

Hyperbaric oxygentherapy as an adjuvant in the treatment of diabetic foot




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Abstract

Diabetic foot ulcers affect about 20 % of patients. They affect the quality of life and increase the risk of mortality, as main complication. Treatment currently includes the use of drugs and surgical debridement of the ulcerated tissue. Among its coadjuvant therapies, the use of hyperbaric oxygen therapy stands out as it reduces the risk of complications. This study seeks to describe the use of hyperbaric oxygen therapy as an adjuvant in the treatment of diabetic foot. A literature review was conducted using databases: PubMed, Elsevier, SciELO, and in Spanish and English languages, published between 2018 and 2023. Hyperbaric oxygen therapy consists of placing the patient in a higher-pressure environment, with oxygen concentrations close to 100 %, resulting in anti-inflammatory effects. The approach to the diabetic foot should be multidisciplinary in order to achieve early recovery, including a pharmacological approach to manage neuropathic pain and cure infections. Hyperbaric oxygen therapy has been considered as a coadjuvant treatment by increasing the percentage of complete healing to 33.3 %, facilitating healing, increasing and reducing the perceived pain. It concluded that there are publications that support the use of hyperbaric oxygen therapy in addition to conventional therapy, because it improves the healing rate and reduces the risk of major amputations.

Keywords

Hyperbaric Oxygenations, Diabetic Feet, Amputation Surgical, Diabetes *mellitus*, Vascular Disease, Foot Ulcer.

Resumen

Las úlceras de pie diabético afectan alrededor del 20 % de los pacientes. Estas afectan la calidad de vida e incrementan el riesgo de mortalidad, como principales complicaciones. El tratamiento actual incluye la utilización de medicamentos y la desbridación quirúrgica del tejido ulcerado. Dentro de sus terapias coadyuvantes se destaca el uso de la oxigenoterapia hiperbárica que reduce el riesgo de sus complicaciones. Por esto se busca describir el uso de la oxigenoterapia hiperbárica como coadyuvante en el tratamiento de pie diabético. Por lo tanto, se realizó una revisión bibliográfica utilizando bases de datos: PubMed, Elsevier, SciELO, y en los idiomas español e inglés, publicados entre 2018 y 2023. La oxigenoterapia hiperbárica consiste en colocar al paciente en un entorno de mayor presión, con concentraciones de oxígeno cercanas al 100 %, resultando en efectos antiinflamatorios. El abordaje del pie diabético debe ser multidisciplinario con el fin de lograr una pronta recuperación, incluyendo abordaje farmacológico dando manejo al dolor neuropático y a la curación de las infecciones. La oxigenoterapia hiperbárica se ha considerado como tratamiento coadyuvante al aumentar el porcentaje de curación completa a un 33,3 %, facilitando la curación, aumentando y reduciendo el dolor percibido. Se concluye que efectivamente existen publicaciones que respaldan el uso de la oxigenoterapia hiperbárica adicional a la terapéutica convencional ya que mejora la tasa de curación y reduce el riesgo de amputaciones mayores.

Palabras clave

Oxigenoterapia hiperbárica, pie diabético, amputación quirúrgica, diabetes *mellitus*, úlcera de pie.


Introduction

Diabetes *mellitus* has affected almost 500 million people around the world; the most serious and most frequent complication is the diabetic foot, which evolves from diabetic neuropathy, vascular disease, diabetic foot ulcer (DFU) to osteomyelitis.^{i,ii}

Diabetic foot disease develops in patients who abandon their treatment

or do not attend their medical check-ups,ⁱⁱⁱ which usually leads to amputation and disability.^{iv}

About 20 % of diabetic patients develop DFU, which increases visits to emergency departments and hospitalization, raises the risk of mortality, and elevates the costs of patients with diabetes in the healthcare system by up to 40 %.^v

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Between July 2014 and August 2018, about 26 million people with DFU were registered worldwide, and 130 million were at risk of developing diabetic peripheral neuropathy.^{vi} There is evidence that 19 to 35 % of UPDs do not heal, and 10 to 20 % progress to amputation despite careful treatment with conventional therapies.^{vii}

