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Review of Evidence of Topical Oxygen Therapy and Chronic Wounds

Abstract

Chronic wounds represent a significant burden and danger for the affected patient population. Prevalence estimates for pressure ulcers, venous ulcers and diabetic ulcers combined suggest that as many as 3% of the total population are affected by these conditons. Therefore the treatment of chronic wounds is a major challenge for caregivers and places a significant financial burden on the healthcare system. One approach to treatment of these wounds is the Hyperbaric Chamber. The widespread use of this mehod is however limited by costs and a number of therapy associated risks. In order to eliminate some of the problems associated with systemic hyperbaric oxygen therapy, a novel approach using topical oxygen has been launched and is discussed in this paper. Chronic wounds are mostly associated with an absolute and relative lack of oxygen. Oxygen plays a key role in the antibacterial response mechanisms as well as a substrate for important repair mechanisms. Latest research indicates that free oxygen (02) radicals are important for cell signaling (redox signaling). The physiological reasoning of the importance of 02 seems to be reflected in clinical studies. The results of about 1,250 patients were published in 27 identified studies of varying quality. The latest studies eliminated the majority of critical issues of the older papers. In addition they seem to underline the advantages of applying oxygen through a cyclical pressure. In conclusion the approach is very promising but there is a clear need for well designed randomized clinical trials.

Keywords: chronic wounds, topical oxygen, literature review, diabetic wounds, hyperbaric oxygen, oxygen and woundhealing

American Indians have believed for centuries their wounds would heal quicker if they hiked down into the "richer" air of the valleys.[1] Modern hyperbaric wound therapy began in the 1960s, when famous oceanographer Jacques-Yves Cousteau built a village under the Mediterranean sea. In 1962, Conshelf 1 was set up off Marseille, France at a depth of ten meters. Cousteau and his team noticed that small scratches and wounds seemed to heal faster in the humid and oxygen-rich environment of the underwater houses. This discovery led to the development and proliferation of modern hyperbaric chambers and Hyperbaric Medicine.

Treating patients in hyperbaric chambers is costly and is associated with a number of risks. With that in mind, American neurosurgeon Boguslav H. Fischer began using a miniature version of a hyperbaric chamber that provided Oxygen topically to the wound.[2] First results were published in 1966 and three years later The Lancet printed a report about 56 patients treated successfully with topical wound oxygen (TWO_2).[3] In the course of the next decades many scientists conducted research with topical oxygen system.[22-28] In spite of very promising results, topical oxygen approaches remained in the shadows of more mainstream treatments.

Today a next generation TWO_2 device is available in Europe providing enough reason for a critical appraisal of its biochemical mechanisms and clinical evidence of this new yet old concept.

Oxygen and Wound Healing

Oxygen (O_2) is one of the major prerequisites for life. In mammals, all processes at the cellular level require O_2 which is provided in the majority via the adenosine triphosphate (ATP) pump. ATP cannot be stored and its synthesis requires O_2 and glucose. Interestingly the molecular mechanism and the ATP were only clarified in the 1980s. The scientists Paul D. Boyer and John E. Walker received the Nobel Prize in 1997 for their elucidation of the enzymatic mechanism underlying the synthesis of ATP. Most human organs receive their required O_2 via the circulatory and respiratory systems the largest human organ however is partly supplied with O_2 by diffusion directly from the ambient atmosphere. The border between external and internal supply seems to be the stratum corneum of the skin.[29]

A number of different factors play an important role in the development of chronic wounds. One of the most important is underlying disease associated with diminished perfusion and resultant reduced oxygen supply to the tissues. Among the most common are Diabetes Mellitus, arteriosclerosis and age. A wound requires O_2 to fight infection, to build up missing tissue and most other important processes in wound healing. In the wound healing cascade different cell types are important at different points of time, macrophages

Figure 1. Disposable device for home care use

to fight infection, fibroblast for the synthesis of the extracellular matrix (ECM), collagen to fill the wound and epithelial cells to close the wound. All these cells need adequate O_2 to fulfill their purpose. But O_2 is not only the main source of energy.

