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ORIGINAL ARTICLE

Treatment of refractory venous stasis ulcers with autologous platelet-rich plasma and light-emitting diodes: a pilot study

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Background: Stasis dermatitis with secondary ulcer formation is not only therapeutically challenging but also significantly decreases the quality of life for affected individuals. Recently, autologous platelet-rich plasma (PRP) has entered the therapeutic regimen for leg ulcers, while light-emitting diodes (LEDs) are now used to accelerate wound healing. *Objective:* To assess the efficacy and safety of autologous PRP with concomitant LED therapy for the treatment of venous stasis dermatitis with secondary ulceration. *Methods and materials:* In total, 16 Korean patients with ulcers secondary to venous stasis dermatitis were enrolled in this study. Each lesion was treated with autologous PRP weakly, and LED therapy three times per week. Treatments continued for 6 weeks or until the ulcer completely reepithelialized without evidence of drainage. Not only were subjects objectively evaluated by a study investigator, their own subjective satisfaction was also assessed. *Results:* The combined autologous PRP and LED therapy was well tolerated and safe. A statistically significant improvement was observed post-therapeutically in the clinical parameters of pain, itching, heaviness, paresthesia, cramps, and leg swelling. There was also a significant decrease in ulcer size. None of the patients showed worsening of their venous stasis ulcer. Regarding subject satisfaction with the regimen, 75.0% of participants reported being 'satisfied or very satisfied' with their overall improvement after treatment. No significant adverse effects were observed. *Conclusion:* Combined autologous PRP and LED therapy is a promising conservative combination regimen for treating recalcitrant ulcerating stasis dermatitis. Additional studies comparing combined autologous PRP and LED therapy directly with autologous PRP or LED monotherapies are needed to confirm the results reported here.

Key words: leg ulcer, light-emitting diodes, platelet-rich plasma, stasis dermatitis

Introduction

Not only are stasis dermatitis and associated venous leg ulcers severely disfiguring and therapeutically challenging (1,2), they also represent a major cause of morbidity, economic loss, and decreased quality of life for affected patients. Currently, leg elevation, compression, and wound care are regarded as the standard first-line therapies, while aspirin, pentoxifylline, topical steroids, and surgery are viewed as second-line therapies (3). However, despite these measures, there is a subgroup of patients for whom adequate disease control cannot be achieved.

Stored growth factors, including platelet-derived growth factor, transformed growth factor, fibroblast growth factor, and epidermal growth factor, are now believed to be essential for wound repair (4). In fact, the potential therapeutic effects of some of these growth factors in promoting wound healing have been reported (5). As platelet-rich plasma (PRP) contains concentrations of growth factors that are three- to fivefold higher (6), this agent has been associated with enhanced wound healing at concentrations of at least 1 000 000 platelets/μL in 5 mL of plasma. Also, photobiomodulation by red to near-infrared (630–1000 nm) light-emitting diodes (LEDs) has been reported to accelerate wound healing, attenuate degeneration of injured nerves, and promote tissue growth (7,8).

In the current study, we assessed the possible synergistic effects and safety of combined PRP and LED therapy on refractory venous stasis ulcer.

Methods

Study design

Following approval by the local ethics committee, 16 Korean patients with ulcerating stasis dermatitis were enrolled in this prospective, single-arm, pilot study. The study protocol was approved by the Institutional Review Board of Chung-Ang University Hospital. Written informed consent was obtained from all subjects prior to enrollment. All aspects of this study were performed in accordance with the tenets of the Declaration of Helsinki.

Subjects

All patients enrolled in this study had wounds that had failed to heal for more than 3 months and were refractory to conventional medical and physical therapy, such as hydrocolloid dressing, aspirin, pentoxiphylline, and compression bandaging.

The eligible wound size was less than 10 cm^2 with partial-thickness ulcer (extending into the dermis), and diagnosis was based on clinical signs and biopsy. For their wound to be defined as a venous ulcer, all patients needed to have an ankle/brachial index of >0.80, demonstrating adequate arterial perfusion. Inclusion and exclusion criteria aimed to include only those venous ulcers not aggravated by other comorbidities or drugs, and therefore patients were excluded if they had signs of cellulitis,

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Table I. Baseline subject demographics.