Hyperbaric oxygen therapy (HBO) favors the resolution of lesions in diabetic patients by increased tissue oxygenation at the local level and the measurement of transcutaneous oxygen pressure,^{viii} through the reduction of the risk of major amputations; consequently, it improves the patient's quality of life and presents a higher healing rate in patients with DFU,^x because it reduces the surface area of the treated wounds, the pain perceived by the patients,^x and the healing time of DFU compared to the exclusive use of conventional treatment.^{xi} Likewise, HBO has demonstrated a reduction in hospital stays, emergency department visits, and treatment costs.^{xii} For this reason, this review aims to describe the use of HBO as an adjuvant in treating diabetic foot.

Discussion

Hyperbaric oxygen therapy as an adjuvant in the conventional treatment of diabetic foot

The current treatment of the diabetic foot consists of a multidisciplinary approach using three key steps: identification of diabetic patients at risk, treatment of the affected foot, and measures to prevent recurrence.^{xiii} The pharmacological approach to diabetic foot care focuses on the management of neuropathic pain and the prevention or cure of infections, whether localized or systemic, associated with the lesion.^{xiv}

In addition to drugs, there are also different techniques in use, such as surgical debridement of the ulcerated tissue to promote healing, the use of wheelchairs, crutches, customized orthopedic footwear, or other devices that allow weight redistribution.^{xv}

Among these adjuvant techniques is HBO which, according to Salama *et al.*, can reduce the ulcerated surface from an average of 7.5 cm² to 2 cm² after 30 sessions of HBO and, in addition, the complete closure of the wounds was 33.3 % greater, compared to the control group.^{xvi} With this, an ease in DFU healing and a reduction in the need for additional surgical procedures are described^{xvii} and summarized in the patient's quality of life.

In soft tissue infection, HBO has shown to reduce the mortality rate associated with

this condition, with a relative risk of 0.55,^{xviii} although it did not represent significant changes in in-hospital stay ($p = 0.96$) or the number of debridement required for healing of the lesion ($p = 0.17$).^{xix}

It is described that at least 60 % of non-traumatic amputations occur due to diabetes-related complications.^{xx} Hyperbaric oxygen therapy has been shown to have a positive effect in reducing the risk of a major amputation (OR = 0.53, 95 % CI [0.32; 0.90], $p = 0.02$), and has a positive impact on minor amputation when compared to conventional therapy (OR = 0.89, 95 % CI [0.35; 2.24], $p = 0.80$). About the total healing of ulcerated tissue, it is observed that the ulcers of patients who underwent HBO had a complete resolution that was higher at 23 % (OR = 4.00, 95 % CI [1.54; 10.44], $p = 0.005$), compared to the group that received conventional therapy.^{xxi}

The effect of HBO is not limited to its impact on DFU but also reduces glycemia levels and increases insulin sensitivity in patients with type 2 diabetes mellitus (DM2).^{xxii} Heyboerli *et al.* observed that in 75 % of 1825 HBO sessions, there was a reduction in glycemia levels, with a mean decrease of 25 mg/dL in patients with DM2, while they only observed a 51.5 % reduction in patients with type 1 diabetes mellitus (DM1).^{xxiii}

Some absolute counter-indications to the use of HBO include pneumothorax, chemotherapy with cisplatin and doxorubicin, hyperthyroidism, and congestive heart failure with LVEF <30 %.^{xxiv} In addition, adverse effects of HBO were reported, including middle ear barotrauma, most frequently described as hyperoxic myopia, claustrophobia, hypoglycemia, pulmonary barotrauma, and oxygen-mediated central nervous system toxicity.^{xxv}

Mechanism of action and application of hyperbaric oxygen therapy (HBO)

