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Autologous Hair Follicle Transplantation Combined with NB-UVB Phototherapy for Stable Pubic Vitiligo: A Randomized Controlled Trial

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Abstract: The challenge in the management of pubic vitiligo lies in the sensitive nature of the area and the relatively lower efficacy of the existing management approaches. This study aimed to evaluate the efficacy and safety of autologous hair follicle transplantation combined with narrow-band ultraviolet B (NB-UVB) phototherapy for stable pubic vitiligo. Sixty-eight patients were randomly assigned (1:1) to either a combination treatment (hair follicle transplantation followed by NB-UVB phototherapy) or to the control group with only NB-UVB phototherapy for 24 weeks. The key outcome measure was the repigmentation area, as estimated using the Vitiligo Area Scoring Index. The histopathological examination was also carried out on a sample of 40 patients. The combination therapy group demonstrated significantly higher repigmentation rates (68.4% versus 42.3%, $p < 0.001$). The effective response rate (≥50% repigmentation) was 80.6% versus 43.3% ($p = 0.003$). The onset of repigmentation occurred earlier in the combination group (4.2 versus 7.6 weeks, $p < 0.001$), where there was perifollicular repigmentation in 83.9% of patients. Histopathological examination revealed that there was a greater increase in the density of melanocytes (10.4 versus 4.8 cells/mm, $p < 0.001$) and a greater reduction in the density of CD8+ T cells in the combination group. Patient satisfaction was significantly higher among the combination group (87.1% versus 53.3%, $p = 0.004$). Tolerance of these two treatments is excellent, and there were no serious adverse events. This combination of hair follicle transplantation and NB-UVB appears to have a synergistic effect, as it offers an intact melanocyte reservoir and an immune microenvironment, and it may be a promising treatment approach for pubic vitiligo.

Keywords: Vitiligo; Hair Follicle Transplantation; Narrow-Band Ultraviolet B Phototherapy; Melanocyte Repopulation; Immune Privilege

1. Introduction

Vitiligo is an acquired depigmentary condition that involves a gradual reduction of melanocytes within the epidermis, resulting in a typical presentation of well-defined white patches and macules [1]. The estimated global lifetime prevalence of vitiligo is 0.36%, accounting for 28.5 million people [2]. The pathophysiology of vitiligo is explained by complex interactions between genetic predisposition, oxidative injury, and autoimmune disease [3]. The loss of melanocytes is mostly caused by CD8+ cytotoxic T cells and JAK-STAT activation from interferon-γ release [4]. CXCL9 and CXCL10 induce the infiltration of melanocyte-targeted T cells within the epidermis, maintaining the immune-mediated destruction of melanocytes [5]. The infiltration of CD8+ Tissue-resident memory T cells occurs within the depigmented areas, thereby impairing repigmentation [6]. There is considerable psychological suffering in patients with vitiligo, with depression and anxiety being the most common comorbidities [7].

Genital vitiligo represents a special situation during the treatment of vitiligo, taking into account the sensitivity of the area and the fact that it represents mucocutaneous vitiligo [8]. Genital involvement might occur in up to 20% of patients suffering from vitiligo, and the loss of pigmentation seen in the genital area often has a great influence on the health-related quality of life, especially the sexual function aspect [9]. Conventional treatments for this condition, such as topical corticosteroids and calcineurin inhibitors, often yield suboptimal results for genital manifestations, while surgical treatments are limited by issues of scarring due to the naturally mobile region of this body part [10].

The hair follicle is the main reservoir that contains melanocytes necessary for repigmentation in vitiligo patients [11]. Immature pigment cells migrate from melanocyte stem cells that are situated at the bulge region and then proceed with terminal differentiation [12]. The melanocytes display relative resistance against the autoimmune cell damage because of the immune-protected attributes provided by the environment [13]. The epidermal melanocytes are selectively targeted and eliminated in human vitiligo, whereas the follicular melanocytes remain relatively intact since the melanocytes within the epidermal-dermal junction are immunoprivileged sites [14]. Upon an appropriate stimulus, the quiescent melanocytes proliferate, migrate centripetally, and differentiate into functional melanocytes capable of repopulating the depigmented epidermis [15].

Narrow-band ultraviolet B (NB-UVB) phototherapy has been playing a leading role as a therapeutic option for patients with generalized vitiligo. This acts through a dual mechanism of immunomodulation and stimulation of melanocytes [16]. This can act by suppressing the production of pro-inflammatory cytokines and stimulating quiescent melanocyte stem cells localized in the hair follicles [17]. In patients with generalized vitiligo, 74.2% of patients reached at least 25% repigmentation of the lesions at six months [18]. There is a long way to go regarding the response rate of mucocutaneous sites, such as the pubic area.

Current treatment modalities for genital vitiligo are still inadequate despite the increased understanding of the pathophysiology. The study of hair follicle transplantation and NB-UVB phototherapy as individual treatments has already been explored, although there are no randomized controlled trials testing the concept of their combined treatment specifically directed towards pubic vitiligo [19]. On a theoretical level, combination therapy is supported by strong evidence, since hair follicle transplantation provides an intact melanocyte reservoir with inherent immune privilege properties, and, in turn, NB-UVB phototherapy creates a favorable immunological microenvironment and melanocyte activation in the transplanted follicles.

This is a randomized controlled trial aiming to investigate the efficacy and safety of autologous hair follicle transplantation together with NB-UVB phototherapy in the treatment of stable pubic vitiligo, and to analyze the clinical, histopathological, and immunological indices to understand the mechanisms involving the reacquisition of immune privilege and the repopulation of melanocytes. Based on a comprehensive evaluation of the response to the treatment method and an in-depth examination of the changes at the cellular and molecular levels in the affected skin, the study aimed to develop an optimal treatment protocol for this complicated case. The findings of the study can provide imperative support in understanding the underlying processes in melanocyte regeneration in the depigmented skin.