Patient number	Age	Sex	Duration (weeks)	Area (cm^2)
1	42	M	52	2.4
2	43	F	48	7.9
3	63	F	68	6.5
4	59	M	62	9.3
5	43	M	40	9.8
6	40	F	44	4.3
7	46	F	48	8.1
8	52	M	48	1.9
9	54	F	52	6.2
10	57	M	60	8.6
11	61	M	52	1.3
12	53	M	44	5.7
13	52	F	64	8.3
14	51	M	52	9.7
15	46	F	68	1.5
16	42	M	52	8.4
Total	50.25		53.38	6.24
SD	7.12		8.60	3.05

vasculitis or collagen vascular disease, pregnancy, or uncontrolled diabetes mellitus. Patients were also excluded if they had any concomitant illnesses or were taking any drugs that may affect wound healing, including corticosteroids, immunosuppressive agents, and chemotherapeutics. At baseline, a general medical history was obtained and physical examination performed.

Treatment

All patients were treated with PRP weakly as well as LED (SMARTLUX FX®, MEDMIX Corporation, Seoul, Korea) treatment three times a week. Treatments were performed for a period of 6 weeks or until the ulcer showed complete closure without drainage. PRP was produced using a commercially available system (PROSYS®, TOZAI Holdings Inc., Seoul, Korea) and prepared using a double-spin method as described in a previous study (9). First, anticoagulant was aliquotted via a 20-mL syringe at a ratio of 1:10 (anticoagulant/blood); 60 mL of blood was then drawn from the participant's medial cubital vein. The mixture was then centrifuged at 1000 × *g* for 3 min. The blood was separated into platelet-poor plasma (PPP), buffy coat, and red blood cells. Because PRP is a mixture of buffy coat and plasma, red blood cells were extracted from the kit. For further concentration, the separated fraction composed of PPP and buffy coat was centrifuged with the concentration kit for 3 min at 1 200 × *g*. Concentrated PRP was then withdrawn. This process produced approximately 6 mL of PRP for each patient. For LED treatment, 635 nm (red) + 830 nm (infrared) LED sources with a power intensity of 108 J/cm^2 were used.

Efficacy and safety assessments

The degree and time of wound closure were measured as endpoints. Wound status was tracked by weekly digital photographs for up to 6 weeks or until the ulcer completely reepithelialized without evidence of drainage. The healing rate was calculated as per Margolis (10). Subjective criteria with four-scale grading (0, absent; 1, mild; 2, moderate; 3, severe; 4, very severe) of the following symptoms (pain, itching, heaviness, paresthesia, cramps, and leg swelling) were used, and objective evaluation with the same scale grading of tenderness, oozing, and pigmentation was performed by one investigator. In addition, patient's satisfaction level was recorded as unsatisfied, slightly satisfied, satisfied, or very satisfied after completion of treatment. Any side effects of the treatment, including deterioration of the wound bed or changes in the periwound skin, were also recorded.

Statistical analysis

The Wilcoxon rank-sign test was used for analysis of all clinical parameter grading and leg ulcer size data.

Results

In total, 16 patients completed the study. There were nine males and seven females (male-to-female ratio, 1.29:1). The average age of the patients was 50.25 ± 7.35 years (range 40–63). The duration of the disease was 53.38 ± 8.60 weeks (range 40–68). The baseline information is summarized in Table I. Median ulcer size was 6.24 ± 3.05 cm^2 (range 1.3–9.8) at baseline.

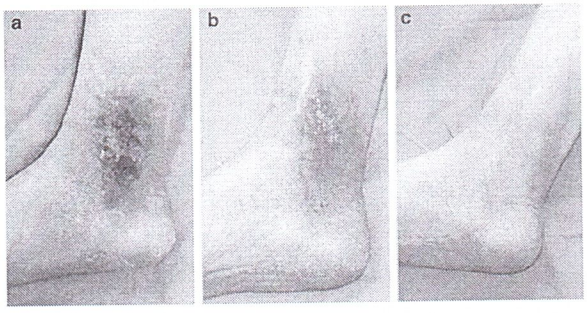

Figure 1. (A) Long-standing venous stasis ulcer on the right lower leg prior to treatment with PRP and LED therapy. (B) Marked improvement of the lesion after 3 weeks of combined PRP and LED treatment. (C) Nearly complete lesion healing without evidence of recurrence 1 year after combined PRP and LED treatment.

