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Livedoid vasculopathy: long-term follow-up results following hyperbaric oxygen therapy

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Summary

Background Livedoid vasculopathy, also known as atrophie blanche, is a recurrent painful vasculopathy appearing mostly on the lower limbs. Treatment is challenging and relapses are frequent.

Objectives To analyse the long-term effect and safety of hyperbaric oxygen (HBO) therapy in treating livedoid vasculopathy.

Methods Twelve patients with active livedoid vasculopathy were included in this study. All patients underwent HBO therapy five times a week. Each week photographs were taken and the total dose of analgesics was recorded. Side-effects were documented and assessed. Recurrence was defined as the presence of skin ulceration.

Results Of the eight patients who completed the treatment, resumption of ambulation and reduction of analgesics were achieved at an average of 4·9 HBO therapy sessions. Leg ulcers in all eight patients healed completely at a mean of 3·4 weeks (range 2–5 weeks). Six patients suffered relapses of ulceration and responded to additional HBO therapy. No significant side-effects were found.

Conclusions HBO is a relatively safe, fast and effective method to treat patients with livedoid vasculopathy.

Livedoid vasculopathy is a distinct disease entity characterized by intermittent purpuric macules that develop and become ulcerations on the lower extremities. Pain is the major complaint even when lesions appear small.[1] The histological feature of livedoid vasculopathy is the deposition of fibrinoid material in the superficial vessel walls. Areas of necrosis involving the epidermis and dermis may be the sequelae of ischaemic infarction caused by vascular occlusion.[2] Some authors claim that this disease is related to local hypercoagulability or local failure of fibrinolysis.[3] Hyperbaric oxygen (HBO) therapy delivers high concentrations of oxygen to hypoxic tissue systemically and allows patients to breath in 100% oxygen while in the pressurized cabin. HBO therapy has been widely used in the treatment of various problematic wounds such as diabetic foot and chronic osteomyelitis. Having reported two patients with refractory livedoid vasculopathy treated successfully with HBO therapy,[4] we here extend further our previous study to assess the safety and long-term effectiveness of HBO therapy in 12 patients with livedoid vasculopathy.

Patients and methods

Twelve patients with confirmed diagnosis of idiopathic livedoid vasculopathy were enrolled in this study. Two of these patients have been described and reported previously.[4] The diagnosis was made both clinically and histopathologically. All patients presented with multiple ulcers associated with significant pain, atrophic scars on bilateral lower limbs and active lesions resistant to conventional fibrinolytic treatment. All complained of significant pain that interfered with their daily ambulation. Laboratory studies including complete blood cell count, platelet count and basic blood chemistry revealed no abnormalities. Weakly positive speckled antinuclear antibody (titre 1 : 40) was found in two of the 12 patients. Abnormal serum cryoglobulin levels were detected in three patients. All patients underwent chest X-ray, pulmonary function test and eardrum examination before HBO therapy. Patients with a history of chest or ear surgery, pregnancy, seizure or malignancy, which were contraindications of HBO therapy, were excluded from this investigation. Informed consent was obtained from all patients.

HBO therapy was given in a multiplace hyperbaric chamber (Sigma II-4; Perry Baromedical Corporation, FL, U.S.A.). The patient was first placed in the compression chamber and the pressure was gradually raised to 2·5 atmospheres of pressure over a 15–20-min period. During the treatment, pressurized air filled the cabin and the patient breathed in 100% oxygen through a facemask. The patient was then treated for 1 h, after which the pressure was gradually reduced down to 1 atmospheric pressure over a 15-min period. The overall treatment

Table 1 Clinical features and response of patients with hyperbaric oxygen (HBO) therapy

Patient	Age/sex/ duration (years)	Previous therapy	Total HBO (sessions)	Analgesics before[a]	Analgesics		Complete healing (weeks)	Follow-up period (months)	Recurrence (at 'x' months)
					After first week	After second week			
1	18/M/4	A, D, P, H	16	I, 350 mg; M, 3500 mg	M, 1750 mg	0	3	31	17 and 26
2	37/F/3	A, D, P, H	7	Dc, 1550 mg	M, 750 mg	0	3	29	12
3	23/F/8	A, D, P	5	M, 3500 mg	0	0	3	19	No recurrence
4	27/M/1	A, D, P, C	19	M, 1750 mg	0	0	5	16	10
5	26/M/2·5	A, D, P, H	10	M, 3000 mg; Dc, 275 mg	Dc, 175 mg	0	3	18	8, 12 and 17
6	33/M/4	A, D, P	20	M, 3500 mg	M, 3500 mg	0	4	23	8, 21 and 23
7	20/F/1	A, D, P, H, C	14	I, 11 200 mg	I, 11 200 mg	I, 10 000 mg	4	17	No recurrence
8	20/M/1	A, D	5	Dc, 350 mg	Dc, 350 mg	Dc, 125 mg	2	13	6, 8 and 10
Mean	25·5/–/3·1		12				3·4	20·8	6/8 patients had recurrence