2. Materials and Methods

2.1. Study Design and Participants

This clinical trial was conducted at the University of Cyberjaya, Malaysia, from January 2022 through to December 2024. The study was approved by the Research Ethics Committee of the University of Cyberjaya (Approval Number: UoC-REC-2022-0153). This trial fully followed the guiding principles set out by the Helsinki Declaration and was registered in the National Medical Research Register, Malaysia (Registration Number: NMRR-22-01796-IIR). Informed consent was sought from all participants before recruitment after they were fully informed about the study objectives, procedures, and possible risks and benefits.

Inclusion criteria: (1) aged 18–60 years; (2) clinically diagnosed as having non-segmental vitiligo with lesions confined to the pubic area, with confirmed chalk-white fluorescence upon Wood's lamp examination; (3) stable disease course, as evidenced by the absence of new lesions and the lack of expansion of any existing lesions for at least 12 months before study entry; (4) depigmented lesions in the pubic area measuring between 1 cm^2 and 100 cm^2; (5) presence of terminal hair follicles within or adjacent to the affected region as assessed by dermoscopy.

Exclusion criteria were as follows: (1) segmental vitiligo or mixed-type vitiligo; (2) active disease showing signs of confetti-like depigmentation or positive Koebner phenomenon; (3) any topical or systemic treatment for vitiligo within the preceding 3 months or phototherapy within 6 months; (4) history of keloidal scarring tendency; (5) presence of active skin infections in the treatment area; (6) known photosensitivity disorders; (7) concurrent autoimmune conditions requiring systemic immunosuppressive therapy; (8) pregnant or lactating women; (9) severe hepatic or renal dysfunction; (10) psychiatric disorders that could impair compliance.

Qualified participants were randomized 1:1 into two groups: combination therapy (autologous hair follicle transplantation plus subsequent NB-UVB phototherapy) or NB-UVB phototherapy alone. A computer-generated randomization sequence with block sizes of four and six was used to ensure balanced allocation throughout recruitment. Sequentially numbered opaque sealed envelopes, generated by an independent statistician with no involvement in enrollment or treatment administration, ensured allocation concealment. Owing to the nature of the surgical intervention, blinding of participants and treating physicians was not feasible; therefore, the study was conducted as an open-label trial. However, to minimize assessment bias, outcome assessors evaluating clinical repigmentation and the statistician performing data analysis remained blinded to treatment allocation. The study flow diagram for participant screening and enrollment is presented in **Figure 1**.

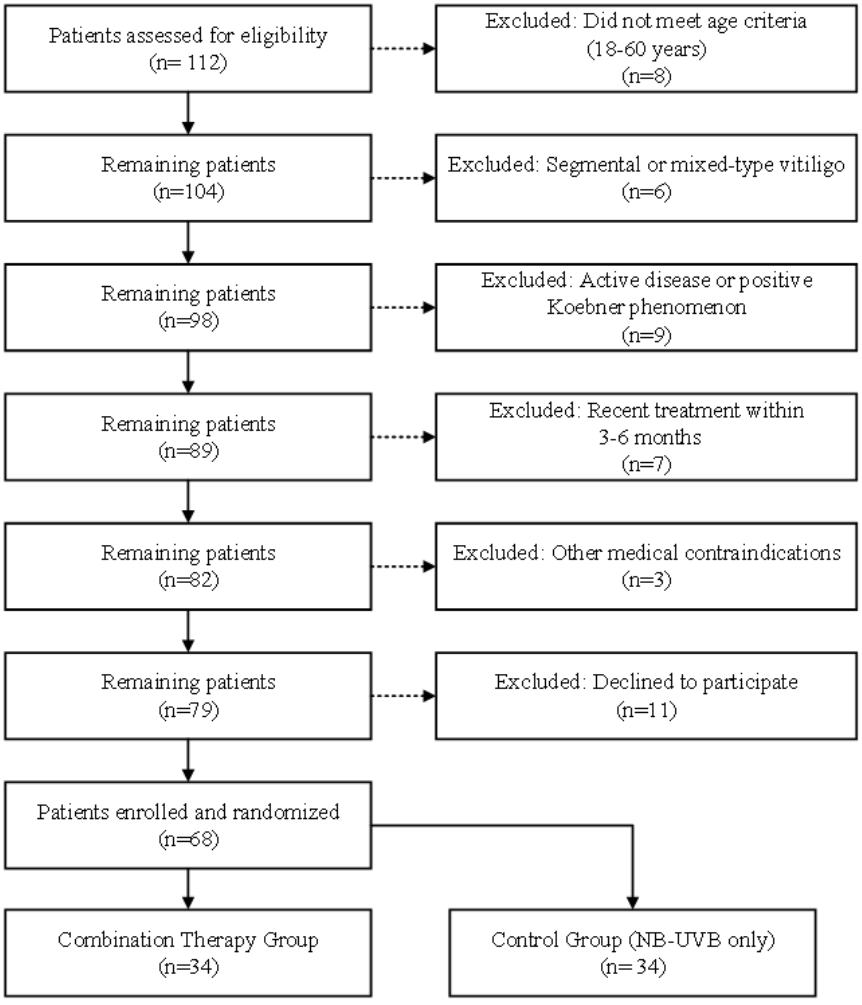

Figure 1. Flow diagram of participant screening and enrollment.

2.2. Intervention Procedures

Participants in the combination therapy group received autologous hair follicle transplantation followed by NB-UVB phototherapy, while those in the control group received NB-UVB phototherapy alone. All procedures were

performed by experienced dermatologists with expertise in surgical and phototherapy treatments for vitiligo.

