UPDATES ON ADJUVANT TREATMENT OF CHRONIC LEG ULCERS USING OXYGEN THERAPY

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Keywords: chronic ulcerations, oxygen role, hyperbaric oxygen, topical therapy with oxygen **Abstract:** Chronic ulcerations are an important cause for morbidity, with impact mainly on the elderly population. In the present article we bring up the role of oxygen in curing ulcerations, by involving it in all healing stages, respectively inflammation, proliferation and remodeling. The therapeutic options existent for improving the local oxygenation are presented: therapy with hyperbaric oxygen (TOHB), topical therapy with oxygen (TTO) and bandages which generate oxygen (OxyzymeTM); also, the results of recent studies are synthesized, studies regarding the effect of these therapies with regard to the improvement of the cure rate of chronic leg ulcers, with no tendency of cure based on classic treatments. Taking into consideration the heavy evolution and the resistance to classic treatments of chronic ulcerations, as well as high nursing costs, the devices that increase the oxygen concentration on ulcerations can represent an adjuvant treatment against this pathology.

Chronic ulcers represent the persistence of ulceration for more than 3 months, which delays ulcer healing and removal in one of the healing stages, most often in the inflammation stage.

Peripheral venous pathology is the main etiology of chronic ulcers of the lower limbs (legs), with percentages of 50% to 80%.(1) Diabetes contribution to the etiology of chronic ulcers is 10-25 %.(2) We mention two studies that reported close data in terms of etiology of ulcers, respectively venous ulcers etiology in 47.6% *versus* 43% of cases, arterial ulcers 14.5% *versus* 4% of cases, while 17.6% respectively 15% among chronic ulcers had mixed etiology.(3,4) Another study reported a prevalence of 35.5% of the chronic venous disease and a prevalence of 1.5% of ulcerations in patients with severe chronic venous insufficiency.(5) Recent data have pointed to the alarming increase in peripheral arterial pathology and of diabetes, both conditions being involved in the etiology of chronic leg ulcers estimating an increase of 50.81 % in the number of patients with diabetes by 2030.(6)

Taking into consideration the difficult evolution and the resistance to classic treatments of chronic ulcerations, as well as high nursing costs, the devices that increase the oxygen concentration on ulcerations can represent an adjuvant treatment against this pathology.

Nowadays, the cellular and biological mechanisms involved in the process of cellular proliferation and aging are well known, oxygen being involved in different stages of this process. By methods of transcutaneous oximetry has been proven that on the level of chronic ulcerations there are different stages of tissue hypoxia, thus, the improvement of oxygenation at this level being a logical consequence. Besides the classic interventions of improving local oxygenation by ameliorating circulation, using procedures of for patients with peripheral vascular affectation, several methods of local or systemic increase of oxygen supply on the level of hypoxic tissues were attempted. Thus, new methods and oxygen delivery devices were developed, that provide oxygen locally only in the hypoxic ulcer; a great advantage of these devices is portability and accessibility by much lower cost.

The role of oxygen in curing

Oxygen has an important role in all stages of the cure process, respectively inflammation, proliferation and remodeling (figure no. 1).

The healing process begins with haemostasis achieved by vasoconstriction of arterioles with platelet aggregation and degranulation which activate factor XII and fibrin formation. A fibrinous clot is formed, which behaves as a preliminary matrix for subsequent cell migration. Fibrinolysis is an important process that prevents excessive extension of the clot.(7) The inflammatory phase follows immediately, with the migration of granulocytes, macrophages and lymphocytes under the action of mediator divers. Neutrophils are the first cells to arrive at the site of injury, from 24 to 48 hours after its generation. Tissue macrophages derive from blood monocytes and arrive at the injury site in 2-3 days after generation thereof.(7,8) Cytokines involved in the healing process, platelet -derived growth factor (PDGF), transforming growth factor β (TGF β), epidermal growth factor (EGF), are secreted by the cells present at the injury site and have multiple biological functions: role of mediators, role in proliferation, migration, extracellular matrix synthesis, antibacterial role etc.(8)

In the proliferative phase, the main role is played by fibroblasts through collagen and extracellular matrix proteins synthesis: collagen, fibronectin, proteoglycans, glycosaminoglycans.(9) This stage usually starts in 3 days after injury and lasts several weeks. At this stage, fibroblasts undergo proliferation and increase the synthesis activity. The angiogenesis occurs simultaneously in all healing stages. The main cell involved in angiogenesis is the endothelial cell, which comes from the locally destroyed vessels and capillaries. The endothelial cells invade the extracellular matrix and coalesce into a network. In the last stage occurs maturation and remodeling of the collagen matrix, wound contraction, decrease in cellularity and blood vessels with scar formation. This phase begins after 7 days of the injury and may last up to 1 year. It forms a fibrous network consisting of fibronectin, hyaluronic