[a]Analgesics before: average dose of analgesics per week in 2 weeks before receiving HBO therapy. A, Aspirin; D, dipyridamole; P, pentoxifylline; H, heparin; C, systemic corticosteroids; I, ibuprofen; M, mefenamic acid; Dc, diclofenac.

cycle took 90 min. This treatment regimen was given 5 days a week (mean duration 3.4 weeks, range 2–5 weeks).

During the period of HBO therapy, topical neomycin–bacitracin ointment and hydrocolloid dressing (Duoderm®; ConvaTec, Princeton, NJ, U.S.A.) were used for the leg ulcers. No oral medications were prescribed concurrently except non-steroidal anti-inflammatory drugs as needed for pain control. At the completion of all HBO therapy sessions, each patient received oral aspirin 150 mg, dipyridamole 400 mg and pentoxifylline 400 mg per day for 1 month. Photographs were taken weekly to assess the effectiveness of therapy. The total dose of analgesics used was recorded before and after HBO therapy.

Results

Eight of the 12 patients completed the study, as summarized in Table 1. Of the four patients who did not complete the study, two had exacerbated leg pain following the first HBO treatment and were reluctant to receive further treatment. One patient had syncope for a few seconds in the hyperbaric chamber during her second HBO treatment. The aetiology of her syncope was obscure and no abnormalities were found following a thorough physical and neurological examination. The fourth patient did not continue because his health insurance did not cover the cost of HBO therapy. One patient did complain of ear pain during HBO treatment, but the eardrum

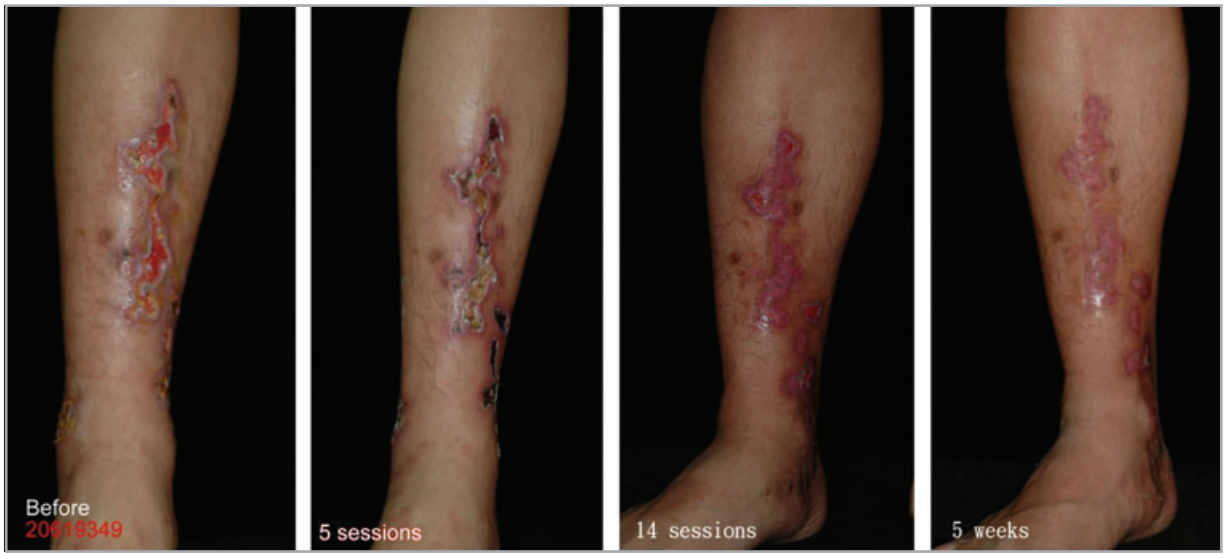

Fig 1. Patient 4. Multiple livedoid vasculopathy ulcerations are found on the lower leg. Most of the ulcers healed on the 14th session. Wounds healed completely after the patient underwent 5 weeks of hyperbaric oxygen therapy.

