

Photodynamic Therapy for Chronic Venous Ulcers

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SUMMARY Some laboratory findings and a few case reports support the treatment of chronic venous ulcers with photodynamic therapy. We treated 19 patients with refractory chronic venous ulcers using photodynamic therapy. The ulcers healed in 15 cases (78.9%) after an average of 6.8 photodynamic therapy sessions (range 6.0-8.0). In the remaining 4 cases, the ulcers showed marked improvement after 10 photodynamic therapy sessions. Photodynamic therapy seems to represent a good alternative therapeutic choice for refractory chronic venous ulcers.

KEY WORDS: chronic venous ulcer, photodynamic therapy, treatment

Received: January 27, 2013

Accepted: May 15, 2014

INTRODUCTION

Chronic venous ulcers (CVU) are a defect in the skin with surrounding pigmentation and dermatitis, located in the lower leg, which has been present for greater than 30 days. They are characterized by persistent venous hypertension and abnormal venous function without a primary or associated arterial, immunologic, endocrine, or systemic cause. CVU represent the severest and most debilitating form of chronic venous disease, as well as a major cause of working days being lost and increased health care costs. Evidence-based data suggest that the most effective treatments for CVU are compression and wound dressing.

Already widely used for the treatment of cutaneous precanceroses and superficial nonmelanoma skin cancer, topical photodynamic therapy (PDT) is emerging as an effective therapeutic option for a number of other dermatologic conditions, including inflammations (acne vulgaris, psoriasis) and infections (warts/condylomas, leishmaniasis, tineas).

There is substantial *in vitro* and *in vivo* data showing that PDT is effective in treating ulcers, mainly due to its antibacterial properties (1). Also, some case reports have recently shown that PDT may be effective in treating CVU (2-4).

We report on a case of CVU treated with topical PDT and review the literature on the topic.

MATERIALS AND METHODS

Upon informed consent, subjects affected by CVU and recalcitrant to conventional treatments were enrolled in this off-label, prospective, and monocentric case series, carried out in Italy according to the Declaration of Helsinki (6th revision, 2008). All patients had undergone only topical treatments (antiseptic measures and hyaluronic acid-containing dressings) for two months prior to entering the study. Swabs had revealed infection with *Staphylococcus aureus* and/or *Enterococcus faecalis* in all cases.

Table 1. Main characteristics of our case series

Patient	Sex	Age	N. CVU	Location	Swab	Associated conditions	N. PDT	Outcome
1	F	58	2	Malleolus	<i>E. f., S. a.</i>	NIDDM	10	Improved. Healed via autologous graft
2	F	83	1	Medial malleolar	<i>E. f.</i>		6	Healed
3	F	50	1	Medial malleolar	<i>E. f., S. a.</i>	NIDDM	7	Healed
4	F	78	1	Medial malleolar	<i>S. a.</i>	NIDDM	6	Healed
5	F	72	4	Lower third of the leg	<i>E. f., S. a.</i>	NIDDM	10	Improved. Healed via autologous graft
6	F	76	1	Medial malleolar	<i>S. a.</i>		6	Healed
7	F	86	3	Lower third of the leg	<i>S. a.</i>	Raynaud phenomenon	8	Healed
8	F	73	1	Medial malleolar	<i>S. a.</i>		6	Healed
9	F	79	3	Lower third of leg	<i>E. f., S. a.</i>	Raynaud phenomenon	10	Improved. Healed via autologous graft
10	F	53	3	Lower third of leg	<i>E. f., S. a.s</i>		8	Healed
11	F	51	1	Medial malleolar	<i>S. a.</i>		6	Healed
12	M	63	1	Medial malleolar	<i>S. a.</i>		6	Healed
13	M	61	1	Medial malleolar	<i>E. f., S. a.</i>	NIDDM	6	Healed
14	M	74	1	Medial malleolar	<i>E. f., S. a.</i>	NIDDM	6	Healed
15	M	82	2		<i>S. a.</i>	NIDDM	8	Healed
16	M	76	1	Medial malleolar	<i>E. f.</i>		7	Healed
17	M	71	2	Malleolus	<i>E. f., S. a.</i>	NIDDM	10	Improved. Healed via autologous graft
18	M	60	4	Lower third of the leg	<i>S. a.</i>		8	Healed
19	M	58	2	Malleolus	<i>E. f.</i>	NIDDM	8	Healed

Legend: N. CVU: number of chronic venous ulceration; N. PDT: number of photodynamic therapy sessions; F: female; M: male; NIDDM: non insulin-dependent diabetes mellitus, *E. f.*: *Enterococcus faecalis*; *S. a.*: *Staphylococcus aureus*

Before starting PDT, patients were administered a galenic anesthetic cream (lidocaine 20% + prilocaine 5% + tetracaine 5% in jojoba oil) (Farmacia Parati, Lentate sul Seveso, Monza Brianza, Italy) followed by delicate surgical debridement. A galenic gel containing 16% 5-aminolevulinic acid (Farmacia di Santa Maria Nuova, Florence, Italy) was applied topically on

the ulcers and surrounding abnormal areas, and covered with a polyethylene dressing. After 3 hours, the application sites were irradiated perpendicularly to the cutaneous surface with 140 mJ/cm²/sec of continuous-mode red light with peak emission at 618 nm (PDT-CLD 100; E.P.E.M. s.r.l., Florence, Italy; tip diameter: 5 cm), for a total dose of 100 J/cm² (average irra-