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acid and proteoglycans. Collagen storage confers strength to the network. 3 weeks after the injury, it reaches about 20% of the initial resistance, followed by the maximum resistance of 70-80% to be reached in time.(10)

Figure no. 1. Stages of healing of the ulcer with inflammation, proliferation and remodeling



Recent studies have shown the role of warning messengers of reactive oxygen species, with the input of release and of function of cytokines and chemokine involved in the cellular proliferation and migration, as well as in the angiogenesis. By means of nitric oxide synthase, the oxygen determines the mobilization of endothelial and progenitor cells from the bone marrow and their migration on the level of the ulcer, with role in angiogenesis. On the mitochondrial level, oxygen is used as final acceptor of electrons in the glucose's aerobe metabolism, with generating energy adenosine triphosphate (ATP).(11)

Oxygen intervenes in the collagen synthesis as cofactor in the hydroxylation of lysine and proline during the formation of pro-collagen and, also, in the synthesis of adult collagen by means of prolyl-hydroxylase and lysyl hydroxylase, enzymes which depend on oxygen.(11) Oxygen interferes with the antimicrobial defense by producing reactive oxygen species in the neutrophils, with oxidative destruction of the bacterial wall.

Evaluation of tissue hypoxia

Nowadays, the best method to evaluate tissue hypoxia is the oxygen's measure of partial pressure through transcutaneous oximetry, with implications in the evaluation of the cure potential, selection of patients for the oxygen treatment, monitoring the gradation during the treatment and in the decision of amputation.

Thus, various algorithms take into consideration the presence or absence of the peripheral pulse, the possibility of revascularization, oxygen's partial pressure in respect of the ulcer and peripheral ulcer, when the patient is breathing air or oxygen at the pressure of 1 Atm. If the oxygen's partial pressure is > 40 mmHg with the patient breathing atmospheric air, he benefits from classic treatment. If the oxygen partial pressure is < 40 mmHg with the patient breathing atmospheric air and the pressure increases > 200 mmHg when administrating hyperbaric oxygen, the patient will benefit from oxygen therapy. In case the oxygen's partial pressure stays < 100 mmHg when administrating hyperbaric oxygen, classic treatment or

amputation is recommended.(12)

Types of oxygen therapies in the treatment of chronic ulcerations

Therapy with hyperbaric oxygen was the first of this kind, which tries to improve oxygenation of the hypoxic tissues, and especially of chronic ulcers. This therapy uses 100% oxygen and pressures between 1.9 and 2.5 Atm, in sessions of 90-120 minutes daily, 5 days a week.(12)

Topical therapy with oxygen consists of administrating concentrated and humidified oxygen on the level of the ulcer, thus not being dependent on vascularization. Several chambers are used which are fitted with valve mechanism for preventing tourniquet effect. 1-2 sessions a day are practiced by this method, with duration between 60 minutes and 3 hours, until obtaining the granulation tissue. The advantages of this method consist in the easier accessibility to these types of devices, due to lower costs and the possibility to complete the procedure at home, with portable devices.

The third method of administrating oxygen on the level of hypoxic tissues of chronic ulcers is represented by two revolutionary bandages OxyzymeTM and IodozymeTM, which work as a molecular pump. These bandages, with double layer of hydrogel, allow the allotment of atmospheric oxygen on the ulcer. Thus, oxygen crosses the first membrane where later on is converted in peroxide of hydrogen by glucosoxidase. The peroxide of hydrogen crosses the second membrane due to its high solubility, where is again transformed in oxygen. Thus, a concentration gradient is realized, which allows additional oxygen to enter the ulcer. Additionally, IodozymeTM contains iodine, which has a disinfecting and antibacterial role.

The beneficial effect of the topical treatment with benzoyl peroxide 20% -33% in chronic ulcers is also known.

