Low-energy helium-neon laser therapy induces repigmentation and improves the abnormalities of cutaneous microcirculation in segmental-type vitiligo lesions

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Segmental vitiligo (SV) is a special form of vitiligo occurring in a dermatomal distribution, and an abnormality involving the sympathetic nerves supplying the affected dermatome is known to underlie this disorder. Previously, we have shown that SV is associated with an abnormal increase in cutaneous blood flow and adrenoceptor responses in the affected areas. Since SV is resistant to conventional forms of therapy, its management represents a challenge for dermatologists. Low energy helium-neon lasers (He-Ne laser, wavelength 632.8 nm) have been employed as a therapeutic instrument in many clinical situations, including vitiligo management and repair of nerve injury. The purpose of this study was to evaluate the effectiveness and safety of He-Ne lasers in treating SV, and determine their effects on the repair of sympathetic nerve dysfunction. Forty patients with stable-stage SV on the head and/or neck were enrolled in this study. He-Ne laser irradiation was administered locally at 3.0 J/cm² with point stimulation once or twice weekly. Cutaneous microcirculatory assessments in six SV patients were performed using a laser Doppler flowmeter. The sympathetic adrenoceptor response of cutaneous microcirculation was determined by measuring cutaneous blood flow before, during and after iontophoresis with sympathomimetic drugs (phenylephrine, clonidine and propranolol). All measurements of microcirculation obtained at SV lesions were simultaneously compared with contralateral normal skin, both before and after He-Ne laser treatment. After an average of 17 treatment sessions, initial repigmentation was noticed in the majority of patients. Marked repigmentation (>50%) was observed in 60% of patients with successive treatments. Cutaneous blood flow was significantly higher at SV lesions compared with contralateral skin, but this was normalized after He-Ne laser treatment. In addition, the abnormal decrease in cutaneous blood flow in response to clonidine was improved by He-Ne laser therapy. Our study showed that He-Ne laser therapy is an effective treatment for SV by normalizing dysfunctions of cutaneous blood flow and adrenoceptor responses in SV patients. Thus, the beneficial effects of He-Ne laser therapy may be mediated in part by a reparative effect on sympathetic nerve dysfunction.

Key Words: cutaneous microcirculation, He-Ne laser, segmental-type vitiligo, sympathetic adrenoceptor response

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induce. By definition, low-energy lasers do not produce temperature elevations above 0.1–0.5°C in irradiated tissues [1–3]. Low energy lasers have potential therapeutic applications in rheumatoid arthritis [4], wound healing [5], postherpetic neuralgia [6,7], and recovery following nerve injury [8,9]. The continuous wave He-Ne laser has been most frequently employed in these clinical situations [10]. Recently, studies have demonstrated that low-energy lasers induce biostimulatory effects on cultured cells. He-Ne laser irradiation stimulates the release of various growth factors by macrophages and other cells and results in the proliferation of fibroblasts and keratinocytes [11–14]. We have previously shown that He-Ne laser irradiation could induce the release of basic fibroblast growth factor (bFGF) and nerve growth factor (NGF) from cultured keratinocytes, and stimulate migration and proliferation of cultured melanocytes [15]. Moreover, He-Ne lasers have been found to induce locomotion of immature melanoblasts and promote melanogenesis of differentiated melanoblasts in vitro [16]. These results suggest that He-Ne lasers may have biostimulatory effects on various cell types residing in the skin.

Vitiligo is a common pigmentary disorder characterized by depigmented macules due to the loss of melanocytes. The mechanisms underlying how melanocytes disappear from vitiliginous skin is still not completely defined. Clinically and physiologically, vitiligo can be classified into two distinct types: nonsegmental-type vitiligo (NSV), which is associated with autoimmune diseases, and segmental-type vitiligo (SV), which occurs in a dermatomal distribution and is associated with a dysfunction of the sympathetic nerves in affected skin [17,18]. The sympathetic nervous system has a profound effect on cutaneous blood flow, mainly by influencing arterioles and arteriovenous anastomoses (thermoregulatory vessels) [19]. Therefore, measurement of cutaneous blood flow and its adrenoceptor response can reflect the sympathetic nerve function of a certain skin area. Previously, we demonstrated that cutaneous blood flow and adrenoceptor responses are abnormally increased in SV lesions [18].

