

## Hyperbaric oxygen treatment of intractable ulcers in a systemic sclerosis patient.

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**ABSTRACT:** Development of ischemic ulcers is a major clinical manifestation of systemic sclerosis (SSc). The management of these ulcers is often difficult despite the variety of the therapeutic approaches that are used. This report presents a case of intractable ulcers in a patient with SSc, successfully treated with Hyperbaric Oxygen Treatment.

*Key Words:* Chronic wounds, Hyperbaric oxygen therapy.

### INTRODUCTION

Development of ischemic ulcers, due to the underlying occlusive vasculopathy, is a major clinical manifestation of systemic sclerosis (SSc) occurring in 35% to 60% of patients<sup>1</sup>. They tend to appear in the digits but also larger vessels of the lower extremities can be affected<sup>2</sup>. Scleroderma ulcers are associated with pain, reduced quality of life, disability, risk of infection, gangrene and amputation. Their management is often difficult. Therapeutic strategies include mainly vessel-wall acting agents. The dual endothelin-1 receptor antagonist bosentan was shown ineffective in ulcer healing<sup>1</sup>. Intravenous iloprost is effective but not all patients respond as well and its effect on prevention has not been studied<sup>3</sup>. Phosphodiesterase inhibitors are currently lacking sufficient data on ulcer healing.

In this context, hyperbaric oxygen therapy (HBOT) has been used successfully to treat chronic ulcers of vascular etiology. These ulcers are characterized by tissue hypoxia and HBOT has been demonstrated to increase oxygenation of hypoxic wound tissues and promote an anti-inflammatory effect thus stimulating angiogenesis and wound healing<sup>4</sup>.

We discuss a case of intractable ulcers in a patient with SSc, successfully treated with HBOT.

### CASE REPORT

A 75 year old Caucasian woman presented with sclerodactyly and Raynaud's phenomenon in 1962 and was subsequently diagnosed with limited cutaneous SSc. Serologically, antinuclear antibodies were found to be positive at a titer of 1/1280 and she was also positive for antitopoisomerase I antibodies. Later in the course of the disease, contractures of the joints of the hands developed as well as pulmonary fibrosis, diastolic dysfunction of the heart and dilatation of esophagus. The patient had recurrent ulceration of the dorsal surface of the fingers of the hands, which were initially treated conservatively with dressings and administration of bosentan. In December 2009, the patient developed a painful ulcer at the left ankle (Figure 1). At that time, sildenafil was added instead of bosentan; still, three months later the ulcer worsen and in addition a second ulcer appeared at the first toe of the right foot (Figure 2).

Six months after the appearance of the ulcer at the left ankle a progressive deterioration of both ulcers



**Figure 1.** The painful ulcer at the left ankle of the patient.



**Figure 2.** The ulcer at the first toe of the right foot of the patient.

was apparent despite the performed therapy and the patient was referred by the vascular surgeon to the Hyperbaric Medicine Department.

In order to predict patient's response to HBOT, Doppler, ankle / brachial pressure index and transcutaneous oximetry (TcPo<sub>2</sub>) were used (the patient had not undergone digital angiography).

TcPo<sub>2</sub> is measured in normobaric versus hyperbaric hyperoxia conditions and is considered to be the gold standard in the estimation of the diffusion of oxygen in the tissues during hyperbaric tissue hyperoxia (TcPo<sub>2</sub> > 300 mmHg) being reliable both in the selection of patients suitable for treatment as well as in the prediction of the response to treatment. In this particular case, though the TcPo<sub>2</sub> at the left foot under normobaric hyperoxic conditions was not in favor, it presented remarkable results under hyperbaric hyperoxia. Specifically the TcPo<sub>2</sub> at the left foot under hyperoxic conditions was over 350 mmHg and at the right foot over 770 mmHg.

A series of 34 HBO sessions at 244 kPa (2.4 ATA) for 90 minutes was performed plus daily ulcers debridement in order to remove necrotic tissues—exudates and to provoke tissue granulation.

One month after the end of the treatment protocol the patient showed complete healing of the ankle ulcer and a remarkable improvement in the ulcer of the toe. It should be noted that the patient did not need any more to undergo amputation of the toe, according to the vascular surgeon's plan in the beginning. At 6

months follow up healing remained intact (Figures 3, 4). There were no complications associated with the HBO treatment.