Local infiltration anesthesia with 2% lidocaine solution was administered prior to hair follicle harvesting with 1:100,000 epinephrine. The occipital scalp was selected as the donor site due to its abundant melanocyte reservoir and resistance to androgenetic alopecia. The donor area was trimmed to approximately 1 mm and disinfected with povidone-iodine solution. The FUE technique was employed for follicular unit harvesting with a 0.8 mm diameter sharp punch. The extraction depth was carefully controlled to preserve the integrity of the hair bulb and the surrounding outer root sheath containing melanocyte stem cells. A total of 20 to 40 follicular units per square centimeter of recipient area were harvested, depending on the lesion size. The recipient site was prepared by creating microincisions in the depigmented pubic area using a 19-gauge needle at an angle of 30 to 45 degrees to mimic natural hair growth direction. Extracted follicular units were immediately immersed in sterile normal saline at 4 °C to maintain cell viability and were implanted within 30 min of extraction using fine-tipped forceps. After transplantation the treated area was covered with sterile non-adhesive gauze, and patients were instructed to avoid washing or rubbing the area for 72 h.

The combination therapy group began NB-UVB phototherapy on day 14 post-transplant to allow for wound healing and follicular engraftment, while the control group began immediately following randomization. Phototherapy was administered using a Waldmann UV 7001K cabin with TL-01 fluorescent lamps emitting radiation at 311 to 312 nm. The initial dose was determined based on Fitzpatrick skin type: 200 mJ/cm^2 for types III-IV and 150 mJ/cm^2 for type II. Dose escalation was guided by erythema response according to a modified minimal erythema dose protocol, with subsequent doses increased by 10% to 20% per session if no erythema was observed. In cases of mild asymptomatic erythema, the dose was maintained at the previous level. Treatment was suspended in cases of painful erythema or blistering until resolution and resumed at a reduced dose. Phototherapy treatment was administered three times a week, with at least 24 h between each treatment, and it continued for a period of 24 weeks. The cumulative dose of treatment was restricted to 100 J/cm^2 and the actual cumulative dose of each patient is also recorded. No treatment of vitiligo, whether topically and/or systemically, is allowed during the study.

2.3. Outcome Measures and Safety Assessment

Clinical evaluations were carried out at baseline and at the end of weeks 4, 8, 12, 16, 20, and 24. Digital pictures of the treatment area were taken using a Canon EOS 80D camera with a ring flash, under standardized lighting conditions, at each assessment.

The key endpoint was the rate of repigmentation at week 24, measured using the Vitiligo Area Scoring Index (VASI) [20]. VASI was determined by multiplying the percentage of body involvement by vitiligo and the extent of depigmentation at each site. Repigmentation percentage was calculated as: (baseline VASI − follow-up VASI)/baseline VASI × 100%. Responses were graded as excellent (≥75%), good (50–74%), moderate (25–49%), or poor (<25% repigmentation).

Secondary outcomes included the time to onset of repigmentation, which was the time from the start of the treatment until the appearance of the first perifollicular pigmentation, as confirmed by two independent observers via dermoscopy and documented with photographs. Repigmentation patterns were classified as perifollicular, marginal, diffuse, or mixed. Patient satisfaction at week 24 was measured on a 5-point Likert scale (very dissatisfied to very satisfied). Quality of life was evaluated using the Dermatology Life Quality Index (DLQI) at baseline and week 24, with scores ranging from 0 to 30 and higher values indicating greater impairment [21].

Safety monitoring was performed throughout the trial. Adverse events were documented at each visit and categorized as treatment-related or unrelated according to investigator's assessment. For hair follicle transplantation the following complications were assessed: donor site pain and bleeding and infection and scarring. Donor site pain was managed with oral acetaminophen as needed. For NB-UVB phototherapy adverse events included erythema and pruritus and xerosis and blistering and hyperpigmentation of perilesional skin. Pruritus and xerosis were managed with topical emollients. Adverse event severity was graded as mild, moderate, or severe based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

2.4. Histopathological and Immunological Analysis

Histological assessments were performed in a subgroup of 40 participants (20 per group), consisting of the first 20 consecutive patients in each group who provided additional informed consent for skin biopsies, to minimize

selection bias. Skin biopsies of 3 mm diameter were obtained from the lesional area at baseline and week 24 under local anesthesia. Specimens were fixed in 10% neutral buffered formalin, paraffin-embedded, and sectioned at 4 μm thickness for hematoxylin-eosin staining and immunohistochemical analysis.

Melanocyte density was determined by Melan-A immunohistochemical staining. Following deparaffinization, heat-mediated antigen retrieval was performed using citrate buffer (pH 6.0). Sections were blocked and incubated overnight at 4 °C with mouse anti-human Melan-A monoclonal antibody, followed by horseradish peroxidase-conjugated secondary antibody and diaminobenzidine visualization. Melanocyte density was quantified as Melan-A-positive cells per millimeter of basement membrane. CD8+ T cell infiltration was assessed using a mouse anti-human CD8 monoclonal antibody following the identical protocol. CD8+ cells were counted in five randomly selected high-power fields (400× magnification) per section. Two independent pathologists blinded to treatment allocation performed all histological evaluations, with interobserver agreement assessed using Cohen's kappa coefficient.

2.5. Statistical Analysis

Statistical analyses were conducted using SPSS 26.0 and GraphPad Prism 9.0. Continuous variables were presented as mean ± standard deviation or median with interquartile range based on distribution normality assessed by the Shapiro-Wilk test; categorical variables were reported as frequencies and percentages. Between-group comparisons of baseline characteristics utilized an independent samples *t*-test or Mann-Whitney U test for continuous data and chi-square or Fisher's exact test for categorical data. The rate of repigmentation was compared between groups by using an independent samples *t*-test, and the response to treatment was compared by chi-squared tests. The changes in VASI and DLQI scores from baseline to 24 weeks were compared by paired *t*-tests or signed-rank tests. The results of histological variables, including melanocytes and CD8+ T cells, were compared by the Mann-Whitney U test. The rate of adverse events was compared by Fisher's exact tests. All statistical analyses used two-tailed tests with statistical significance at $p < 0.05$.