Conventional therapies for patients with vitiligo include topical corticosteroids, phototherapy, and photochemotherapy. Recent investigations have reported 63% effectiveness for ultraviolet-B light (UVB), 75% for NB-UVB, 45% for topical psoralens and ultraviolet-A light (PUVA), 63% for oral PUVA, and 44% for topical steroid therapy in vitiligo treatment (including all types of vitiligo) [20–22]. Twenty to 40 sessions of PUVA treatments are usually required before initial repigmentation occurs [21]. Although these therapeutic modalities may induce varying degrees of repigmentation in vitiligo lesions, potential undesirable effects, including erythema, bullous formation, and hyperpigmentation, may occur. In particular, chronic irradiation of periocular vitiligo lesions may lead to ophthalmic damage, such as cataract and visual acuity deterioration. Furthermore, SV responds poorly to these forms of treatment, with only surgical intervention during the stable stage showing efficacy [23–26], but patients fear surgery and anesthesia. Thus, finding a safe and effective treatment for SV is an important aspect of current research.

Previous reports have shown that He-Ne laser irradiation leads to biological effects, such as an improvement in nerve injury [8,27]. We have also shown in our pilot study that a low energy He-Ne laser is effective for treating patients with SV [15]. The purpose of this study was to further evaluate whether He-Ne laser therapy is a safe and effective treatment modality for SV, and to clarify its biological effects on the repair of sympathetic nerve dysfunction.

**Materials and Methods**

**Subjects**

Forty patients with facial and/or neck stable-stage SV were selected for this study. There was no history of autoimmune diseases (such as thyroid disease, Addison’s disease, pernicious anemia, insulin-dependent diabetes mellitus or alopecia areata) or other systemic diseases among these patients. None of the patients had received treatment for vitiligo in the preceding 3 months. There were 17 females and 23 males, with ages ranging from 3 to 43 years (mean age, 20 ± 12 years). Assessments of cutaneous blood flow and sympathetic adrenoceptor responses were performed and analyzed in six patients who experienced obvious repigmentation (50%) after He-Ne laser treatment. In addition, 10 healthy individuals without vitiligo were enrolled as normal controls for the experiments on cutaneous blood flow. The study was approved by the Institutional Review Board of the Kaohsiung Medical University.
Treatment of vitiliginous lesions with He-Ne laser irradiation

A continuous wave He-Ne laser (OMNIPROBE™ Laser Biostimulation System, Physio Technology, Topeka, KS) with an average power output of 1.0 mW was used for treatment as previously described in our pilot study [15]. It was designed for point stimulation (irradiation point by point) once or twice a week, and the irradiating flux for each treatment point was 3.0 J/cm². No other therapeutic interventions were employed during the course of He-Ne laser treatment.

Evaluation of repigmentation

Vitiliginous lesions in all patients were manually traced and the square centimeters of involvement counted on an overlaid grid. The lesions were recorded regularly before, during and after He-Ne laser therapy. The percentage of repigmentation after He-Ne laser treatment was defined as follows: (area of repigmented vitiligo lesion ÷ area of vitiligo lesion prior to He-Ne laser therapy) × 100%.

Laser Doppler flowmetry

Cutaneous microcirculatory assessments were performed as previously described in our pilot study [18]. A laser Doppler flowmeter (PeriFlux, PF3, Perimed, Sweden) was used for cutaneous blood flow measurement. For comparison, the blood flow of contralateral normal skin was also measured. Standard probes (PF408) were fixed on lesions and the contralateral normal skin, and measurements were made simultaneously before He-Ne laser treatment. The blood flow (blood cell flux or perfusion) was expressed in perfusion units (PUs). The flow was calculated by the product of the number of red blood cells moving in the measured volume (within the surface capillaries of the skin) and the mean velocity of these cells. The perfusion ratio (PR) is defined as: (perfusion units of lesional skin ÷ perfusion units of contralateral normal skin) × 100%. After obvious repigmentation induced by regular He-Ne laser treatment, standard probes were fixed on the lesions (residual vitiligo lesion or repigmented area) and the contralateral normal skin, and measurements were made simultaneously. All measurements were repeated three times.

Statistical analysis

Statistical analysis was performed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± standard deviation. Statistical significance was tested using paired and unpaired Student’s t tests or one-way ANOVA. Statistical significance was defined as p < 0.05.

