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A Supersaturated Oxygen Emulsion for Wound Care and Skin Rejuvenation

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ABSTRACT

Although oxygen is essential for proper wound healing, wounds are often hypoxic with diminished oxygen delivery to the healing tissue. Since oxygenation of the outer layers of skin is almost exclusively provided by the atmosphere, increasing the presence of external oxygen enhances the healing process. Hyperbaric oxygen therapy is beneficial for treating nonhealing wounds, such as diabetic ulcers, and has been used to speed post-treatment recovery following aesthetic procedures; however, it is not suitable for home use. Recently, perfluorocarbon emulsions have been developed that can absorb large amount of oxygen. Preparations containing 2% of these compounds can absorb up to seven-times more oxygen than water at 37°C. A topical perfluorocarbon emulsion consisting of perfluorodecalin, water, plant derived emulsifiers, and a preservative, has been developed for use in dermatology (Cutagenix™ & Cutavive™ Professional Skin Care Emulsion; Cutagenesis, Niwot, CO). Designed to be applied 2 to 4 times daily following skin rejuvenation procedures, this topical oxygen emulsion reduces the incidence of post-procedure complications. The application of a topical emulsion is well-suited for patient application to enhance recovery following energy-based aesthetic procedures.

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BACKGROUND

Wound healing is a complex process during which the skin and underlying tissues are repaired through several well-defined phases.[1] One of the key factors in the healing process is tissue oxygenation, especially during the early phases of healing.[2] Although initial hypoxia is required to initiate the healing process,[3] increased oxygen tension becomes necessary to stimulate phagocytosis, provide mitochondrial energy, enhance angiogenesis, increase keratinocyte differentiation, migration, and re-epithelialization, enhance fibroblast proliferation and collagen synthesis, and promote wound contraction. Oxygen is also essential for producing superoxide by polymorphonuclear leukocytes which is necessary for destroying invading pathogens.[2-5]

Unfortunately, wounds are typically hypoxic with diminished oxygen delivery to the healing tissue.[6] It has been estimated that wounds require a tissue oxygen tension ≥20 mm Hg to heal while non-healing wounds have transcutaneous oxygen pressure ($tcpO^2$) as low as 5 mm Hg.[7] In one study, $tcpO^2$ ≥30 mm was a predicter of healing success.[8] The $tcpO^2$ is especially worrisome for wounds associated with peripheral arterial occlusive disease and diabetic foot ulcers.[9] Consequently, the use of occlusive dressings can increase the oxygen deficit and further diminish wound healing.[10] Since oxygenation of the outer layers of skin to a depth of 250 to 400 μM is almost exclusively provided by the atmosphere with little coming from circulating blood,[11] increasing the presence of external oxygen will enhance the healing process.

Hyperbaric Oxygen

Hyperbaric oxygen therapy (HBOT) refers to the administration of 100% oxygen at ≥1.4 atmosphere within a pressurized chamber.[12] During HBOT, tissue oxygen levels of 200 to 400 mm Hg can be achieved.[13]

HBOT has been shown to upregulate the production of vascular endothelial growth factor (VEGF), variants of platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) partially through nitric oxide modulation. VEGF and PDGF are responsible for stimulating capillary budding and wound granulation by altering signaling pathways leading to cell proliferation and migration. FGF plays a similar role in angiogenesis, but also induces neural development, keratinocyte organization, and fibroblast proliferation leading to wound granulation and epithelialization.[14]

HBOT can also enhance the antibacterial effects of oxygen at wound sites. As neutrophils and macrophages enter these environments to kill bacteria and remove necrotic material, they require large amounts of oxygen which is used to create hy-

drogen peroxide, superoxide anions, hydrochloric acid, and hydroxyl radicals. These reactive oxygen species can destroy bacteria both intra- and extracellularly by disrupting cell membranes and denaturing protein.[14]

Clinically, HBOT has beneficial effects on nonhealing ulcers that do not respond to standard care[15] such as Grade 3 (abscess, osteomyelitis, or tendonitis) and Grade 4 (gangrene involving forefoot or toes) diabetic ulcers.[16-18] HBOT promotes wound neovascularization and improves the overall rate of healing and limb salvage.[16,17,19]

HBOT has also found a place in dermatology. Animals models have been used to demonstrate the ability of HBOT to stimulate significant angiogenesis,[20] protect against oxidative damage, increase skin elasticity,[21] and increase collagen synthesis, even when administered intermittently.[22] Not surprisingly, HBOT has rejuvenating effects on the skin.[23] It has been used clinically to hasten post-treatment recovery following aesthetic procedures. The effect of HBO to enhance recovery following phenol chemical peels was assessed in a randomized trial.[24] Subjects treated with five consecutive daily HBOT sessions had significantly decreased erythema, scaling, and pruritus while control subjects had significantly more severe skin tightness, edema, erythema, crusting, and scaling. HBOT resulted in greater epithelialization and confidence to appear in public.