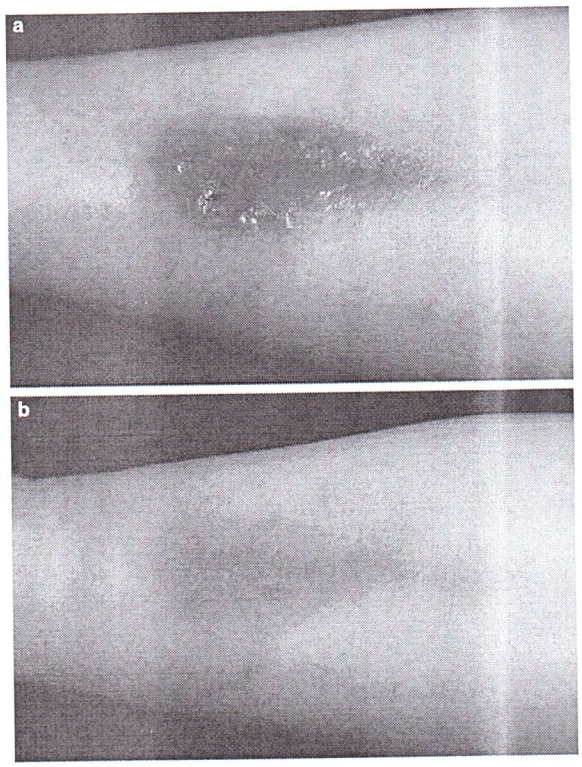

Figure 2. (A) Dusky red ulcerative patch with secondary small vesicles on the left lower left lower leg prior to combined PRP and LED treatment. (B) Marked improvement of the lesion with secondary postinflammatory pigmentation 6 weeks after combined PRP and LED treatment.

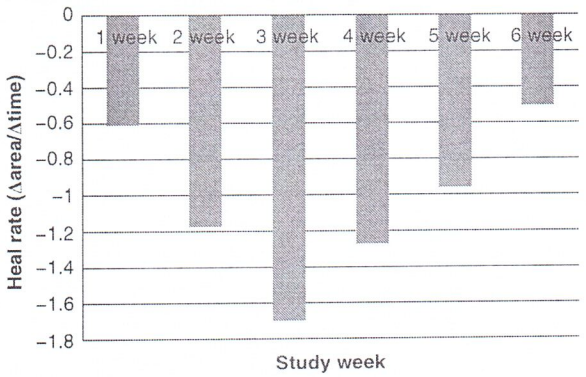

Figure 3. Healing rate analysis demonstrating mean weekly healing rate (cm^2/week). A negative rate is indicative of a positive healing response and progression toward closure.

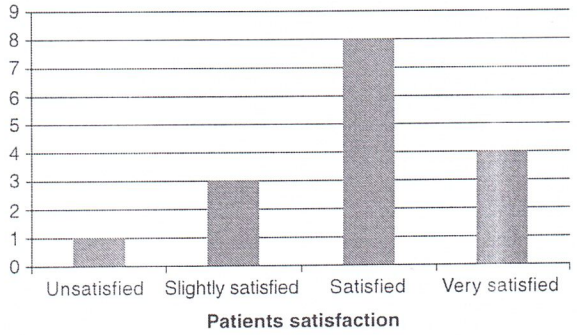

Figure 4. Patient satisfaction levels at the end of treatment with combined PRP and LED treatment.

A decrease in the mean area of the ulcers was observed from 6.24 ± 3.05 cm^2 before treatment to 0.48 ± 0.95 cm^2 after 6 weeks of therapy (Figures 1, 2 and 3), which was highly significant ($p < 0.001$). Overall, about 75.0% of patients reported subjective improvement in stasis ulcers, and graded the treatment as 'satisfied or very satisfied,' which was in agreement with the clinical judgment and was demonstrated statistically.