RESULTS

Low-energy He-Ne laser therapy is a safe and effective treatment modality for SV

Patients with SV were treated with a He-Ne laser once or twice a week; their treatment responses are shown in Table 1. Among the 40 patients who received He-Ne laser treatment, the majority exhibited initial repigmentation at the edges (perilesional repigmentation) after receiving an average of 17 ± 10 treatments. After further treatment, both perilesional and perifollicular repigmentation could be seen in most patients. Marked repigmentation (>50%) was observed in 60% of patients following successive treatments. The repigmented areas were similar in color to normal skin, and no obvious hyperpigmentation was noticed. Three patients (7.5%) experienced complete repigmentation.
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after 20 ± 4 treatment courses, but needed to maintain one to two treatments per month in order to avoid redepigmentation. Six patients (15%) achieved 76–99% repigmentation after 158 ± 32 treatments; 15 patients (37.5%) showed 51–75% repigmentation after 132 ± 76 treatments; 12 patients (30%) displayed 26–50% repigmentation after 89 ± 47 treatments; two patients (5%) achieved <25% repigmentation after 69 ± 45 treatments; and two patients (5%) had no repigmentation at all. One of these patients had had vitiligo for 16 years, the other for 30 years. This is consistent with earlier reports indicating that patients with longer duration of the disease are more resistant to therapy [29].

There was no significant difference between the early-onset (≤12 years old, 52.8 ± 19.7%) and late-onset (>12 years old, 55.6 ± 31.1%) groups in terms of treatment response. Nine patients (22.5%) were lost in follow-up due to schoolwork, busy jobs, distant residence, poor treatment response or other reasons. There was no obvious discomfort or side effects during or after He-Ne laser therapy for any of the patients.

In the Figure, we show one typical case of SV demonstrating obvious repigmentation following He-Ne laser treatment. This was a 5-year-old girl who had vitiligo on the right cheek for 1 year. She had previously accepted short-term topical PUVA combined with topical steroid treatments in another hospital. Obvious perilesional hyperpigmentation, hypertrichosis and telangiectasia were noted, in addition to no clinical improvement. After 174 treatment sessions, there was 84% repigmentation. In addition, the previous perilesional hyperpigmentation, hypertrichosis and telangiectasia gradually improved after the former treatment was stopped.

Improvement in microcirculation at the lesional site of SV after He-Ne laser treatment

Six patients with marked repigmentation following He-Ne laser treatment underwent microcirculatory assessments. As shown in Table 2, the pretreatment PR between lesion sites and contralateral normal skin for

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Table 1. Effectiveness of He-Ne laser treatment in 40 SV patients

<table>
<thead>
<tr>
<th>Repigmentation, %</th>
<th>Patients, n (%)</th>
<th>Initial repigmentation, number of treatments</th>
<th>Total number of treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>3 (7.5)</td>
<td>7 ± 1</td>
<td>20 ± 4</td>
</tr>
<tr>
<td>76–99</td>
<td>6 (15)</td>
<td>19 ± 13</td>
<td>158 ± 32</td>
</tr>
<tr>
<td>51–75</td>
<td>15 (37.5)</td>
<td>17 ± 8</td>
<td>132 ± 76</td>
</tr>
<tr>
<td>26–50</td>
<td>12 (30)</td>
<td>20 ± 11</td>
<td>89 ± 47</td>
</tr>
<tr>
<td>≤ 25</td>
<td>2 (5)</td>
<td>16 ± 1</td>
<td>69 ± 45</td>
</tr>
<tr>
<td>0</td>
<td>2 (5)</td>
<td></td>
<td>53 ± 13</td>
</tr>
<tr>
<td>Total</td>
<td>40 (100)</td>
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</table>

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Figure. (A) A 5-year-old girl who had vitiligo on the right cheek for 1 year. She had undergone treatment with short-term topical PUVA combined with topical steroids in another hospital. Obvious perilesional hyperpigmentation, hypertrichosis and telangiectasia were noted, in addition to no clinical improvement. (B) After 174 treatment sessions, there was 84% repigmentation. In addition, the previous perilesional hyperpigmentation, hypertrichosis and telangiectasia gradually improved after the former treatment was stopped.

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these six patients was $2.9 \pm 0.6$, while the PR between lesion side normal skin and contralateral normal skin was $1.4 \pm 0.2$. This difference was statistically significant ($p < 0.01$). After He-Ne laser treatment with obvious repigmentation, the PR between the residual lesions and contralateral normal skin decreased to $1.6 \pm 0.2$, and the PR between the repigmented lesions and contralateral normal skin decreased to $1.5 \pm 0.2$. The PRs of the residual lesions and repigmented areas of SV patients after He-Ne laser treatment were not significantly different compared to normal controls ($1.4 \pm 0.2$).

After He-Ne laser treatment, there was a significant normalization of cutaneous microcirculation in the SV lesional skin.

We also found that the PU was not the same between the two sides in normal controls (the PR between the high PU side and the low PU side was $1.4 \pm 0.2$). It was not possible to predict which side would have the higher PU, and it is not related to hand dominance. The physiologic significance of this PU difference is unclear.