3. Results

3.1. Participant Flow and Baseline Characteristics

From January 2022 to December 2024, a total of 112 patients with pubic vitiligo were screened for the study. Forty-four patients were excluded: 30 were not eligible, while 11 refused to participate and 3 had medical contraindications. A total of 68 patients were then randomly assigned to the combination therapy group (n = 34) and the control group (n = 34). In the combination therapy group, 31 participants completed the 24-week treatment course, with 3 discontinuations (relocation, n = 1; personal reasons, n = 1; lost to follow-up, n = 1). In the control group, 30 participants completed the study, with 4 discontinuations (relocation, n = 1; non-compliance, n = 2; consent withdrawal, n = 1). The overall completion rate was 89.7%, with no significant between-group difference (91.2% vs. 88.2%, $p = 0.692$). Efficacy analyses were performed on the per-protocol population (n = 61). With the low and balanced dropout rate among groups, a per-protocol analysis could be considered appropriate to determine the effectiveness of the treatment.

Table 1 describes the baseline demographic and clinical characteristics. The mean age in the combination therapy group and the control group was 35.8 ± 10.2 and 34.6 ± 9.8, respectively. Female participants were 52.9% in the combination therapy group and 55.9% in the control group. Mean disease duration was 6.2 ± 3.8 years versus 5.8 ± 4.1 years, and mean lesion area was 18.4 ± 12.6 cm^2 versus 17.2 ± 11.8 cm^2. Baseline VASI scores were comparable (2.8 ± 1.4 vs. 2.6 ± 1.3). Most patients had Fitzpatrick skin types III to IV (85.3% and 82.4%, respectively). There were no statistically significant differences in all the baseline factors among the groups, signifying successful randomization (all $p > 0.05$).

3.2. Clinical Repigmentation Outcomes

The clinical results of repigmentation at week 24 are shown in **Table 2**. The combination group showed a significantly greater degree of repigmentation compared with the control group, with means of 68.4% ± 18.6% versus 42.3 ± 21.4% ($p < 0.001$). The rate of excellent repigmentation (≥75%) was 48.4% with combination vs. 16.7% with control ($p = 0.008$), with 32.3% and 26.7% having a good response (50–74%), respectively. The rate of

successful repigmentation (≥50%) was substantially greater with the combination (80.6% vs. 43.3%, $p = 0.003$).

Table 1. Baseline demographic and clinical characteristics of participants.

Characteristic	Combination Therapy Group (n = 34)	Control Group (n = 34)	*p*-Value
Age (years), mean ± SD	35.8 ± 10.2	34.6 ± 9.8	0.618
Sex, n (%)			0.804
Male	16 (47.1)	15 (44.1)	
Female	18 (52.9)	19 (55.9)	
BMI (kg/m^2), mean ± SD	23.4 ± 3.2	23.8 ± 3.5	0.624
Disease duration (years), mean ± SD	6.2 ± 3.8	5.8 ± 4.1	0.673
Lesion area (cm^2), mean ± SD	18.4 ± 12.6	17.2 ± 11.8	0.684
Baseline VASI score, mean ± SD	2.8 ± 1.4	2.6 ± 1.3	0.541
Baseline DLQI score, mean ± SD	12.4 ± 5.6	11.8 ± 5.2	0.647
Fitzpatrick skin type, n (%)			0.756
Type II	2 (5.9)	3 (8.8)	
Type III	14 (41.2)	13 (38.2)	
Type IV	15 (44.1)	15 (44.1)	
Type V	3 (8.8)	3 (8.8)	
Previous treatment history, n (%)			0.621
Topical corticosteroids	22 (64.7)	20 (58.8)	
Topical calcineurin inhibitors	18 (52.9)	16 (47.1)	
Phototherapy	8 (23.5)	10 (29.4)	
Family history of vitiligo, n (%)	6 (17.6)	5 (14.7)	0.743
Comorbid autoimmune disease, n (%)	4 (11.8)	3 (8.8)	0.690

Note: SD: standard deviation; BMI: body mass index; VASI: Vitiligo Area Scoring Index; DLQI: Dermatology Life Quality Index.

Table 2. Clinical repigmentation outcomes at week 24.

Outcome	Combination Therapy Group (n = 31)	Control Group (n = 30)	*p*-Value
Repigmentation rate (%), mean ± SD	68.4 ± 18.6	42.3 ± 21.4	<0.001
Treatment response, n (%)			0.002
Excellent (≥75%)	15 (48.4)	5 (16.7)	
Good (50–74%)	10 (32.3)	8 (26.7)	
Moderate (25–49%)	4 (12.9)	10 (33.3)	
Poor (<25%)	2 (6.5)	7 (23.3)	
Effective response rate (≥50%), n (%)	25 (80.6)	13 (43.3)	0.003
Onset time (weeks), mean ± SD	4.2 ± 1.8	7.6 ± 2.4	<0.001
Pattern of repigmentation, n (%)			0.002
Perifollicular	26 (83.9)	14 (46.7)	
Marginal	3 (9.7)	11 (36.7)	
Diffuse	1 (3.2)	3 (10.0)	
Mixed	1 (3.2)	2 (6.7)	
DLQI score change, mean ± SD	−8.2 ± 3.4	−4.6 ± 2.8	<0.001
Patient satisfaction, n (%)			0.004
Very satisfied	17 (54.8)	6 (20.0)	
Satisfied	10 (32.3)	10 (33.3)	
Neutral	3 (9.7)	9 (30.0)	
Dissatisfied	1 (3.2)	4 (13.3)	
Very dissatisfied	0 (0)	1 (3.3)	

Note: SD: standard deviation; DLQI: Dermatology Life Quality Index.