Unfortunately, HBOT is not a benign treatment. Potential adverse events include middle ear, sinus and pulmonary barotrauma; CNS and pulmonary oxygen toxicity, adverse ocular effects and is unsuitable for claustrophobic individuals.[25] The absolute contraindication to HBO is untreated pneumothorax.[26] Relative contraindications include sinusitis, seizures, pregnancy, congestive heart failure and implanted devices.[12,26] Because of the high levels of oxygen used, there is the danger of fire in the hyperbaric chamber.[12]

Supersaturated Oxygen Emulsion

Recently, perfluorocarbon emulsions have been developed which can absorb large amount of oxygen. Preparations containing 2% of these compounds can absorb up to seven- times more oxygen than water at 37°C.[27] The oxygen-carrying capacity of perfluorocarbon-based compounds is so great they have been studied for use as artificial blood.[28] Administration of supersaturated oxygen to the left main coronary artery diminished infarct size following acute myocardial infarction,[29,30] leading to its FDA-approval for this indication.[31]

Using a porcine model, researchers at the University of Miami School of Medicine assessed the use of a topical perfluorodecalin-based oxygen emulsion which significantly enhanced the rate of epithelialization of second-degree burns and partial-thickness wounds.[32] Histology revealed increased angiogenesis, tissue granulation and increased type I and type III collagen deposition. In a similar randomized study, the application of topical oxygen emulsion to partial thickness burns resulted in epithelialization, angiogenesis, and tissue granulation, which occurred significantly sooner and faster than controls.[33] Burn tissue treated with topical oxygen emulsion also demonstrated increased expression of type I and type III collagen and vascular endothelial growth factor.

Subsequently, a topical perfluorocarbon emulsion was developed[32] which has found therapeutic applications in dermatology. This product consisting of perfluorodecalin, water, plant derived emulsifiers and a preservative (Cutagenix™ & Cutavive™ Professional Skin Care Emulsion; Cutagenesis, Niwot, CO) is currently available as a post-laser treatment from skin care professionals.

Application of this topical oxygen emulsion to patients every 6 hours for 7 days following fully ablative CO2 laser alone or in combination with a fractional ablative CO2 laser was associated with a reduced incidence of post-procedure complications.[34] In one case report, a woman who underwent deep fractional CO2 resurfacing in the neck developed worsening neck skin tightness, inflammation, and erythema 4 days after treatment.[35] She was subsequently diagnosed with deep second degree burns throughout the neck. After unsuccessful treatment with topical silver sulfadiazine, the patient was started on a topical perfluorodecalin emulsion four times daily and the patient continued to improve for more than 1 year with minimal visible scarring remaining.

This emulsion is also capable of rejuvenating photoaged skin and premature aging due to smoking. The negative effects of smoking are caused by diminished oxygenation due to the action of nicotine on the dermal microvasculature and its toxic effects on keratinocytes and fibroblasts and reduced collagen synthesis resulting in excess skin wrinkles.[36] A study demonstrated the rejuvenating effects of the topical oxygen emulsion on smoker's skin.[37] Healthy adult smokers (n=10) and nonsmokers (n=10) with ≥ type II Glogau photodamage classification were enrolled. Subjects applied the topical oxygen emulsion to their entire face twice daily. Study endpoints were changes in baseline skin hydration measured with a corneometer and skin oxygen levels measured with a radiometer after 3 and 6 weeks of treatment. Subjects also completed a self-assessment questionnaire and rated the appearance of their skin based on skin texture, color, fine wrinkles, blotchiness, dryness, pore size, firmness, and overall improvement.

At week 6, all subjects completing the trial (n=17) perceived some improvement in skin appearance and most (n=12) rated the improvement as moderate (25-50%) or marked (50-75%) overall improvement. Smokers showed significantly greater

improvement than non-smokers in skin color, blotchiness, and dryness. At week 6, all smokers rated their improvement to be at least moderate in every category while nonsmokers rated their improvement to be at least moderate in all categories except skin color and blotchiness. The mean increase in moisture content was 16.5% across all subjects. Baseline oxygen levels for smokers and nonsmokers were 36.3 and 57.2 mm Hg, respectively, increasing to 72.3 and 76.6, respectively, at week 6. This represents a 34% increase for nonsmokers and a 99% increase for smokers.

DISCUSSION

Many energy-based techniques have been developed for facial rejuvenation including radiofrequency, laser resurfacing, intense pulsed light, microneedling, dermabrasion, chemical peels, and focused ultrasound.[38] The basis for these treatments is denaturing collagen and stimulating neocollagenesis and neoelastogenesis by causing superficial injury to the skin. While these techniques can improved wrinkles and overall skin appearance, they all require recovery time that can last up to 4 weeks depending on the procedure.[39] During this time, patients may experience erythema, edema, bruising, and scaling, which may interfere with social activities.

The application of oxygen under hyperbaric conditions or as a topical emulsion has been shown to enhance healing of chronic wounds as well as aesthetic procedures.[17,34] The application of a topical emulsion is well-suited for patient application to enhance recovery following energy-based aesthetic procedures and longer-term treatment for skin rejuvenation.

CONCLUSION

A topical perfluorocarbon oxygen emulsion consisting of perfluorodecalin, water, plant-derived emulsifiers and a preservative that carries in excess of 700 TORR of oxygen has been developed for use in dermatology. Designed to be applied following skin rejuvenation procedures, this topical oxygen emulsion improves healing time and reduces the incidence of post-procedure complications. The application of a topical oxygen emulsion is well-suited for patient application to enhance recovery following energy-based aesthetic procedures and may also serve as an effective, stand-alone procedure for skin rejuvenation.

DISCLOSURES

The authors have no financial or other conflicts of interest to disclose.

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