Evaluation of the Occlusive Arterial Disease and Diabetic Angiopathy Treatment Effects by Hyperbaric Oxygenation

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ABSTRACT

Introduction: One of the most severe complications of atherosclerosis is arterial occlusive disease (AOD) and with diabetic angiopathy (DA), is a common chronic problem in clinical practice worldwide. Hyperbaric oxygen (HBO) therapy is a therapeutic modality for solving all forms of hypoxia. Aim: To compare the treatment with HBO therapy in patients with AOD and DA ischemic symptomatology with standard treatment i.e. vasodilators, antibiotics, antiplatelets and statins, and to demonstrate the benefit of the therapeutic modality itself. Methods: We conducted a clinical prospective study and included a total of 80 patients, divided into two groups: 40 patients with the arterial occlusive disease and lower-extremity wounds, with sub-group (n=20) treated with HBO therapy on the top of the standard therapy and 40 patients with diabetic angiopathy and diabetic lower-extremity wounds, with sub-group (n=20) treated with HBO therapy on top of the standard therapy. Results: The efficacy of therapy in patients treated with HBO therapy on the top of standard therapy was significantly higher than in the group of HBO non-treated patients. There was a significant improvement in 9 patients treated with HBO therapy, while in HBO non-treated patients the significant improvement effect was observed only in one patient. Conclusion: HBO therapy is an effective therapeutic component in the healing of diabetic lower-extremity wounds in the patients with AOD and DA. In our patients HBO therapy on the top of standard therapeutic protocol has an effect of reducing the number of lower-limb amputations in patients with AOD and DA. These results support clinical use of HBO therapy for diabetic lower-extremity wound healing.

Keywords: Hyperbaric oxygen therapy, Arterial occlusive disease, Diabetic angiopathy, Lower-extremity wounds.

1. INTRODUCTION

Atherosclerosis still represent the main cause of morbidity, mortality premature incapacity and disability worldwide. Current predictions suggest that by 2025, atherosclerotic cardiovascular disease (ASCVD) will become the leading cause of all diseases and social burden, defined as years deprived of a healthy life due to inactivity or premature death (1-3). One of the most severe complications of atherosclerosis is arterial occlusive disease (AOD) that affects the aorta, extracranial arteries as well as the arteries of upper and lower limbs. AOD occurs at different clinical stages, in particular the stage of clinically significant flow reduction with ischemia of the tissue and the development of ischemic ulceration or gangrene. The overall treatment of these patients represents a tremendous medical and socio-medical problem for each society due to long-term hospitalization, complicated surgical-reconstructive interventions, and/or intervention procedures, and premature disability (3, 4). The AOD prevalence varies depending on life expectancy, disease duration, type of vascular disease, as well as possible presence of diabetes mellitus and arterial hypertension (HTA). The general prevalence of AOD varies from 0.9 to 6.9%, especially in the age group 50-60 (5, 6). Total mortality depends on correlation between AOD, cerebrovascular and congenital diseases. Total cardiovascular mortality in AOD patients is 20-30% after 5 years, 60% after 10 years and 75% after 15 years of disease duration (2). According to World Health Organization indicators, diabetes mellitus is one of the diseases that are currently the most widespread worldwide. Diabetes mellitus is a metabolic disorder caused by insulin deficiency (insulinopenia), and it is a condition of...
diabetes-induced angiopathy can be divided into: macrovascular and microvascular. The vascular system can, in the narrow sense, be divided into: the macrovascular and microvascular system by the size of the blood vessels. Consequently, diabetes-induced angiopathy can be divided into: macrovascular and microvascular angiopathy. Both of these complications of diabetes are chronic in their course and are caused by various mechanisms, while at the same time causing different changes. Microangiopathy mainly affects arterioles, venules and capillaries (i.e. blood vessels involved in microcirculation) of the kidneys, retina and nerves. Macroangiopathies include large blood vessels that participate in macro-circulation mainly of the heart, brain and the limbs (8).