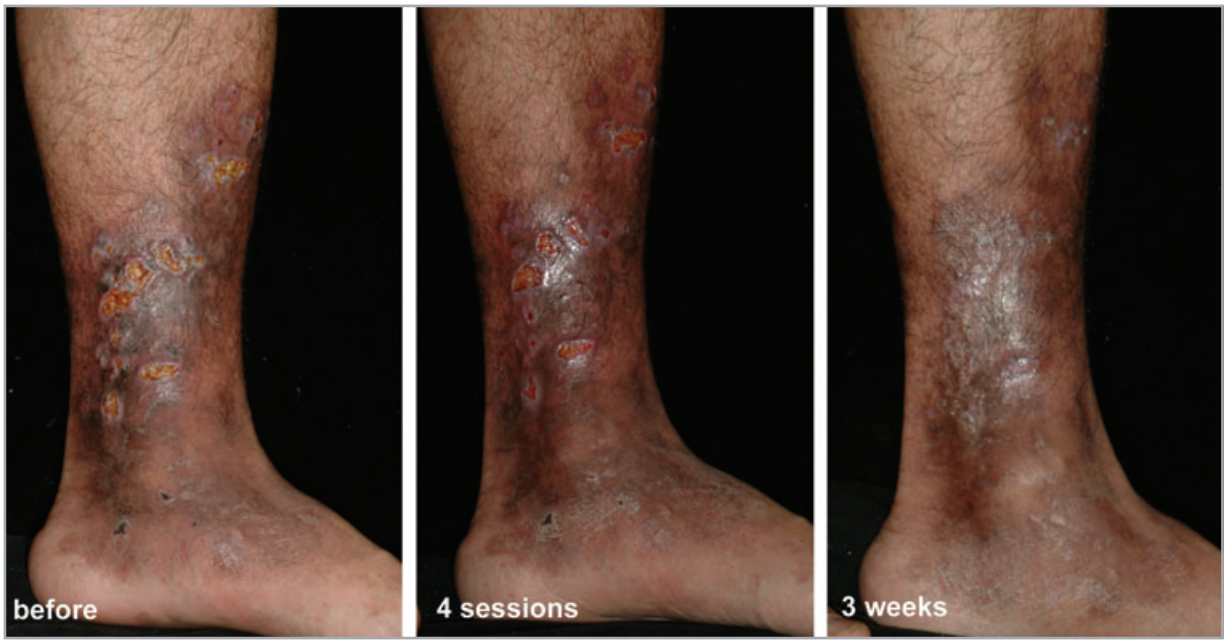

Fig 2. Patient 5. Multiple livedoid vasculopathy ulcerations were noted on the lower leg. Formation of red granulation tissue on the ulceration achieved after four sessions of hyperbaric oxygen (HBO) therapy. Wounds healed completely after 3 weeks of HBO therapy.

examination and hearing function test were normal. Such discomfort was relieved after performing the Frenzel manoeuvre by pinching the nose with the mouth closed and forcing air through the Eustachian tube into the middle ear. Two additional patients also experienced transient exacerbation of the leg pain for 1–3 h during their first and second HBO treatment sessions. The pain diminished after continuing HBO therapy. Table 1 summarizes the clinical data.

The eight patients who completed this study noted pain reduction and received fewer analgesics after about 1 week of HBO therapy. These patients were able to resume ambulation properly without regular oral analgesia medication after four to seven (mean 4·9) sessions of HBO therapy. Concurrent with wound pain relief, new lesions ceased to develop. All eight patients had complete healing of all ulcers, leaving white polygonal scars with peripheral hyperpigmented macules (Figs 1–3). The mean time needed for complete healing was 3·4 weeks.

During the average follow-up period of 20·8 months, six of the eight patients experienced single or multiple recurrences of skin ulcerations, which occurred as early as 6 months after initiating HBO therapy. Additional HBO sessions were arranged and all six patients reported resolution of the pain with noticeable improvement of ulcerations during the following course of HBO therapy.