## DISCUSSION

Digital ulcers develop in up to 35-60% of patients with scleroderma;<sup>1</sup> they are intensely painful, slow to heal (3-15 months), and affect the quality of life significantly. Their treatment remains suboptimal with amputation being an unavoidable final event in many cases. Thus treatment modalities that could facilitate healing of these ulcers are of great interest.

HBOT consists of inhalation of 100% (FiO<sub>2</sub> 1) oxygen when ambient pressure is higher than the atmospheric one. Oxygen gradient and thus diffusion in plasma is highly elevated and may restore impaired healing and immune response in different diseases<sup>5</sup>. HBO therapeutic effect is well recognized so far through experimental and controlled clinical trials in different kind of ulcers. However evidence for its potential efficacy in SSc ulcers is sparse<sup>6</sup>. HBO promotes the angiogenesis response of the lesion, a function known to be severely disturbed in SSc, through enhancement of fibroblasts proliferation, collagen maturation and bone marrow-derived endothelial precursor cells (EPCs) recruitment (de novo vessels formation)<sup>7,8</sup>.

Although hypoxia is the main stimulator of wound healing, impaired microcirculation and tissue PO<sub>2</sub> < 20 mmHg may lead to inappropriate repair-



**Figure 3.** Complete healing of the ulcer at the left ankle of the patient.



**Figure 4.** Great improvement of the ulcer at the first toe of the right foot of the patient.

ing mechanisms. Vascular endothelium growth factor (VEGF) has been identified as the primary growth factor implicated in neovascularisation. HBOT enhances the VEGF receptors response on endothelial cells (while hypoxia up-regulates them) promoting angiogenesis and vasculogenesis<sup>9</sup>.

Furthermore impaired basal NO production may contribute greatly to the development of SSc vascular lesions by enhancing vasospasm, platelet aggregation and the up-regulation of endothelial and leucocyte adhesion molecules (selectins,  $\beta$  integrins and intercellular cell adhesion molecule/ ICAM1 1)<sup>10</sup>.

HBOT has being shown experimentally and clinically to promote the NO synthesis and to down regulate the appearance of pro-inflammatory cytokines. HBOT exhibits its anti-inflammatory effect by stimulating phagocytosis of leucocytes and also by inhibiting specific cytokines of monocyte-macrophages as are IL-1, IL-6, IL-8 and TNF- $\alpha$ <sup>7,11</sup>. These cytokines have been shown to be upregulated in SSc<sup>12</sup>.

In this context, HBOT seems to interfere with critical pathways in the development of ulcers in SSc and may have a potential role in their healing. We provide evidence of healing of intractable ulcers in a patient with SSc with HBOT. This treatment modality may be proved a valuable supplement in the treatment algorithm of SSc ulcers. Still, although this case report shows the beneficial effect of HBO, further research is needed to support its therapeutic action in SSc. Given

the fact that HBO mechanisms of action target the pathophysiology of SSc ulcers a controlled randomized study could yield the above therapeutic effect as an adjunctive treatment in the therapeutic armamentarium of these patients.

## Θεραπεία με υπερβαρικό οξυγόνο δυσίατων ελκών σε ασθενή με συστηματική σκλήρυνση: Περιγραφή περιστατικού.

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**ΠΕΡΙΛΗΨΗ:** Η ανάπτυξη ισχαιμικών ελκών αποτελεί μείζονα κλινική εκδήλωση της συστηματικής σκλήρυνσης (ΣΣ). Η αντιμετώπιση των ελκών αυτών είναι συχνά δύσκολη παρά την ποικιλία θεραπευτικών μεθόδων που χρησιμοποιούνται. Αυτή η εργασία παρουσιάζει ένα περιστατικό δυσίατων ελκών σε μία ασθενή με ΣΣ, τα οποία αντιμετωπίστηκαν επιτυχώς με θεραπεία με Υπερβαρικό Οξυγόνο.

Λέξεις Κλειδιά: Χρόνια έλκη, Υπερβαρικό οξυγόνο.

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