HBO consists of placing a patient in a high-pressure environment and boosting an inspiration of 100 % oxygen at the usual minimum acceptable pressure of 1.4 atmospheres absolute (ATA), under specific indications (Table 1),^{xxvi} with an average duration of two hours daily, with two ten-minute breaks.^{xxvii}

Oxygen dissolves in the plasma and increases oxygen pressure (pO_2) from 2.0 to 3.0 ATA to achieve an arterial oxygen pressure (PaO_2) between 1200 and 2000 mmHg. This hyper-oxygenation causes therapeutic effects at the molecular level because it triggers functional and structural changes that allow tissue recovery.^{xxviii,xxix}

Table 1. Specific indications for hyperbaric oxygen therapy

Arterial or venous air or gas embolisms.
Severe or symptomatic carbon monoxide poisoning.
Myositis and clostridial myonecrosis (gaseous gangrene).
Selected crush injuries, compartment syndrome and other acute traumatic ischemia.
Decompression sickness.
Selected arterial insufficiencies, including central retinal artery occlusion and improved healing in selected problematic wounds.
Specific intracranial abscesses.
Chronic refractory osteomyelitis.
Delayed radiation injuries with bone or soft tissue necrosis.
Acute thermal burn injuries.

Source: Essentials of Hyperbaric Oxygen Therapy: 2019 Review.^{xxxv}

Moghadam *et al.* describe that the most relevant effect that HBO allows is the production of free radicals in a therapeutic range for the initiation of cell signaling that induces oxidative stress and generates in the short term, an improvement in oxygen supply; consequently, it produces anti-inflammatory effects and reduces the injury caused by ischemia, while, in the long term, it induces neovascularization, angiogenesis and collagen production.^{xxxviii}

The pathology of delayed healing of lesions is associated with a prolonged oxygen deficit explained by hypoxia, which generates an imbalance that delays the appearance of proinflammatory cells causing an expression of growth factors, angiogenesis, and defective extracellular matrix formation. A hyperglycemic state destabilizes the hypoxia-inducible factor, and therefore, dysregulation of the activation of varied factors appears, contributing to the progression of the disease.^{xxxix}

Hanley *et al.* described inadequate skin oxygenation as a risk factor triggering complications that lead to amputation. The use of HBO in patients with DFU Wagner classification 3 or higher, who have undergone recent surgical debridement, generates a reduction in the risk of amputation; therefore, the use of this treatment is considered an adjuvant in those patients who have not improved after 30 days of conventional therapies.^{xxxix}

According to Menmar *et al.*, HBO increased the frequency of DFU healing, and decreased the need for amputations and debridement, thus decreasing the need for surgical treatment with amputa-

tions and debridement.^{xxxiv} Sharma *et al.* identified a significantly lower amputation rate compared to conventional therapy with a significant statistical difference (HBO 27/232 compared to ST 46/23, $p = 0.02$);^{xxxv} in addition to a decrease in HbA1c levels in Wagner 3-4 patients.^{xxxvi}

Characteristics of the systemic oxygen therapy and local oxygen therapy

HBO represents a therapeutic approach that can be delivered systemically, placing the patient in a completely closed environment, in a pressurized chamber known as a hyperbaric chamber, in which an ambient pressure higher than the conventional atmospheric pressure is administered. During this session, pure oxygen is applied, which generates a significant increase in oxygen pressure (pO_2) higher than one atmosphere in the body, and leads to the removal of oxygen in tissues and body fluids.^{xxxvii}

The alveolar pO_2 increases significantly and consequently triggers a series of biological reactions, such as an increase in the oxygen content present in the blood plasma, an increase in the metabolic activity of the cells that receive optimized amounts of oxygen, and the positive influence of the HBO that is not limited to the cellular level but extends to the systemic level. Therefore, the elevation of alveolar pO_2 generates a biological environment conducive to counteract tissue hypoxia through regeneration, repair, and reduction of the inflammatory reaction.^{xxxviii} The treatment is administered in a monoplane chamber, where only one person is placed at a time, although there are also larger chambers, called multiple, where two or more people can be treated at the same time.^{xxxix}