The time to first apparent repigmentation was shorter in the combination treatment group, with a mean of 4.2 ± 1.8 weeks compared to 7.6 ± 2.4 weeks for the control group ($p < 0.001$). The pattern of repigmentation also showed a difference between the two groups, with perifollicular repigmentation occurring in 83.9% of the combination treatment group compared to 46.7% of the control group ($p = 0.002$). Marginal repigmentation was more common in the control group (36.7% vs. 9.7%, $p = 0.014$). The combination therapy group also showed significantly greater improvement in quality of life with a mean DLQI score reduction of 8.2 ± 3.4 points compared with 4.6 ± 2.8 points in the control group ($p < 0.001$). Patient satisfaction rates were higher in the combination therapy group, with 87.1% of participants reporting satisfied or very satisfied compared with 53.3% in the control group ($p = 0.004$). The 24-week treatment course showed variations in VASI scores, categories of treatment response, repigmentation distribution, and satisfaction levels as represented in **Figure 2**.

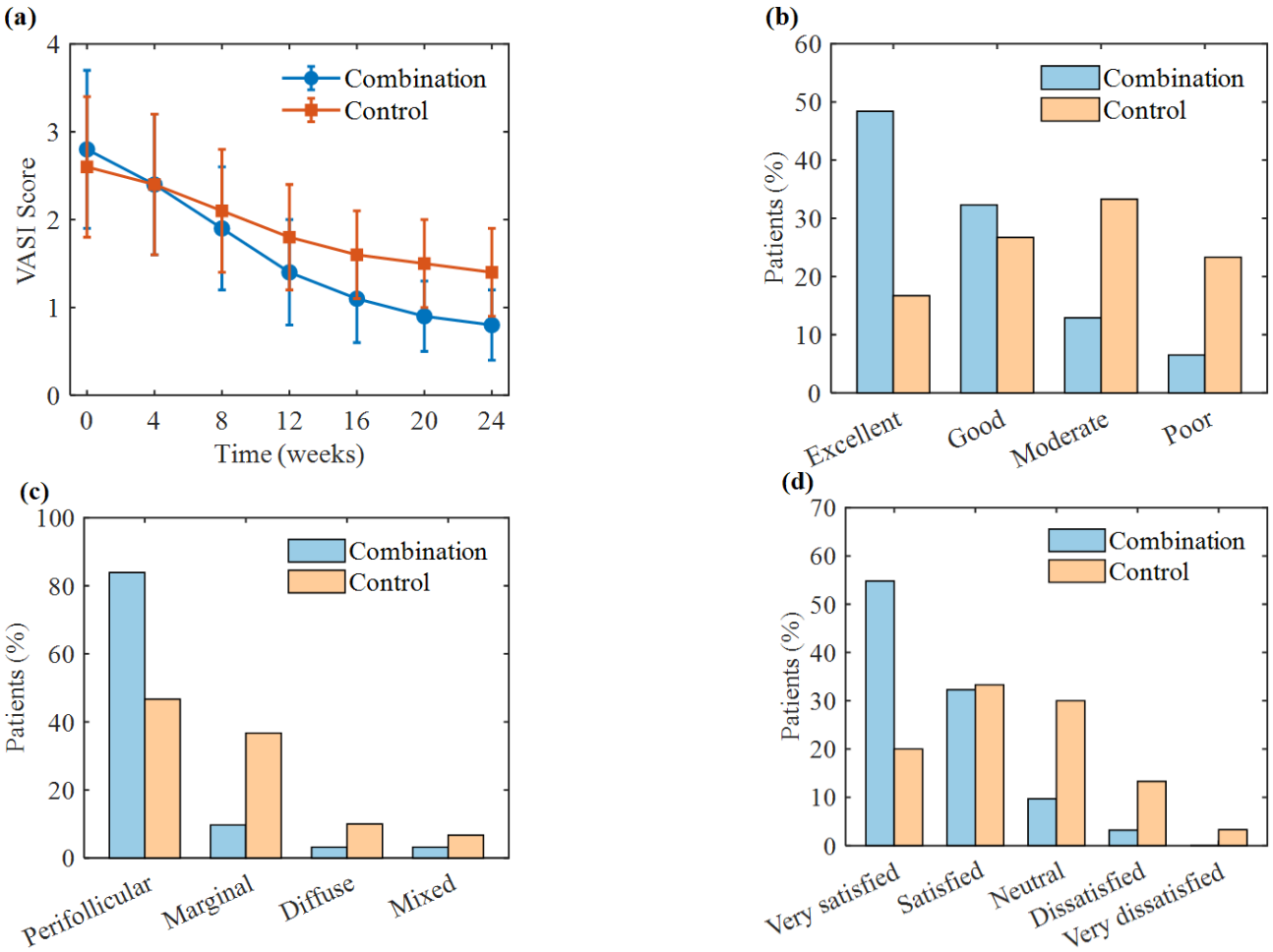

Figure 2. Clinical repigmentation outcomes. (**a**) Dynamic changes in VASI scores over the 24-week treatment period; (**b**) Treatment response categories at week 24; (**c**) Patterns of repigmentation; (**d**) Patient satisfaction.

3.3. Histological and Immunological Findings

Histopathologic examination was also performed in a subset of 40 patients (20 per group) who had provided separate consent for skin biopsies at baseline and week 24. All biopsy specimens were adequate for immunohistochemical evaluation and were independently assessed by two blinded dermatopathologists with excellent interobserver agreement. The histopathological findings are summarized in **Table 3** and illustrated in **Figure 3**.