Macrovascular diabetic angiopathy, as a chronic complication of the major arterial system within diabetes, has a clear and proven basis in the so-called. accelerated atherosclerosis, accelerating atherosclerotic processes in diabetics (7). The basic process in the development of diabetic angiopathy is the process of atherosclerosis and numerous studies have shown that the process has a systemic character. Changes resulting from diabetic angiopathy at the lower limbs lead to a range of symptoms such as: flatulence of the skin, foot and foot paesthesia, loss of thermal sensation, loss of pain, fungal infections, ischemic changes (skin lesions, fingers and/or feet) and necrotic changes. Risk factors that cannot be influenced are: age, sex and type of diabetes. Risk factors that can be influenced include: smoking, hypercholesteremia, hypertension, obesity, hyperglycemia, hyperfibrinogenemia (9).

Hyperbaric Oxygenation (HBO therapy) is a therapeutic method of solving all forms of hypoxia (2). HBO therapy is based on normalization of oxygen system transport functions, reduction of arterial hypoxemia, reduction of HbA1c, increased myocardial contractility, decreased pulmonary hypertension, increased blood flow in the limbs, decreased adhesion and platelet aggregation activity. HBO therapy have the advantage of reduction of tissue hypoxia, edema, increase angiogenesis and erythrocytes deformability, antimicrobial effects and increase fibroblastic activity (8-11).

2. AIM

To compare the treatment with hyperbaric oxygenation in patients with AOD and DA hypertension with standard treatment (vasodilators, antibiotics, anti aggregation drugs and statins), and to demonstrate the benefit of the therapeutic modality itself.

3. METHODS

This is a clinical prospective study, and included follow up of 80 AOD and DA patients during the 12 months divided into two groups: 40 patients with AOD and lower-extremity wounds, sub-group (n=20) treated with HBO therapy on the top of the standard treatment, and 40 patients with DA and diabetic lower-extremity wounds, sub-group (n=20) treated with HBO therapy on the top of the standard treatment. Both sub-groups i.e. AOD with lower-extremity wounds (n=20) and DA with diabetic lower-extremity wounds (n=20), were treated with standard therapies.

The examination and treatment of the patient was performed at the Department of Angiology, Clinical Center University of Sarajevo (CCUS) and approval was obtained by the CCUS Ethics Committee.

The inclusion criteria were: confirmed diagnosis of arterial occlusive disease and diabetic lower-extremity wounds, confirmed diagnosis of DM and diabetic angiopathy and patients who have informed consent.

Exclusion criteria were: confirmed diagnosis of arterial occlusive disease and diabetic lower-extremity wounds, confirmed diagnosis of DM and diabetic angiopathy but reliable indication for vascular surgery or interventional procedure, and patients who have not informed consent.

The chamber used was the “monoplace” chamber made by BARA-MED SMOOTH-RIDE, produced by Environmental Tectonics Corporation, Southampton USA. The patient was placed in lying position with visual and audio surveillance by trained medical staff. Patient treatment took place under the MEDWOUND program for a total duration of 80 minutes. The skin changes recorded prior to HBO treatment and were monitored continuously, with a review of the changes in the wound size as well as the wound depth, granulation, exudation, surrounding inflammation, and hence determined the outcome of the therapy.

Student t test was used for statistical data processing, with Shapiro-Wilk test because data followed normal distribution. All analysis results at p<0.05 or 95% confidence levels were considered statistically significant. For the statistical analysis of the data obtained, the software package SPSS for Windows (version 21.0, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel (version 11 of Microsoft Corporation, Redmond, WA, USA) were used.

4. RESULTS

We included total of 80 patients, divided in two groups: HBO therapy in a patient with AOD and lower-extremity wounds (n=40) and group of patients with DA treated with HBO therapy on top of standard therapy (n=40). Statistical analysis showed no significant differences in sex, age, cigarette smoking, total cholesterol level, LDL.
choler level, fibrinogen value at initiation of treatment, and the existence of diagnosed hypertension among the patient groups analyzed. The fibrinogen value at the end of the treatment was slightly higher in patients who were not treated with HBO therapy compared to the group of patients treated with HBO therapy and the established differences were significant (p<0.02). The improved in patients with AOD treated with HBO therapy was significantly higher (p<0.01) than in the sub-group of AOD patients who had not been treated with HBO therapy (Figure 1).