### Improvement in adrenoceptor response of the SV lesional site after He-Ne laser treatment

As shown in Table 3, the six SV patients with marked repigmentation were given iontophoresis with phenylephrine ($\alpha_1$-agonist), clonidine ($\alpha_2$-agonist), and propranolol ($\beta$-blocker) before He-Ne laser treatment, resulting in a marked decrease in blood flow at the lesional sites. The average decreases in blood flow were $20.5 \pm 7.8\%$ (phenylephrine), $46.4 \pm 13.0\%$ (clonidine), and $32.3 \pm 9.8\%$ (propranolol). Following He-Ne laser treatment with significant repigmentation, there was a partial normalization of blood flow. At residual vitiligo lesion sites, the average decreases were $22.8 \pm 18.9\%$ (phenylephrine), $30.1 \pm 15.8\%$ (clonidine) and $27.7 \pm 8.3\%$ (propranolol). At the repigmentation sites, the average decreases were $19.6 \pm 10.2\%$ (phenylephrine), $18.1 \pm 11.6\%$ (clonidine) and $24.0 \pm 11.4\%$ (propranolol). The normalization of blood flow was statistically significant in the clonidine group (one-way ANOVA, $p < 0.05$).
caused a normalization of sympathetic adrenoceptor responses to clonidine (α2-agonist), and may have reparative effects on adrenoceptor dysfunction.

**DISCUSSION**

Vitiligo is an acquired disorder of pigmentation in which depigmentation of skin and hair occurs due to a loss of melanocytes from the epidermis. SV occurs in an asymmetric dermatomal distribution. Due to its earlier onset, recalcitrant course, and decreased association with autoimmune diseases, SV is regarded as a special form of vitiligo [24,30]. After various forms of therapy, repigmentation of vitiligo lesions may occur. This involves the proliferation of inactive melanocytes in the outer root sheath of the hair follicle, followed by their upward migration to the adjacent epidermis to form perifollicular pigment islands [31].

Low energy He-Ne laser treatment has been shown to be a safe and effective treatment modality for patients with vitiligo [15]. In a study involving 18 vitiligo patients, Mandel et al (1997) reported that after 6–8 months of He-Ne laser therapy, marked repigmentation was seen in 63.9% of patients and some follicular repigmentation was seen in 34.4% of patients [32]. In this study, initial repigmentation was noticed after an average of 17 He-Ne laser therapy sessions. Marked repigmentation (>50%) was observed in 60% of patients following successive treatments and three patients (7.5%) showed 100% recovery. Thus, our results confirm that He-Ne laser irradiation is effective in treating SV. The effectiveness of He-Ne laser treatment is comparable with that of conventional therapies for vitiligo (Table 4) [20–23,26,29,33–35].

The mechanisms by which He-Ne laser treatment induces repigmentation of vitiligo lesions are still unclear, although several hypotheses have been proposed. Previously, we have demonstrated that He-Ne laser irradiation can induce the release of basic fibroblast growth factor (bFGF) and nerve growth factor (NGF) from cultured keratinocytes and stimulate the migration and proliferation of cultured melanocytes [15]. bFGF is a melanocyte growth factor, whereas NGF promotes melanocyte survival in skin. Thus, by stimulating the release of these two cytokines, He-Ne laser therapy may induce perilesional and perifollicular repigmentation in SV patients. In addition, there have been reports indicating that He-Ne laser therapy has reparative effects on the microcirculation and nerve cells [9,37–39]. Since we have shown that SV is associated with dysfunctions of the cutaneous microcirculation and sympathetic nerves, it is possible that He-Ne laser therapy may lead to improvements in these abnormalities. In this study, the increase in microcirculation at SV lesional sites was normalized after He-Ne laser therapy. In fact, the residual lesions and repigmented areas of SV patients after He-Ne laser treatment showed no significant differences in PR compared with normal controls. In addition, the assay of sympathetic adrenoceptor function in residual lesions and repigmented areas demonstrated progressive...
## Table 4. Comparisons of the effectiveness of the He-Ne laser and common vitiligo therapies