At baseline, melanocyte density as determined by Melan-A immunohistochemistry was comparable between the two groups (2.4 ± 0.6 vs. 2.6 ± 0.7 cells/mm basement membrane, $p = 0.624$), confirming the marked reduction of functional melanocytes in the lesional epidermis characteristic of vitiligo. At week 24, the combination therapy group demonstrated significantly higher melanocyte density compared with the control group (12.8 ± 2.2 vs. 7.4 ± 1.8 cells/mm, $p < 0.001$). The mean increase in melanocyte density was 10.4 ± 2.0 cells/mm in the combination therapy group versus 4.8 ± 1.6 cells/mm in the control group ($p < 0.001$). Histological examination of the repigmented areas of the combination therapy group demonstrated that there were evenly spaced melanocytes lining the basal layer of the epidermis, along with developed dendritic processes that stretched towards the suprabasal layers, suggestive of active transfer of melanin to the surrounding keratinocytes. Melanocytes in the control group were sparsely and irregularly placed, with fewer dendritic processes.

The presence of CD8+ T cell infiltration in both the perilesional dermis and the lesional dermis was examined. The initial number of CD8+ T cells had similarities between the two groups of subjects (8.6 ± 1.8 vs. 9.2 ± 2.0 cells/HPF, $p = 0.582$), consistent with the T cell-mediated autoimmune process characteristic of vitiligo. By

week 24, there had been a substantial decrease in infiltration of CD8+ T cells (**Table 3**). The combination therapy group demonstrated significantly lower residual CD8+ T cell counts compared with controls (2.4 ± 0.6 vs. 4.8 ± 0.8 cells/HPF, $p < 0.001$), with a mean reduction of 6.2 ± 1.4 versus 4.4 ± 1.2 cells/HPF ($p = 0.018$). The CD8+ cells in the combination therapy were mostly found in the deep dermis, away from the dermoepidermal junction, compared to the control, where they were close to the basal layer. These results indicate that the combination of hair follicle transplantation and NB-UVB phototherapy has increased immunomodulatory effects, creating an ideal environment for survival and multiplication of melanocytes.

Table 3. Histopathological findings at baseline and week 24.

Parameter	Combination Therapy Group (n = 20)	Control Group (n = 20)	*p*-Value
Melanocyte Density (Cells/mm)			
Baseline	2.4 ± 0.6	2.6 ± 0.7	0.624
Week 24	12.8 ± 2.2	7.4 ± 1.8	<0.001
Change from baseline	10.4 ± 2.0	4.8 ± 1.6	<0.001
CD8+ T Cell Infiltration (Cells/HPF)			
Baseline	8.6 ± 1.8	9.2 ± 2.0	0.582
Week 24	2.4 ± 0.6	4.8 ± 0.8	<0.001
Change from baseline	−6.2 ± 1.4	−4.4 ± 1.2	0.018

Note: Data are presented as mean ± SD. SD: standard deviation; HPF: high-power field (×400 magnification).

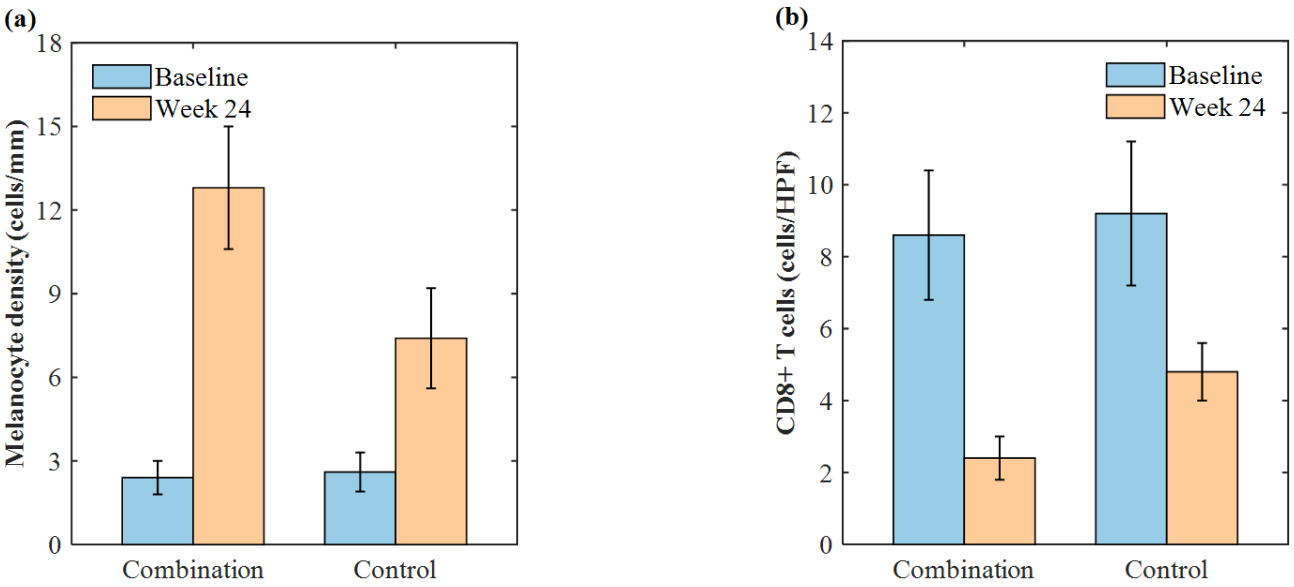

Figure 3. Histopathological findings at baseline and week 24. (**a**) Melanocyte density; (**b**) CD8+ T cell infiltration.

3.4. Adverse Events

Treatment-related adverse events are presented in **Table 4** and **Figure 4**. Both regimens demonstrated favorable tolerability, with no serious adverse events occurring during the 24-week study period. No participant withdrew due to adverse events, and all reported events were grade 1 or 2 per CTCAE version 5.0.