Adverse effects of TOHB

Although is thought to be a safe one, the therapy with hyperbaric oxygen presents some potential side effects. These can be determined by the increase of atmospheric pressure: barotrauma of the middle ear and pneumothorax, or can be tied by the increase of oxygen's partial pressure: cerebral toxicity manifested by spasms, pulmonary toxicity and transitory myopia.(13,14)

Contraindications of TOHB

There are some conditions in which therapy with hyperbaric oxygen is contraindicated due to the risk of barotrauma or due to the increase of oxygen toxicity. Absolute contraindications are: uncontrolled pneumothorax, simultaneous treatment with Adriamycin, Bleomycin, Doxorubicin, Disulfiram. Among the relative contraindications, we specify: respiratory infections, lung diseases, fever, corticosteroid treatment, spasmodic affections, pregnancy, history of optic neuritis.(13)

Most studies that have evaluated the effectiveness of topical oxygen therapy in the treatment of chronic ulcers, reported higher cure rates and lower total costs, compared with the conventional therapy. Thus, in a study conducted in an acute care hospital, which evaluated the evolution of necrotic and gangrenous chronic ulcers, healing was obtained in most ulceration treated with topical oxygen therapy within 2 to 12 weeks.(15) Regarding the comparative examination of the costs of care with topical oxygen therapy *versus* conventional treatment, were reported costs decreased by 28% to 45% in patients who underwent hyperbaric oxygen therapy.(15) It has also been reported the decrease in bacterial colonization at the level of chronic ulcers by 84.21% in patients treated with hyperbaric oxygen, compared to a decrease of only 25% in the case of patients treated by conventional methods.(16)

Several studies which have pursued, mainly, the

evolution of ulcerations of diabetic foot after the treatment with hyperbaric oxygen, have shown positive results with respect of decreasing the cure time and reducing complications in these ulcerations with heavy evolution.(16-19) A randomized control study completed by *Duzgn et al.* has included 100 patients with ulcerations of the diabetic foot, wounds of which have not responded to any treatment. They reported that, by comparison to the wound's standard treatment, TOHB was associated with the considerable higher degree regarding the cure of ulcerations (66% vs. 0%) and lesser limb amputations (8% vs. 82%).(20)

Other two publications that have evaluated the results OxyzymeTM and IodozymeTM therapy showed a favourable evolution of ulcers that have benefited from these treatments. Thus, the first study conducted on patients with chronic venous ulcerations reported a significant improvement in 58% of the patients and a complete healing in 32% of ulcers treated with OxyzymeTM.(21) The second study that included patients with different etiology ulcerations (venous ulcers, post radiotherapy, diabetes, pressure) and treatment with OxyzymeTM, showed the following results: 18 % complete healing, 68%, improvement, 5 % stationary and worsening in 9%.(22)

Another study performed on 100 patients with ulcers of different etiologies (venous 39%, arterial 14%, mixed 21%, diabetic 13%, of pressure 13%) has reported favourable results of using active bandages, especially of those which bring oxygen to the ulceration. The results presented were considerable, especially taking into account that all patients have benefited before by conventional treatment with a medium duration of 31.8 months. Thus, at the end of the study, 10% of ulcerations were cured, 63% of them have presented improvement, while 16% have been steady and 11% have shown worsening.(23)

Regarding the results of the topical treatment with benzoyl peroxide, a study that evaluated its efficacy in different concentrations and different means, on the rate of epithelization of the wounds, showed that benzoyl peroxide in a concentration of 20% as lotion increased the re-epithelization rate by 33%. In exchange, the benzoyl peroxide in the form of gel and the same concentration or 10% in the form of lotion, had a minimal influence on the process of re-epithelization, while the benzoyl peroxide lotion form of the lotion in concentration of 50% has slowed down the healing process.(24) Another study also highlighted the favourable effect of benzoyl peroxide 20% with faster clinical healing, while microscopic changes showed the giant cell infiltration and early appearance of granulation tissue in the group treated with benzoyl peroxide. The beneficial effect of benzoyl peroxide could be explained by attracting macrophages and histiocytes in the wound, with a role in initiating the healing process of ulcers.(25)

Conclusions:

Taking into consideration the heavy evolution and the resistance to classic treatments of chronic ulcerations, as well as high nursing costs, the devices that increase the oxygen concentration on ulcerations can represent an adjuvant treatment against this pathology. The benefits of increasing the oxygen concentration in the ulcer are represented by its involvement in the generation of reactive oxygen species acting as signalling messengers and playing an antibacterial role, the role of oxygen in angiogenesis by mobilization and migration of endothelial progenitor cells and, last but not least, by participating as a cofactor in the enzymatic processes involved in the synthesis of collagen. The use of these devices represents only a part of the therapeutic arsenal necessary for curing ulcers, especially the chronic type, together with etiologic treatment and appropriate local treatment.

factors which intervene in the curing process of ulcers and by developing and improving methods of topical administration of oxygen, a larger usage of these therapies may be obtained. There are also necessary ampler, randomized studies, performed on a larger number of patients, that can allow the analysis of the efficiency of adjuvant treatment of chronic leg ulcers using oxygen therapy, as well as the establishment of a treatment algorithm where oxygen therapy can be included.

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