In all phases of wound healing O_2 is also needed as a substrate for essential enzymatic process. In the first (Inflammatory) phase, neutrophils and macrophages build reactive oxygen species (ROS) which are important in fighting infection, intracellular and extracellular. When infected, the NADPH-linked oxidase can increase the O_2 consumption by as much as 50-fold. Up to 98% of the oxygen consumption of neutrophils is needed for ROS production[30]. Newer research indicates that free O_2 radicals are important for cell signaling to stimulate cell migration, cell proliferation and neovascularisation.[31]

A means to describe the amount of O_2 available is its partial pressure (pO_2). While the normal pO_2 in arterial blood is around 100mmHg, it is reduced to values around 40 at the wound edges and usually below 10mmHg at the center of chronic wounds. There are a number of reasons for low pO_2's at the wound center. Trauma can destroy capillaries altering the diffusion distance for O_2. Edema due to trauma or infection also increases the diffusion distance. As mentioned earlier, chronic wounds often are associated with age or diseases which are associated with limited blood flow. Simultaneously there is an increased need for O_2 within the chronic wound. High inflammatory activity, the need to build new ECM to fill the wound gap, the building of granulation tissue – all of these repair mechanisms need oxygen as a source of energy, as a substrate or signaling molecule.

It is worthwhile to have a more detailed look into the enzyme kinetics. The KM is the substrate concentration at which the reaction rate reaches half of its maximum value (Vmax/2). The concentration of O_2 necessary to achieve half maximal ROS production (the Km) is in the range of 45–80 mmHg, with maximal ROS production at pO_2 at > 300 mmHg.[30] As the pO_2 in the center of the wound is regularly below a pO_2 of 10 mmHg, the maximal effects of respiratory burst-dependent wound infection management can only be achieved through the administration of supplemental O_2 to attain wound pO_2 levels beyond those encountered when breathing room air.[35] This also explains why the state of wound tissue oxygenation is a sensitive indicator for the risk of infection in surgical patients.[36,37]

Figure 2. Rigid device for hospital and institutional use

Another important milestone in wound healing is the development of granulation tissue. Granulation tissue contains many capillaries and is of intense red color. Granulation tissue contains cells and extracellular Matrix (ECM). The ECM is built by fibroblasts and contains glycosaminoglycans, proteoglycans and collagen. Collagen is the main protein of the ECM and the human body. About 30% of the total proteins in humans is collagen. In the skin, collagen represents about 80% of the total protein mass. Consequently the production of collagen is essential for wound healing. Collagen synthesis requires O_2 as a substrate in different enzymatic processes. Three peptide chains are hydroxilated in the endoplasmic reticulum to form a triple helical structure. This process is supported by the proline hydroxylase. After secretion outside the cell the lysyl oxidase needs O_2 to form collagen fibrils via covalent cross-linking. This cross linking is essential for the stabilization of collagen fibrils and for the integrity and elasticity of elastin. When the function of the lysyl oxidase is reduced collagen is incomplete and less robust. Both Collagen and elastin are synthesized by fibroblasts. Endothelia cells need them in the building of vessels to stabilize the walls and keep the vessels elastic. Collagen synthesis is half maximal (KM) at a pO_2 of 20-25 mmHg. Vmax is approximately 250 mmHg, suggesting that new vessels cannot even approach their greatest possible rate of growth unless the wound tissue pO_2 is as high as 66.[38] As the pO_2 in the center of the wound is regulary below a pO_2 of 10 mmHg, hypoxic wounds deposit collagen poorly and are more likely to become infected.[38]

Systemic hyperbaric therapy with pressures up to 2.5 atmospheres (2.500mbar) enhances the arterial pO_2 multiple but requires an intact capillary network to enhance the wound pO_2. Consequently, local tissue oxygenation seems reasonable as no intact vasculature is needed. Unfortunately O_2 has a very low solubility in watery environments. Therefore most experts believe that the topical application of oxygen would not be able to enhance the pO_2 in the tissue.

Modern topical oxygen devices (like AOTI – Advanced Oxygen Therapy Inc.) address this problem with 2 components. First, highly concentrated O_2 is administered directly onto the wound. Secondly, the devices work with a cycling pressure between 5 and 50mbar in order to further improve the diffusion gradient. The cycling pressure leads to a massaging compression without touching the wound.