In the combination therapy group, donor site complications related to hair follicle harvesting were generally mild and transient. Transient pain at the occipital donor site was reported in 9 participants (29.0%), which was managed with oral acetaminophen as needed and resolved within 24 to 48 h in all cases. Mild erythema at the harvesting site occurred in 6 participants (19.4%), which resolved spontaneously in 5 to 7 days without sequelae. No patients had prolonged bleeding, wound dehiscence, or lasting alopecia at the harvesting site. Reactions at the recipient site in the pubic area occurred in 8 participants (25.8%), which manifested as mild perilesional edema that appeared in the initial 24 h after the transplant and resolved in 48 to 72 h. No evidence of infection, scarring, hypertrophic scarring, or keloid formation was noted in either the harvesting or the recipient sites during the entire

period of follow-up. One patient complained of mild pain during the operation in spite of local anesthesia, yet the procedure was uneventful.

Table 4. Adverse events during the 24-week treatment period.

Adverse Event	Combination Therapy Group (n = 31)	Control Group (n = 30)	*p*-Value
Donor Site (Hair Follicle Harvesting)			
Transient pain	9 (29.0)	—	—
Erythema	6 (19.4)	—	—
Recipient Site (Transplantation)			
Mild edema	8 (25.8)	—	—
Infection	0 (0)	—	—
Scarring/keloid	0 (0)	—	—
Phototherapy-Related			
Erythema	12 (38.7)	14 (46.7)	0.524
Pruritus	5 (16.1)	7 (23.3)	0.487
Xerosis	4 (12.9)	5 (16.7)	0.728
Blistering	0 (0)	0 (0)	—
Serious adverse events	0 (0)	0 (0)	—
Discontinuation due to AE	0 (0)	0 (0)	—

Note: Data are presented as n (%). AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events.

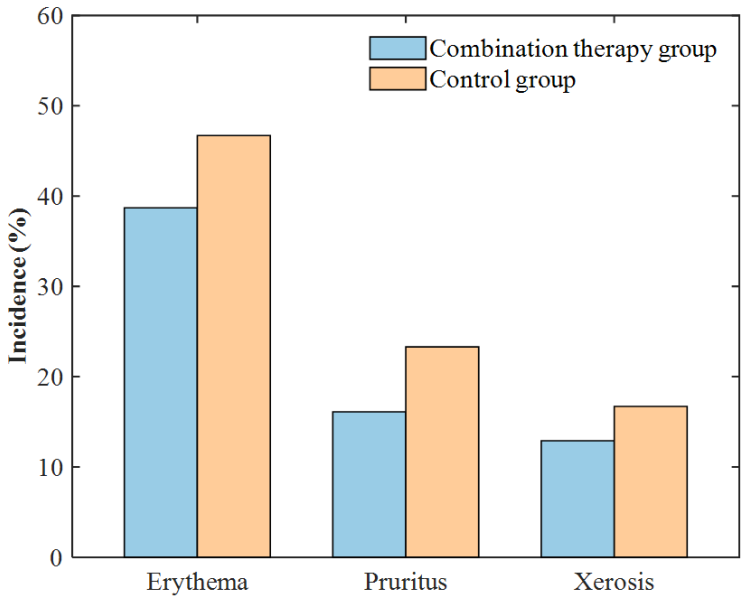

Figure 4. Incidence of phototherapy-related adverse events during the 24-week treatment period.

Phototherapy-related adverse events showed no significant between-group differences. Erythema was most common, affecting 12 (38.7%) and 14 (46.7%) participants in the combination and control groups, respectively ($p = 0.524$). Most erythema episodes were grade 1, presenting as faint redness resolving within 24–48 h without dose adjustment; grade 2 erythema necessitating temporary dose reduction occurred in 2 participants per group. Pruritus was reported in 5 (16.1%) versus 7 (23.3%) participants ($p = 0.487$), effectively managed with topical emollients. Xerosis occurred in 4 (12.9%) and 5 (16.7%) participants, respectively ($p = 0.728$). No phototoxic reactions, blistering, or post-inflammatory hyperpigmentation requiring treatment modification occurred in either group (**Table 4** and **Figure 4**). Mean cumulative NB-UVB doses remained within predefined safety limits: 68.4 ± 12.6 J/cm^2 in the combination group and 71.2 ± 14.8 J/cm^2 in controls.

4. Discussion

This randomized controlled trial demonstrated that combining autologous hair follicle transplantation with NB-UVB phototherapy yields superior clinical outcomes compared with NB-UVB monotherapy for stable pubic vi-

tiligo. The combination therapy group exhibited a significantly higher repigmentation rate of 68.4% versus 42.3% in the control group, with 80.6% of participants achieving at least 50% repigmentation. Ju et al. [22] reported that follicular cell suspension transplantation as monotherapy achieved only 36% repigmentation rate greater than 50%. Previous studies of suction blister epidermal grafting combined with NB-UVB reported mean repigmentation rates of 67.5% at 6 months in non-genital vitiligo, with complete repigmentation observed in 20.6% of patients and excellent repigmentation (>50%) in 51.6% of patients [23,24]. The superior efficacy observed in the present study suggests that the combination produces synergistic effects exceeding either modality alone. Hair follicle transplantation provides an effective melanocyte reservoir [19] and the sustained availability of intact follicular units may contribute to the higher efficacy compared with other surgical approaches.