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness</td>
<td>41–54%</td>
<td>41–58%</td>
<td>57–67%</td>
<td>45–69%, but poor in SV (2.4%) [23]</td>
<td>56–90%</td>
<td>60% in our study in SV</td>
</tr>
<tr>
<td>Advantages</td>
<td>Easy &amp; convenient application</td>
<td>Easy &amp; convenient application</td>
<td>Suitable for lesions involving large BSA, easy application</td>
<td>Suitable for lesions involving large BSA</td>
<td>Suitable for intractable lesions</td>
<td>Simple, convenient, safe &amp; effective</td>
</tr>
<tr>
<td>Contraindications or limitations</td>
<td>Steroid allergy</td>
<td>Tacrolimus allergy</td>
<td>Photoallergy, history of skin cancer; not suitable for periorbital or genital lesions</td>
<td>Pregnancy, breastfeeding, photoallergy, history of skin cancer; not suitable for periorbital or genital lesions; need psoralen pretreatment</td>
<td>Active stage; phobia of anesthesia or surgery</td>
<td>None</td>
</tr>
<tr>
<td>Possible adverse effects or potential risks</td>
<td>Skin atrophy, purpura, rosacea-like dermatitis, telangiectasia, folliculitis or acne</td>
<td>Pruritus, burning sensation, local infection, acne</td>
<td>Hyperpigmentation, pruritus, xerosis, photoaging, carcinogenesis</td>
<td>Nausea, vomiting, GI upset after psoralen intake, hyperpigmentation, bulla formation, focal hypertrichosis &amp; hyperkeratosis, pruritus, xerosis, photoaging, carcinogenesis</td>
<td>Scar formation, Koebner phenomenon, uneven color</td>
<td>None</td>
</tr>
</tbody>
</table>

BSA = body surface area; GI = gastrointestinal.
improvement (namely, the percent of lesional PU after iontophoresis decreased in the following order: before treatment > residual vitiligo after treatment > repigmented area after treatment). The phenylephrine and propranolol groups showed improvement, but only the clonidine group showed statistical significance. Thus, the beneficial effect of He-Ne laser therapy on vitiligo lesions may be mediated partially by reparative effects on the cutaneous microcirculation and damaged sympathetic nerves. One possible explanation for this phenomenon may be that a He-Ne laser, through biostimulation, regulates the local physiologic condition of the lesion and creates an environment favorable for melanocyte survival. Normalization of PR is an important indicator of the biostimulatory regulation for melanocyte survival. Normalization of PR is an easier treatment modality to administer, less expensive and has no adverse effects compared with other conventional therapies. Hence, we conclude that He-Ne lasers can effectively treat SV and have reparative effects on damaged sympathetic nerve function.

ACKNOWLEDGMENTS

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REFERENCES


低能量氦氖雷射可促使分節型白斑病灶
色素恢復並改善其交感神經機能異常

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分節型白斑是一種特殊型的白斑，其病灶分布於單側的神經節段上，目前的研究認為
是由於病灶交感神經機能異常所致，我們過去的研究發現分節型白斑病灶有皮膚血液
流量上升及交感神經腎上腺接收器亢進的異常表現。臨床上其頑固的治療反應對皮膚科
醫師而言是一項艱鉅的挑戰。低能量氦氖雷射 (波長 632.8 nm) 在臨床上已被廣泛
運用於治療許多疾病，其中包括白斑治療與神經損害的修復在內。本研究之目的在評
估以低能量氦氖雷射治療分節型白斑的療效與安全性，並進一步探討其對病灶交感神
經機能異常的修復作用。我們選取 40 位病灶位於頭頸部的穩定型分節型白斑患者，
低能量氦氖雷射以點治療的模式 (3.0 J/cm²) 每週治療 1−2 次；另外在 6 位經氦
氖雷射治療後有明顯色素回復的分節型白斑患者以雷射都卜勒血流測定儀測定病灶治
療前後皮膚血流量的差異，並以離子電泳導入測交感神經藥劑觀察病灶皮膚血流量的
變化，藉以評估其交感神經腎上腺接收器機能在治療前後的變化，所有檢查均同時監
測正常側對照部位作為比較。平均在 17 次治療後，即可發現病灶開始出現色素恢
復的現象，而在持續接受治療的患者中 60% 可以觀察到有顯著的治療效果 (色素恢
復 > 50%)，而且所有接受治療者完全沒有任何不適反應或副作用出現；同時在 6 位
規則治療的分節型白斑患者發現治療前異常上升的病灶皮膚血流量已恢復正常，而交
感神經腎上腺素接收器對於 clonidine 的異常反應亦有逐漸恢復正常的趨勢。由以
上的結果我們相信：低能量氦氖雷射不僅可以有效地治療分節型白斑，其對於病灶部
位異常的交感神經機能亦可能有相當程度的修復或調控的作用。

關鍵詞：皮膚微循環，低能量氦氖雷射，分節型白斑，交感神經腎上腺接收器

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