A statistically significant improvement was observed in the clinical parameters examined post-therapeutically after 6 weeks. In particular, the clinical symptoms which showed a remarkable response were pain, itching, heaviness, and leg swelling (Table II); however, no significant changes were observed in paresthesia and cramps. Patients noted a subjective decrease in oozing and tenderness, although this was not statistically significant (Figure 4).

No abnormality was noted in the laboratory investigations, namely hemogram, renal and liver function tests, serum electrolytes including calcium, urinalysis, and random blood sugar levels, post-therapeutically. All patients were followed up for 1 year after the completion of the combined autologous PRP and LED therapy. Only two patients showed recurrence of leg ulcers, one of whom experienced an increase in ulcer size to almost the initial size over the next 2 months.

Discussion

Stasis dermatitis is characterized by erythema, scaling, pruritus, erosions, oozing, crusting, and occasional vesicles that may occur during any stage of chronic venous insufficiency (3). Venous stasis ulcer is associated with chronic morbidity, economic loss, and reduction in the patients' quality of life. Thus, there has been a renewal of interest in the development of new medical measures for the management of such conditions, as venous ulcers do not require surgical intervention as often as arterial ulcers (11).

Table II. Clinical parameters and symptoms before and after 6 weeks of treatment with PRP and LED.

Clinical parameter	Before therapy (mean ± SD)	After therapy (mean ± SD)	p^*
Pain	3.06 ± 0.93	0.31 ± 0.60	<0.001
Itching	2.69 ± 1.20	0.69 ± 0.70	<0.001
Heaviness	3.44 ± 0.63	0.63 ± 0.62	<0.001
Paresthesia	3.63 ± 0.50	1.12 ± 0.81	>0.05
Cramps	3.44 ± 0.73	1.19 ± 1.11	>0.05
Leg swelling	3.19 ± 1.11	0.19 ± 0.40	<0.001

*Wilcoxon signed rank test.
SD = standard deviation.

This study highlights the successful treatment of refractory venous stasis ulcer with combined autologous PRP and LED therapy. PRP is defined as a portion of the plasma fraction of autologous blood that has a platelet concentration above baseline (6). Platelets initiate wound repair by releasing locally acting growth factors via degranulation of α-granules. The secretory proteins contained in the α-granules of platelets include platelet-derived growth factor, transforming growth factor-β, platelet factor 4, vascular endothelial growth factor, and epidermal growth factor (4). How light promotes tissue repair is not fully known, but treatment with light has repeatedly been shown to promote fibroblast proliferation, collagen synthesis, and related granulation tissue formation, as well as the underlying metabolic processes that enhance collagen formation, ATP synthesis, and lymphocytic action (7,8). Furthermore, phototherapy has been shown to promote blood flow and the formation of new blood vessels in experimental animal models of injury and repair (12). A recent study reported that combined 660 and 890 nm LED phototherapy promoted healing of diabetic leg ulcers that failed to respond to other therapies. By day 90, 75% with LED treatment had achieved 90–100% healing, but only one placebo-treated ulcer healed fully (13). Driver et al. (14) carried out a prospective, randomized, controlled multicenter trial regarding the use of PRP for the treatment of diabetic foot ulcers. They reported that wounds in the PRP gel group healed after a mean of 42.9 days as compared to 47.4 days in the control (normal saline gel) group. The present study demonstrated a remarkable decrease in mean leg ulcer area, as well as subjective improvement in pain, itching, heaviness, and leg swelling, after treatment with autologous PRP and LED. All of these observations indicate wound healing effect in the patients. Present studied cases treated with combined autologous PRP and LED attained ≥90% healing within 4 weeks. Also, the treatment was well tolerated and no serious side effects were noted in the present study. This open and single treatment arm study is limited by the absence of randomization and placebo control. Clearly, the absence of direct comparison with the single modalities is a significant limitation. Nevertheless, data regarding the efficacy of PRP and LED as a monotherapy already exist, and the results presented here can be used to design future randomized trials for combination regimens.

Conclusions

In conclusion, combined PRP and LED treatment represents an effective, safe, and non-surgical therapy for patients with refractory venous stasis ulcers. Further studies with larger sample sizes and comparing combined autologous PRP and LED therapy

directly with autologous PRP or LED monotherapies are clearly warranted.

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