Discussion

Livedoid vasculopathy is difficult to manage.[5,6] These skin ulcerations are painful and patients usually suffer difficulty in walking and need narcotics for pain control even when the lesions appear small. Conventional therapeutic approaches, as summarized in Table 2,[5,7–18] usually have slow response and unsatisfactory results. In this study, the most dramatic benefit of HBO therapy for livedoid vasculopathy was rapid pain relief. Patients who had poor ambulation with chronic demand for analgesics resumed ambulation with fewer analgesics after only four to seven sessions, approximately 1 week's time, of HBO therapy. This clinical observation correlated with the finding of substantial reduction of analgesics used by patients in the first to second week after HBO therapy. In our study, the skin ulcerations also resolved rapidly following HBO therapy. The remaining lesions continued to resolve even after cessation of HBO therapy. All ulcers healed in an average of 3·4 weeks. The number of treatments required for complete healing of ulceration depended on the size and number of wounds. Generally, larger-sized wounds required more sessions of HBO therapy. We also observed the resolution of chronic purpuric dermatosis-like lesions on the legs of some patients.

The rationale for using HBO therapy as a treatment modality for livedoid vasculopathy may be related to (i) stimulation of vascular fibrinolytic activity by increased tissue plasminogen activator and urokinase plasminogen activator,[19] (ii) acceleration of vascular proliferation or angiogenesis,[20] (iii) acceleration of fibroblast proliferation and collagen deposition,[21] (iv) diminishing tissue reperfusion injury,[22] and (v) bacteriostatic and bactericidal effects.[23] HBO therapy is associated with aiding the accelerating growth of granulation tissue and faster wound healing rates than in earlier experiences with combinations of oral thrombolytic agents and minidose heparin injection therapy.[9] It is noteworthy that the after-effects of HBO therapy