In his first paper from 1966 Fisher reported that he didn't achieve any healing results using devices with application pressures under 10mmHg.[7] Therefore, the applied pressure seems to be extremely important in the topical application of O_2. In 1975 Fisher measured the capillary pO_2 in the finger tip as a comparison.[4] The pO_2 in the capillaries of the wound was less than 80mmHg at start and using a topical oxygen device with a pressure of 22mmHg the pO_2 in the wound capillary was raised after one hour to 115mmHg and 120mmHg after two hours. The fingertip pO_2 stayed constant at 96-97mmHg.

One year later Olejniczak also reported positive results in a study with 174 patients using a device using only 12mmHg.[7] He measured the pO_2 in granulation tissue near the wound surface and at a depth of 1 mm. pO_2 in the plasma of the wound surface was raised from 50mmHg to 450mmHg and fell down to 50mmHg 2 minutes after stopping the O_2 therapy. Olejniczak reported about great difficulties to measure the pO_2 at 1mm depth back in 1976. He didn't observe a raise of the pO_2 during the therapy using 12mmHg pressure in the delivery device. When using nitrogen as a gas for the topical application the pO_2 in the plasma of the wound surface fell from 50mmHg to 12mmHg after 5 minutes and stabilized later at 4.5mmHg. Since in this case any source of outside oxygen was eliminated the low values obtained represent an arterial supply of oxygen. This demonstrates →

NR.	AUTHOR/YEAR	TITLE	STUDY DESIGN	WOUND ETIOLOGY	RESULTS
1	Gorecky, 1964	Oxygen Under Pressure Appllied directly to Bed Sores: Case Report	Case study with on patient	Pressure ulcer	2 Ulcer with no tendency to heal for 9 moth healed within 4 month under TWO_2
2	Fischer, 1966	Low Pressure Hyperbaric Oxygen Treatment of Decubit and Skin Ulcers	Cas study	15 patients with meningocele, diabetic/ arteriosclerotic ulcers and pressure	Very good healing in all cases
3	Fischer, 1969	Topical hyperbaric oxygen treatment of pressure sores and skin ulcers	Case study with 58 patients and controlled with 6 patients	Diabetic ulcers (2), venous ulcers (19), pressure ulcers (29), ischaemic (6), trauma (2)	52/58 heald completely. 4 out of 6 wound that did not heal had underlying osteomyelites unknown at therapy begin
4	Torelli, 1973	Topical Hyperbaric Oxygen for Decubitus Ulcers	Description of treatment and case study	70 pressure ulcers	Practical and safe method with very good results on pressure ulcers
5	Fischer, 1975	Treatment of ulcers on the legs with hyperbaric oxygen	Case study with 30 patients	All wound on the lower extremeties. (5), pressure ulcer (16), venous ulcer (3), post surgical (2), rheumatoide arthritis (3), hyper-gamma-globulinaemia (1)	28/30 wounds healed completely
6	Olejniezak, 1976	Topical Oxygen Promotes Healing of Leg Ulces	Case study with 174 of various etiologies	Venous ulcers (102), arteriosclerotic ulcers (33), post surgical (33), sickle cell anaemia (4), lupus erythematodes (2)	Improvement in all wounds. 96% healing in venous wounds, 70% in ischemic ulcers
7	Diamond, 1982	The effect of Topical hyperbaric oxygen on lower extrimemity ulcerations	Case study	11 patients with wounds of various etiologies	Healing in "all cases"
8	Heng, 1983	Hyperbaric oxygen therapy for a foot ulcer in a patient with polyarteritis nodosa	Case study	1 patient with ulcer and panarteritis nodosa	Healing
9	Heng, 1984	Hyperbaric oxygen therapy for pyoderma gangrenosum	Case study	2 patients with multiple ulcers on lower extremities and pyoderma gangaenosum	Healing in both cases after 6 and 12 weeks
10	Heng, 1984	A simplified hyperbaric oxygen technique for leg ulcers	Prospective, controlled study	Iscaemic wounds	5/6 patients in the TWO_2-group with 27 wounds healed 3 weeks vs. 0/5 in the control group
11	Ignacio, 1985	Topical oxygen therapy treatment of extensive leg and foot ulcers	Case study	15 patients of which 12 had diabetis ulcers, 12 osteomyelitis, 1 elephantiasis and 2 charcot feet	11/15 patients healed (73%)
12	Lehmann, 1985	Human Bite Infections of the Hand: Adjunct Treatment with Hyperbaric Oxygen	Semi-Randomized controlled study	43 patiens with human bite wounds. 16 patients TWO_2 and 27 served as controls	Hospital stay was shortened from 4,7 days vs. 11,2 days in the control group
13	Upson, 1986	Topical hyperbaric oxygenation in the treatment of recalcitrant open wounds. A clinical report	Case study	2 patients with arterial ulcers	Both healed
14	Leslie, 1988	Randomized controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcers	Prospective randomized study over 2 weeks	28 patiens; 12 in TWO_2 group 16 controls	More than 55% reduction in both groups. No significant difference