Total number of patients with DA, those treated with HBO therapy and non-treated with HBO therapy were 20 patients in each group. There were no significant differences in sex, total cholesterol values, LDL cholesterol levels, fibrinogen levels before and after treatment between these two groups.

The difference between the age of the patients between these two groups was significant (p<0.02). In the group of patients non-treated with HBO therapy, there were more smokers than in HBO therapy treated patients, and these differences were significant (p<0.025). Fibrinogen differences at baseline and post-treatment was significantly lower in patient treated with HBO therapy (p<0.01) than patients who did not receive HBO therapy. Statistically significantly higher number of patients (p<0.05) with DA in non-HBO therapy group had HTA compared to the group of patients with DA HBO therapy group. The efficacy in DA patients sub-group treated with HBO therapy was significantly higher compared to a group of patients who were not treated with HBO therapy (p<0.01) (Figure 2). Namely, there was a significant improvement in 9 patients treated with HBO therapy after therapy while in non-treated HBO therapy patients the same effect was observed only in one patient (Figure 2). On the other hand, seven patients who did not receive HBO therapy were reported to have deterioration of condition, while no such case was detected in the HBO therapy group (Figure 2). Namely, there was a marked improvement in 9 patients treated with HBO therapy after therapy while in non-treated HBO therapy patients the same effect was observed only in one patient (Figure 3-5). On the other hand, seven patients who did not receive HBO therapy were reported to have deterioration of condition, while no such case was detected in the HBO therapy group.

5. DISCUSSION

HBO therapy is a therapeutic method for solving all forms of hypoxia (method of treating ischemic wounds occurring in chronic oxygen deficiency and when local
oxygen pressure is below optimal) (2). Mechanisms of hyperbaric oxygenation are based on normalization of oxygen system transport functions, reduction of arterial hypoxemia, reduction of glycolyzed hemoglobin (HbA1c), increased myocardial contractility, decreased pulmonary hypertension, increased blood flow in the limbs, decreased adhesion and platelet aggregation activity (9, 10, 11). It significantly reduces plasma concentrations: anti-insulin hormones, glucagon, catecholamines, lipids, tissue metabolism products and normalizes erythrocyte pH (2, 10, 11). The main effect of HBO is the stimulation of fibroblast proliferation and differentiation, increased collagen formation and cross-linking, increased neovascularization and stimulation of leukocyte destruction of the microbe (7, 12).

Ischemic tissues also benefit from hyperoxygenation through improved maintenance of energy metabolism and reduction of edema. The usual hyperbaric oxygen pressure in the hyperbaric chambers ranges from 2 to 2.5 absolute atmospheres (ATA) for 90 minutes once or twice a day. Perrins and Barr described the results in 50 patients with arteriosclerotic ulcers treated only with HBO (1.5-2.6 ATA). Healing was achieved at 52% and improvement in 20% of patients. These were all geriatric patients and amputation was avoided in 65% of patients (13). The same authors treated 8 other patients with skin transplant and HBO. From baseline 7 were cured and no effect was observed in the last patient. The conclusion of these authors is that many patients with AOD-related ulcer that are resistant to treatment by other methods can be cured by prolonged cholema HBO, the reaction depends on the dose; some ulcers react to 1.5 ATA while others need 2.6 ATA. Some do not respond to treatment in a total of 2 hours per day, while others are treated less than 1h per day. The required treatment period may be significantly reduced if the base of the ulcer is prepared with HBO chest before skin transplantation (11, 12, 13). Our approach is that isolated ischemic ulcer treatments are less successful and less effective, as other authors stated. Kostiunin and colleagues analyzed the HBO treatment of 122 patients with advanced stage AOD and showed that the benefit of HBO can be increased by a combination of constant intraperitoneal infusions and lumbar sympathomimetics. An important factor is also the increase in low heart output (14).