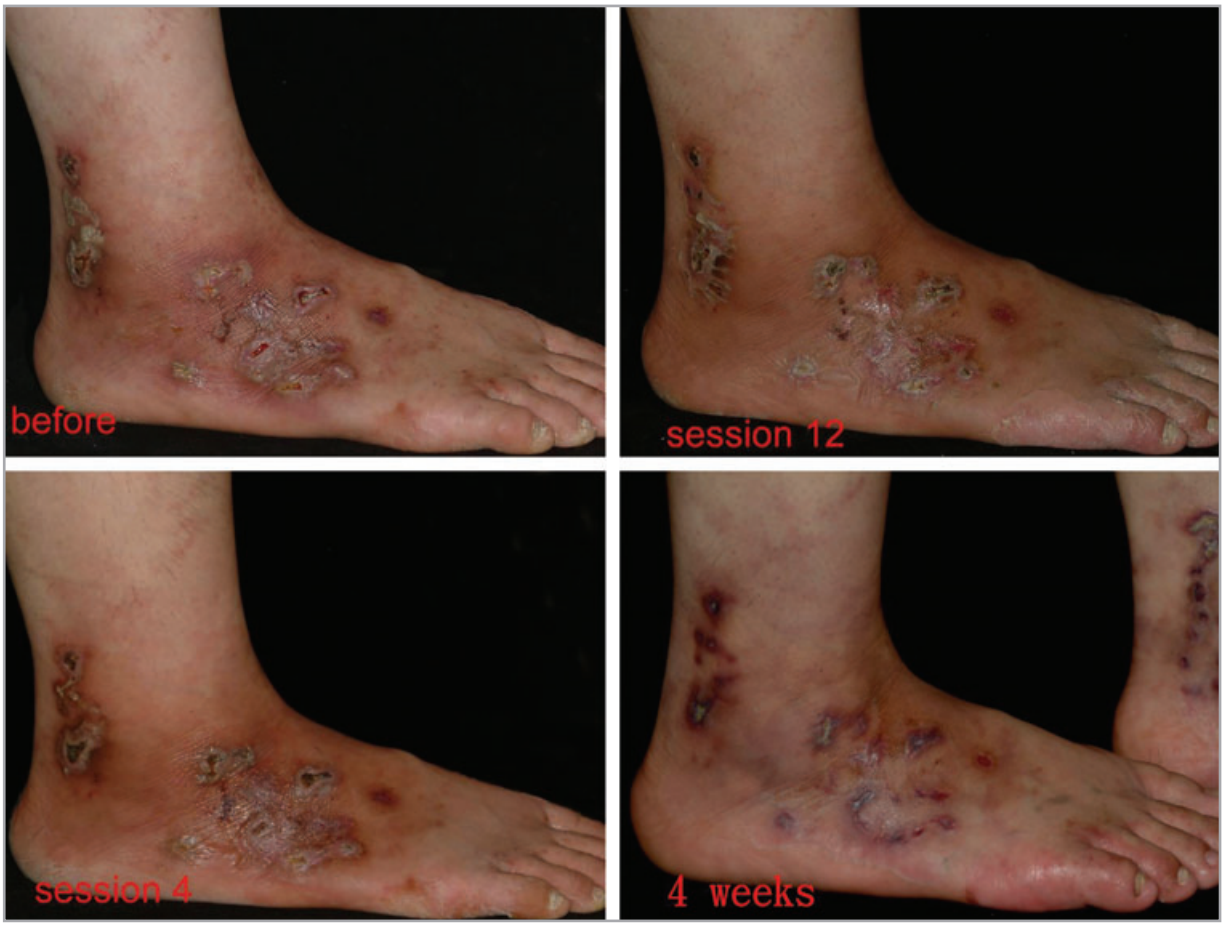

Fig 3. Patient 7. Multiple livedoid vasculopathy ulcerations were noted on dorsal foot. Ulcers healed completely following 4 weeks of hyperbaric oxygen therapy.

could be observed in patients once the treatment had been stopped. The mechanisms involved in such a long-lasting effectiveness may possibly have arisen from the role of HBO therapy in restoring good tissue oxygenation, perfusions and elimination of the above-mentioned factors that are responsible for arrested wound healing.

Although the overall clinical result of HBO therapy was dramatic and had an analgesic-sparing effect, HBO treatment did

Table 2 Summary of conventional therapies used for livedoid vasculopathy

Therapy	First author, year	Responsive case numbers/ total treated	Length of therapy to achieve marked improvement
Dipyridamole and aspirin	Kern, 1982[7]	2/2	1 month
	Drucker, 1982[8]	6/7	2–11 months
	Yang, 1991[9]	13/27	2 months
Pentoxifylline	Sauer, 1986[10]	1/1	9 weeks
	Sams, 1988[11]	7/8	3–11 months
Minidose heparin	Heine, 1986[12]	1/1	3 months
	Yang, 1991[9]	10/14	2 months
Low-molecular-weight heparin	Hairston, 2004[13]	2/2	4–7 months
	Frances, 2004[5]	7/14	3 months
Intravenous immunoglobulin	Ravat, 2002[14]	2/9	1 month
	Kreuter, 2004[15]	9/9	2–22 months
Psoralen and ultraviolet A	Lee, 2001[16]	8/8	10 weeks
Danazol	Hsiao, 1997[17]	6/6	1 month
Tissue plasminogen activator	Klein, 1992[18]	5/6	2 weeks

not prevent disease recurrence. Six of the eight patients completing the study encountered relapses of ulceration. In our limited experience, additional HBO sessions seemed to have resulted in effective responses similar to the initial ones. A longer follow-up period and systemic study may be needed to assess the effect of repeated HBO therapy in these patients.

HBO therapy is generally considered to be a safe therapeutic modality in elective cases with thorough evaluation of patients prior to therapy. Contraindications of HBO therapy, although few, are pneumothorax, malignancy, uncontrolled high fever, pregnancy and seizure disorders.[24] The side-effects, such as chest tightness (15%), reversible myopia (20%), or symptomatic barotrauma of the middle ear (7%), are often mild and reversible.[25,26] One of our patients had a fainting spell in the hyperbaric chamber during the second HBO session. Nevertheless, the situation was particularly unusual in our HBO centre, which had treated over a thousand diabetic foot patients. Four patients reported transient exacerbation of leg pain during the first HBO session, and two patients discontinued HBO therapy for this reason. For the others who continued to receive HBO therapy, this pain diminished shortly afterward. We hypothesized that during the first few HBO sessions, small microthrombi in the vessels of patients with livedoid vasculopathy became lysed. The rapid blood fill-up and elevated oxygen tension can cause tissue reperfusion injury with consequent nerve stimulation and exacerbation of pain. In addition to informing the patients fully of all the possible adverse reactions and treatment outcomes, psychological support is mandatory, particularly when the therapeutic effect of HBO therapy is taking place during the initial treatments, when lesions may be more painful.

Overall, HBO is well tolerated, with few side-effects compared with the use of heparin, aspirin, dipyridamole or pentoxifylline, which may result in life-threatening bleeding disorders of the gastrointestinal tract. HBO therapy is also less expensive compared with other treatment modalities such as low-molecular-weight heparin, intravenous immunoglobulin or tissue plasminogen activator. In this study, HBO therapy has been proven to be a reliable, successful therapeutic alternative for patients with refractory livedoid vasculopathy. Considering that this is an open study without control group, a larger randomized control trial should be done in the future to verify our results further. Whether longer periods of HBO sessions would result in long-term disease remission remains to be determined.

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