decreased after 2 years. Gupta and Kumar⁴ reported that postgraft repigmentation would be permanent if it persists for at least 6 months. We found that some patients re-depigmented or had new lesions on other sites, which may be caused by the activity of the disease.

Gupta and Kumar⁴ also reported that the transplant effect was better in patients younger than 20 years. In our study, we found no difference in the effects on patients younger than 14 years versus those older than 14 years. There was no statistical difference between outcome and gender or age, which was similar to other reports.³ This finding may be due to patients receiving a different number of transplanted sheets depending on their age.

Table 3.

Outcome to Autologous Epidermal Transplantation

Transplant Groups	Repigmentation of Sheets, ^a no. of cases/no. of sheets					Outcome, %
	Excellent	Good	Fair	Poor	Total	
Face	90/300	9/50	12/55	28/93	139/498	81.33
Neck	56/201	6/60	2/11	10/36	74/308	88.31
Hands/feet	26/98	6/32	6/51	2/11	40/192	94.27
Trunk	21/123	4/13	0/0	2/11	27/147	92.51
Arms/legs	10/46	1/3	0/0	0/0	11/49	100
Waist/abdomen	8/37	3/7	0/0	4/16	15/60	73.33
Scalp	2/8	1/2	0/0	0/0	3/10	100
Scrotum	1/2	0/0	0/0	0/0	1/2	100
Total	214/815	30/167	20/117	46/167	310/1266	86.81

^aRepigmentation grading: excellent=95%–100%; good=65%–94%; fair=25%–64%; poor=0%–24%.

There was a statistically significant difference among different anatomic sites ($P=.002$). The less activated sites (eg, arms and legs) had better results than the more activated sites (eg, face, waist/abdomen), which caused the sheets to fasten distinctly. The outcome of some hairy or butyrous areas, such as the eyebrow and nose, was not good. New hair growth and greasiness may make the sheet hard to fix. The result was the same with other reports.⁸ Some leukotrichia also could get repigmentation by this method. We reported 3 lesions on the scalp with 100% repigmentation, which may be caused by the grinding itself.

Eleven patients developed Köbner phenomenon at the donor sites and were more prone to develop depigmentation on the transplanted sites. The Köbner phenomenon on the donor sites, depigmentation on transplanted sites, and new lesions on other sites all suggested the progression of the disease. Mulekar et al⁸ regarded Köbner phenomenon as new lesions of vitiligo, but we found a significant correlation between Köbner phenomenon and depigmentation ($\chi^2=8.369$; $P=.004$). Although Kim and Kang⁹ reported that this method could get positive results even in treating progressing vitiligo, most reports they discussed suggested that the surgical method would not be recommended in progressing disease. Selecting stable vitiligo patients is necessary before grafting is performed.

Awad et al⁷ reported that epidermal grafting for vitiligo requires UVA phototherapy to increase the success rate. Some of our cases required NB-UVB, while others did not. We also found that some patients who failed after surgery gained repigmentation when exposed to NB-UVB, which presumably was a result of the treatment. Narrowband UVB treatment was helpful in spreading pigmentation to the hypopigmented rim. Long-term outcome of the therapy still needs to be observed.

It is obvious that hyperpigmentation is the main side effect, which may make the cosmetology unacceptable. The color of some patients' transplanted sites was the same as normal skin and there was no hyperpigmentation on the donor site. The variance of repigmentation correlated with different abilities of melanosome generation, transportation, redistribution, and degradation.¹⁰ Many factors surrounding the epidermal cells will regulate the pigmentation of the skin through the autocrine and paracrine network. Different patients could have variance in the number of inflammatory factors before accepting the transplantation, which will stimulate a different number of melanocytes, resulting in diverse hyperpigmentation. In addition, we observed that most patients' hyperpigmentation began thinning when

accompanied with the time postsurgery; the color of the transplanted skin would be darker than the normal skin and it would thin with time. We also found that some patients experienced more hyperpigmentation after a 5-year follow-up, but the mechanism was unclear.

Conclusion

Our study, coinciding with the literature, showed that autologous suction blister epidermal transplantation was an easily performed and highly effective method in treating vitiligo, especially on focal and segmental vitiligo with small lesions. The outcome of the therapy had a close relationship with the stability of the disease. The repigmentation appeared to be better when followed by NB-UVB treatment, but the problem of hyperpigmentation still needs to be investigated.

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