The basic treatment should be started by a physician specializing in diagnosing, treating and monitoring the patient, and HBO therapy should be used in conjunction with early treatment, antibiotic therapy, medication and other therapeutic aspects involved in the process (anti aggregation drugs, statins, ACE inhibitors, etc.) (15).

Two basic types of arterial ischemic ulcers are included in the study, those with AOD and DA. The mean age of patients with AOD was 66.65 years, and patients with DA 60.9 years. Researchers in other studies included mainly patients with one type of illness with an average age of 70.

In our study, HBO therapy was performed in an average of 21 days with one-day sessions of 80 minutes with 100% oxygen and a pressure of 2.4 ATA, while in comparative studies HBO therapy was performed at an average of 40 days.

Urayama and colleagues investigated the therapeutic effects of HBO in patients with chronic AOD in 50 patients. These patients had different limbs ischemia: sleeping pain, ulceration, etc. HBO was used at 2 ATA for 60 minutes and the number of sessions ranged from 3 to 40. 5 out of 6 patients with resting pain were cured. Necrosis or ulceration is cured in 16 out of 30 patients. Oxygen transduction was significantly elevated during the HBO session (15).

Kovačević performed a placebo-controlled double-blind study of the HBO effect on AOD in 65 patients. A group of 35 patients received HBO at 2.8 ATA twice a day, during 20 treatments in a 2-week period. A control group of 30 patients received a mormic acid mix (nitrox 7.5) to inhale in the hyperbaric chamber. Both groups had conservative medical therapy and it is recommended that they quit smoking. The treated group showed improvement over the first three months, which was manifested by increasing the walking distance without pain. The improvement continued during the following 6 months (16).

In our study, we noted a significant improvement in both patient groups (AOD and DA) treated with HBO therapy that coincide with other studies, especially in the DA group. In the group of patients with AOD, marked improvement was observed in 25% of patients and improvement in 60% of patients while in 15% of patients the effect of therapy was unchanged. In a group of patients with DA the effect of therapy was significantly higher in patients treated with HBO therapy where there was a marked improvement in 45% of patients and moderate improvement in 40% of patients, whereas the same effect in patients in the control group who did not receive HBO therapy was only 5%. On the other hand, as many as 35% of patients with the exacerbation were observed in the control group, and no cases were detected in the HBO therapy group.

Faglia et al. Also presented effects (17), and recommended a method for everyday use. Clinical implications: Hyperbaric oxygen therapy is an increased benefit in treating problematic wounds, especially in ischemic ulceration of patients with DA (12-15).

However, our results suggest that these options should be used in both groups, in diabetic (as in other studies), but also in non-diabetic foot ulcers (for which we do not have data from other studies). There is also concern about the unnecessary, inadequate and prolonged use of this additional treatment. To prevent excessive use of HBO therapy centers, a multidisciplinary angiology/vascular team should be included. Intermediate correction of hypoxia with early oxygen therapy increases the replication of fibroblasts and collagen production. Early hypoxia can be corrected by oxygen therapy to oxygenate the hypoxic centers of chronic irreducible wounds. Hypoxia may occur in normally perfused tissue when we have a saliva reaction at that site and HBO therapy at 1.8-2.6 ATA has proven to be good for improving tissue oxygenation. Raising oxygen pressure early increases the
ability of leukocytes to kill pathogenic bacteria. Oxygen at 1.8-3.0 ATA increases the degree of epithelialization in ischemic wounds, as well as neoangiogenesis in wounds.

The assessment of the hospital and cost of rehabilitation for patients after diabetic lower-extremity wounds amputation has shown that the use of HBO therapy as an additional treatment of these patients may result in reducing the post-operative cost of medical care.

6. CONCLUSION
Hyperbaric Oxygen therapy is an effective additional therapeutic component in the treatment of diabetic lower-extremity wounds and in non-diabetic arterial occlusive disease. Hyperbaric Oxygen therapy associated with standard aggressive therapeutic protocol can lead to a reduction in the number of complications and amputations in patients with diabetic angiopathy and arterial occlusive disease in non-diabetics.

- **Author’s contribution**: A.B. and M.D. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. M.D. had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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