HBO can also be administered locally, called topical oxygen therapy, which consists of the application of 100 % pO_2 directly to the base of an open wound at a pressure above sea level (>1 ATA),^{xl} through chambers that fit snugly around a limb using disposable polyethylene bags that facilitate administration in a controlled environment.^{xli} Consequently, it increases the amount of oxygen that dissolves in the patient's plasma through the circulatory system; this more efficient and deeper oxygenation of the cells allows them to optimize their metabolic functions.^x

Pasek *et al.* conducted a study about the use of local oxygen therapy in the treatment of DFU, in which 45 patients with diabetic foot received 30 sessions of local HBO therapy at a pressure of 2.5 ATA. The

outcome presented the progress of wound healing, which was evaluated by computerized planimetry. It showed that wound surface area was significantly reduced with a decrease in mean ulcer area from 8.54 ± 3.34 cm² before treatment to 4.23 ± 3.23 cm² ($p = 1 \times 10^{-6}$) after treatment (Table 2).^{xliii}

On the other hand, Stoekenbroek *et al.* studied systemic oxygen therapy, highlighting its benefit due to the accelerated healing process of ischemic ulcers at the local level with a reduction in pain intensity, as perceived by the patient.^{xliiii} Likewise, Abidia *et al.*, conducted a study with 18 patients who received HBO for one year, in which a significantly greater healing process was evidenced; complete healing was achieved in five out of eight ulcers in the group treated with HBO compared to zero out of eight ulcers in the control group ($p = 0.026$).^{xliiv}

In addition, it is worth mentioning that there was evidence of increased healing of grade 3 and 4 ulcers of the Wagner-Merrit Scale classification in persons who received systemic HBO,^{xliv} but there has not been a study comparing the classification with local HBO. It is suggested that systemic HBO may be a valuable adjunctive therapy as it has shown a positive evolution in hypoxic skin of lower limb vascular lesions in acute and chronic lesions.^{xlvi,xlvii}

Research advances show the benefits of systemic and local oxygen therapy for patients with DFU^{xlviii} and continue to clarify the therapeutic effects of these modalities; however, it is recommended that

large-scale randomized controlled trials be conducted to generate more evidence of their effectiveness.

Conclusion

The use of local and systemic HBO as an adjuvant in the treatment of DFU is effective in reducing the size of the ulcer, with better and faster healing, reduction of local edema, and reduction of local pain; however, it represents an additional cost to the treatment due to the use of instruments and studies that define whether a patient is eligible for this treatment.

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Table 2. DFU surface area before and after completion of local HBO procedures

	UPB Surface area (cm ²)			p
	n (%)	Before treatment	After treatment	
		Media ± DE	Media ± DE	
Total	45 (100 %)	8.54 ± 3.34	4.23 ± 3.23	1 x 10 ⁻⁶
Gender				
Male	24 (53.3 %)	8.98 ± 3.67	4.62 ± 3.39	1.8 x 10 ⁻⁵
Female	21 (46.6 %)	8.03 ± 2.94	3.79 ± 3.05	6 x 10 ⁻⁵
p		0.372438	0.36039	
		Age (years)		
<60	11 (24.4 %)	6.66 ± 2.37	2.79 ± 1.44	3.346 x 10 ⁻³
60-70	16 (35.5 %)	8.96 ± 3.58	4.51 ± 3.13	0.438 x 10 ⁻⁴
>70	18 (40 %)	9.31 ± 3.36	4.87 ± 3.9	1.96 x 10 ⁻⁴
p		0.1411	0.4616	
		Foot		
Left	26 (57.7 %)	8.23 ± 3.19	4.13 ± 3.38	8 x 10 ⁻⁶
Right	19 (42.2 %)	8.95 ± 3.6	4.38 ± 3.09	1.32 x 10 ⁻⁴
p		0,690505	0,758774	

Source: Local hyperbaric oxygen therapy in the treatment of diabetic foot ulcers^{xlix}.

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