NR.	AUTHOR/YEAR	TITLE	STUDY DESIGN	WOUND ETIOLOGY	RESULTS
15	Landau, 1988	Topical Hyperbaric Oxygen and Low Energy Laser Therapy for the treatment of diabetic foot ulcers	Case study	50 patients with diabetic ulcers. 15 patients were only treated with TWO_2 and 35 35 in combination of TWO_2 and low energy laser	43/50 patients healed
16	Heng, 2000	Angiogenesis in necrotic ulcers treated with hyperbaric oxygen	Prospective, randomised study	40 patients with mainly pressure ulcers. Many of which associated with diabets and osteomyelitis	90% healed in the TWO_2 group vs. 22% in the controls
17	Heng, 2000	Enhanced healing and cost-effectiveness of low-pressure oxygen therapy in healing necrotic wounds: A feasibility study of technology transfer.	Case study / virtual control group	15 patients with 24 wounds of different orign, 4 patients with osteomyelitis	22 out of 24 ulcers healed within 12 weeks. Significant cost reduction in the TWO_2 treated patients
18	Landau, 2001	Topical Hyperbaric Oxygen and Low Energy Laser Therapy for Chronic Diabetic Foot Ulcers Resistant to Conventional Treatment	Case study	100 patients with diabetic ulcers treated with TWO and low energy lase	81% healed
19	Edsberg, 2002	Topical hyperbaric oxygen and electrical stimulation: exploring potential synergy	Case study	8 patients with pressure ulcers grade III and IV.	6/8 wounds healed within 16 weeks
20	Edsberg, 2002	Reducing epibole using topical hyperbaric oxygen and electrical stimulation	Fallstudie	1 patient with grade IV pressure ulcer	Healed
21	Kallianen, 2003	Topical oxygen as an adjunct to wound healing: a clinical case series	Case study	58 wounds of various aetiology on 32 patients	65% healed without surgical intervention. 72,2% with surgical intervention (surgery/flap/graft)
22	Ishii, 2004	Efficacy of topical hyperbaric oxygen for refractory foot ulcer	Case study	2 patiens with unspecified	Both wounds healt 3 and 9 month
23	Landau, 2006	Topical hyperbaric oxygen and low-energy laser for the treatment of chronic ulcers	Case study	274 patients; 218 patients with diabetic ulcer and 156 with venous ulcer	78% healing in both groups
24	Gordillo, 2008	Topical oxygen therapy induces vascular endothelial growth factor expression and improves closure of clinically pre-sented chronic wounds.	Controlled study	57 patients; 32 HBO vs. 25 TWO_2. Wounds of different etiologies	HBO didn not reduce wound size. TWO_2 reduced wound size and lead to higher VEGF
25	Tawfick, 2009	Does Topical Wound Oxygen (TWO_2) Offer an Improved Outcome Over Conventional Compression Dressings (CCD) in the Management of Refractory Venous Ulcers (RVU)?	Controlled study	83 patients with venous ulcers. 46 patients with TWO_2 and 37 controls receiving compression dressings	80% of TWO_2 treated patients healed vs. 35% in the controls within 12 weeks
26	Aburto, 2010	A Randomized Controlled Trial to Evaluate Different Treatment Regimes with Topical Wound Oxygen (TWO_2) on Chronic Wounds	Randomised, controlled study	20 diabetic ulcers and 20 venous ulcers. Every patient received TWO_2 for 4 weeks. After randomization each 10 patients continued with TWO_2 vs. advanced wound care in controls	Diabetic ulcers: 90% vs. 50% healing; Venous ulcers: 50% vs. 30% healed in 12 weeks
27	Blackman, 2010	Topical Wound Oxygen Therapy in the Treatment of Severe Diabetic Foot Ulcers: A Prospective Controlled Study	Controlled study	28 patients with diabetic ulcers 17 received TWO_2 and 11 advanced dressings	82% of TWO_2 patients healed within 90 days vs. 43% in the controls