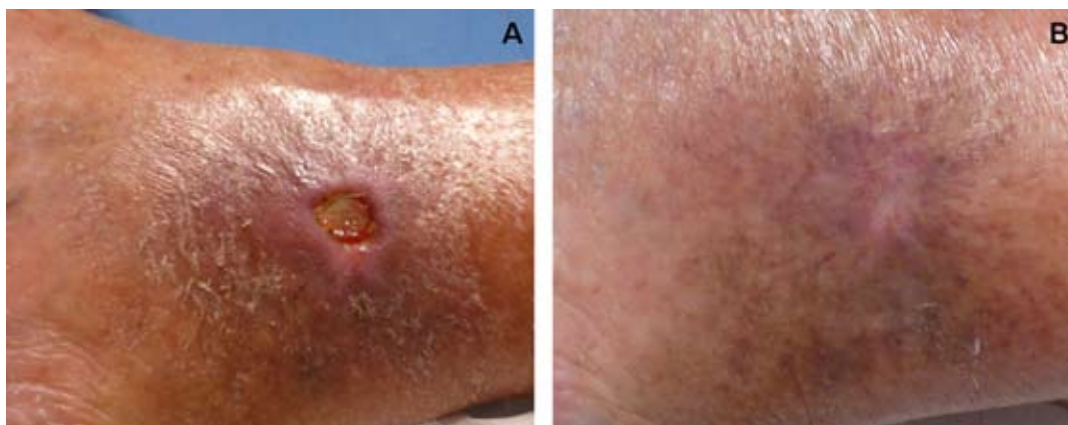


Figure 1. A. Ulcer on the medial aspect of left ankle (patient No. 8). **B.** Ulcer in A has healed after six photodynamic therapy sessions.

diation time: about 12 min). The same procedure was repeated every other week for up to 10 times. Dressings with hyaluronic acid were applied and no other treatment was carried out during the study period.

RESULTS

As detailed in Table 1, 19 patients were enrolled in the study (11 women, 8 men; average age 68.6 years, range 50-86). All patients were suffering from moderate-to-severe chronic venous disease, 9 (47.4%) from non-insulin dependent diabetes mellitus, and 2 (10.6%) from the Raynaud phenomenon. Ulcers were single in 10 cases (52.6%) and multiple in 9 (47.4%); the malleolar/perimalleolar area was involved in all instances.

Ulcers healed in 15 cases (78.9%) after an average of 6.8 PDT sessions (range 6.0-8.0) (Fig. 1). In the remaining 4 cases, ulcers improved greatly after 10 PDT sessions and patients were suggested to undergo an autologous skin graft.

No side effects were recorded beside the usual: well-tolerated pain during light application and mild erythema/edema during the following 24-48 hours.

DISCUSSION

To our knowledge, our 19 patients with CVU treated with PDT represent the largest series reported so far. We showed that PDT be a safe and effective option for healing CVU which are refractory to other topical treatments. Such results confirm the scant data already present in the literature (2-4). In fact, combining the information from such papers (2 case reports (2-4) and a series of six cases (3)), five out of eight patients affected by recalcitrant CVU were completely healed (5 women, 3 men; average age 74.1 years, range 60-86), two greatly improved, and one did not. The average number of PDT sessions was 5.7 (range 2-8).

The exact pathogenesis of CVU remains unknown. Suggested mechanisms include pericapillary fibrin cuffs preventing the passage of oxygen and nutrients, sequestering of growth factors by macromolecules (e.g. fibrinogen and α_2 -macroglobulin) leaked into the dermis, local ischemia and release of proteolytic

enzymes induced by white blood cells, and the detrimental effects of excess tumor necrosis factor- α (as well as of other innate immune system-related cytokines) to the process of wound healing, as observed within CVU (5). The loss of skin integrity provides a favorable environment for bacteria to colonize and proliferate.

Thus, PDT may be effective in CVU treatment through several hypothetical mechanisms, at least in part suggested by *in vitro* and *in vivo* studies carried out in other contexts: modulation of cell-mediated immunity, antimicrobial activity including activity against biofilm-embedded bacteria, restoration of dermal matrix metalloproteinases, and marginal keratinocyte photoactivation.

CONCLUSION

Despite the limitations of the present and previous studies, PDT seems to represent a good therapeutic alternative for refractory CVU. More research is warranted in order to better understand the effectiveness, safety profile, and cost/benefit ratio of PDT in CVU and wound healing in general.

References

1. Sperandio FF, Simões A, Aranha AC, Corrêa L, Orsini Machado de Sousa SC. Photodynamic therapy mediated by methylene blue dye in wound healing. *Photomed Laser Surg* 2010;28:581-7.
2. Clayton TH, Harrison PV. Photodynamic therapy for infected leg ulcers. *Br J Dermatol* 2007;156:384-5.
3. Cardinali C, Gimma A, Schincaglia E, Musio MV, Lo Scocco G. Terapia fotodinamica: nuova modalità terapeutica delle ulcere cutanee croniche. *G Ital Dermatol Venereol* 2008;143:1-4.
4. Devirgiliis V, Panasiti V, Fioriti D, Anzivino E, Bellizzi A, Cimillo M, *et al.* Antibacterial activity of methyl aminolevulinate photodynamic therapy in the treatment of a cutaneous ulcer. *Int J Immunopathol Pharmacol* 2011;24:793-5.
5. Weinstein DA, Kirsner RS. Refractory ulcers: the role of tumor necrosis factor-alpha. *J Am Acad Dermatol* 2010;63:146-54.