The most common pattern of perifollicular repigmentation seen in the combination group (83.9%) reinforces the theory of the bulge area of the hair follicle being the main source of epidermal melanocyte renewal [11]. Hair follicle melanocytes are relatively resistant to autoimmune cells as a result of the mechanism of immune privilege [13], having a better proliferative potential compared to epidermal melanocytes [25]. Unlike epidermal melanocytes, hair follicle melanocytes, to a great extent, escape the destruction in vitiligo, as they do not express antigens in vitiligo and resist T cell-mediated cytolysis [14]. The relatively short onset of action observed in the combination therapy group (4.2 weeks versus 7.6 weeks) indicates that transplanted follicular units provide an immediately available melanocyte population that can be rapidly activated by phototherapy. Hair follicle transplantation was chosen for pubic vitiligo treatment for several reasons relating to its anatomy. The pubic area grows terminal hair, which provides excellent natural coverage for the transplanted area, resulting in better cosmetic results than epidermal transplantation. Scar formation is minimal in follicular unit extraction methods, which is especially important in the pubic area, which is particularly sensitive. The histopathologic findings provide mechanistic insights into the efficacy improvement. The great enhancement of melanocyte density in the combination treatment group (10.4 versus 4.8 cells/mm) indicates more effective melanocyte repopulation. Successful studies by Bishnoi and Parsad [26] demonstrated that NB-UVB phototherapy stimulates melanocyte proliferation through activation of the Wnt/β-catenin signaling pathway. Goldstein et al. [27] confirmed that repigmentation mediated by NB-UVB treatment in vitiligo patients is regulated by GLI1 expression and activation of the β-catenin pathway in hair follicle bulge stem cells. Lin et al. [28] proved that Wnt/β-catenin signaling is crucial to differentiate melanocyte stem cells, with simultaneous suppression of immune activity by reducing CD8+/T-cell infiltration and down-regulating inflammatory chemokines mediated by NB-UVB. The results show that there are fewer residual CD8+ T cells in the combination treatment group (2.4 versus 4.8 cells/HPF), suggesting improved immune modulation. The observation that CD8+ T cells were predominantly located in the deeper dermis indicates restoration of the immune privilege microenvironment [29]. The greater reduction in CD8+ T cell infiltration in the combination therapy group may be attributed to the transplanted hair follicle maintaining its immune privilege status through local secretion of immunosuppressive factors, including transforming growth factor-β, α-melanocyte-stimulating hormone, and indoleamine 2,3-dioxygenase [30,31]. These factors downregulate MHC class I expression and inhibit T cell activation, thereby creating a localized immunosuppressive microenvironment [32]. The therapeutic mechanism by which NB-UVB could show greater immunomodulatory potential in this novel follicular environment could be the regulation of infiltrating regulatory T cells and the reduction of the interferon-γ-driven inflammatory response. In addition, personal variation in immunoreactivity could interact with treatment outcomes. Those patients with greater underlying CD8+ T cell infiltrates or increased plasma CXCL9/CXCL10 could potentially reflect an underlying active autoimmune environment and could help to determine outcomes of melanocyte repopulation.

The aspect of improving the quality of life and patient satisfaction also presents significant clinical importance. In genital vitiligo, the condition impedes the psychological and sexual health of affected individuals to a considerable extent [8]. The satisfied patients in the combination therapy group had a high satisfaction rate of 87.1%, showing that this method adequately meets the concerns of the patients. As found in our study, the consensus statement on vitiligo surgical management highlights the benefit of adjuvant phototherapy conducted post-surgery for optimizing the response [33]. The above data strengthen the hypothesis that the methods combined for addressing the pathogenesis and regeneration of melanocytes show optimal efficacy [34,35].

This study has several limitations. The open-label design may introduce performance bias, although outcome assessors were blinded. The small sample size and single-center design may limit generalizability. The 24-week follow-up schedule may not be adequate for analyzing the lasting efficacy of repigmentation. There are no compar-

ative analyses presented with other types of surgical techniques, such as suction blister grafting and split-thickness skin grafting. The current combination therapy is quite versatile and adaptable to dermatological settings because of the usage of common follicular unit extraction equipment and NB-UVB phototherapy units already found in dermatological institutions. Some of the most pertinent and fundamental questions that have arisen out of the current study are those of the durability of repigmentation at times exceeding 24 weeks, further refinement of maintenance therapies, and determination of predictive biomarkers of response.

5. Conclusion

Autografted hair follicle transplant along with NB-UVB phototherapy, resulted in a greater repigmentation compared to NB-UVB phototherapy alone in patients with stable pubic vitiligo (68.4% versus 42.3%). 80.6% patients had at least 50% repigmentation using the combination therapy. The combination therapy resulted in earlier onset of repigmentation, mainly perifollicular, greater density of melanocytes, and lower density of CD8+ T cells. Neither of the two therapies was found to have any severe side effects.

The data suggests that a synergy can be obtained by using this method, as it maintains the melanocyte reservoir together with the proper immunologic environment. Its great benefit for patient satisfaction and quality of life makes this method very valuable. Provided that further multicenter trials confirm the data, it may come into routine use for the treatment of stable pubic vitiligo, which is difficult to treat and for which a new approach of this type will be of great use.

Author Contributions

Conceptualization, X.W. and M.T.O.; methodology, X.W.; software, X.W.; validation, X.W. and M.T.O.; formal analysis, X.W.; investigation, X.W.; resources, M.T.O.; data curation, X.W.; writing—original draft preparation, X.W.; writing—review and editing, M.T.O.; visualization, X.W.; supervision, M.T.O.; project administration, X.W. Both authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was approved by the Research Ethics Committee of the University of Cyberjaya (Approval Number: UoC-REC-2022-0153). This trial fully followed the guiding principles set out by the Helsinki Declaration and was registered in the National Medical Research Register, Malaysia (Registration Number: NMRR-22-01796-IIR).

Informed Consent Statement

Informed consent was sought from all participants before recruitment after they were fully informed about the study objectives, procedures, and possible risks and benefits.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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