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how important the atmospheric O_2 is for the supply of O_2 for the skin. Almost 30 years later Fries[33] measured the diffusion of O_2 using a device utilizing a higher pressure than Ollejniczak. He measured the pO_2 in pigs with artificial full thickness dermal wounds at a depth of 2mm with a device using 22mmHg of pressure. After 4 minutes of treatment the pO_2 in the center of the wound rose from values between 5-7mmHg to more than 40mmHg. Dual fluorescence staining of the tissue sections for smooth muscle actin and cell nuclei showed that the edge of oxygen treated wounds had a higher density of blood vessels than that in the edge of the room air exposed control wounds. Repeated treatment of the excisional dermal wounds in pigs clearly resulted in a significant acceleration of wound closure. Fries also showed that one of the most crucial vascular growth factors, VEGF was raised substantially in the topically treated wounds compared to the control wounds. These results were confirmed with humans by both, Scott and Gordillo who found enhanced VEGF concentrations after topical treatment with oxygen.[25,34]

Evidence of TWO_2 in wound healing

We conducted a systematic literature review using the search string "topical oxygen" in PubMed. All publications were searched for secondary literature which were followed and obtained. As the number of Randomized Clinical Trials is limited, we abandoned a procedure usually used in health technology assessments that only look at RCTs. We don't question the clear demand for well designed randomized clinical trials but also feel that a neglection of observational studies clearly limits innovation and new approaches.[39] Table 1 summarizes the clinical publications. We limited this table to clinical studies. There are a number of publications that discuss the theoretical use of TWO_2 or review the available evidence. We are aware of a minimum of five position statements of different Hyperbaric societies. With the exception of the paper by Feldmeier in 2005,[40] these position statements appear quite biased and seem to focus on supporting the reimbursement decisions in the countries where HBO is reimbursed as well as to discredit topical approaches. In this respect it seems to be useful information that for instance in the United States one session of hyperbaric treatment is reimbursed with up to 2,000 USD and up to 60 sessions.

Since the first study that we are aware of back in 1964, different authors and research groups have dealt with the subject of TWO and published more than 25 studies in the years thereafter. It is interesting to note that it took almost 50 years until a company developed a device that can be commercialized and is now available in most parts of the world. In summary there are more than 1,250 patients in studies published about TWO_2. One weakness especially in the older publications is clearly that many studies did not clearly describe the population under investigation. Nevertheless more than 500 patients are clearly attributable to diabetic foot ulcers, almost 400 patients with venous ulcers and more than 120 to pressure ulcers.

The sheer number of patients is surprising. In the studies different devices and pressures where used. Some findings stick out. Clearly the applied pressure of the device seems important. Devices using less than 10mmHg seem to have little effect. Pressures around 22 mmHg appear to be clinically effective but may need a daily treatment duration of up to 12 hours. Only one device works with cycling pressures and provides humidified oxygen to prevent the wound from drying out. The cycling pressure reduces edema in a similar manner to compression dressings and shows good healing results with treatment times of 60 to 90 minutes.

Summary

In all phases of wound healing, oxygen plays a key role. Chronic wounds have a difficult challenge in that the need for oxygen is high while the supply of oxygen is low due to trauma, edema, limited vascularisation and underlying disease. Topical application of oxygen enhances the partial pressure of oxygen (pO_2) to levels where various enzymes can effectively start healing. The effectiveness of Topical Wound Oxygen (TWO_2) has been shown in a significant number of studies. However, there is a clear need for well designed randomized clinical trials to measure the true advantage of TWO_2 compared to other modalities like Hyperbaric Oxygen or advanced wound care. A new device is being commercialized that works with pressure gradients between 5 and 50mbar, showing excellent results with a clinically feasible treatment time of 60 to 90 minutes. ■

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