

Topical Oxygen alters angiogenesis-related growth factor expression in chronic diabetic foot ulcers

Gary Scott Ph.D.

University of North Texas Health Science Center, USA

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OBJECTIVE: Following tissue vascular and oxygen delivery disruption, normal wound healing is a complex process requiring restoration of supplies of oxygen and other nutrients through blood vessel regeneration, or angiogenesis. Angiogenesis is stimulated by synergistic interactions of growth factors and cytokines secreted by damaged cells in wound tissues exhibiting hypoxia, high lactate levels and inflammation. Chronic wounds, often complications of diabetes, are characterized by chronic hypoxia, inflammation, nerve damage, and reduced growth factor secretion that is insufficient to support healing. To test growth factor sensitivity to reversed wound hypoxia, we administered pure oxygen topically and used molecular probes to measure growth factors in wound fluid secretions that were previously found to regulate angiogenesis and improve delayed healing.

METHODS: Subjects (3) were referred by physicians of diabetic patients whose plantar foot wounds failed to respond to standard wound care treatments for a minimum of four weeks. By multiplex ELISA assays of growth factor cytokines, we quantified pglog levels of total proteins detectable in fluids collected twice weekly from wounds after exposure to topical oxygen delivered in 0-50 mm Hg pulses at above normal atmospheric pressure (760-810 mm Hg) during 90 minute treatments four days per week over a five week protocol.

RESULTS: Our initial data show increased expression in angiogenesis-related growth factors (FGF2, HB-EGF, HGF, KGF, VEGF) in wound fluid from chronic diabetic foot ulcers using the Topical Oxygen Chamber for Extremities (Advanced Oxygen Therapy, Inc. (AOTI), Farmingdale, NJ). The most crucial angiogenic factor, VEGF, was altered by 3- to 20-fold increases using the described protocol, while FGF2, a VEGF synergistic enhancer, was increased from 5- to 76-fold. Angiopoetin-2 (Ang-2), an anti-angiogenic factor was not expressed. NT-3, a neurotrophic growth factor, was significantly quantified in wound fluids for the first time. This NT-3 detection at levels increased over 11-fold represents a novel discovery indicating a role for nerve growth in angiogenesis.

CONCLUSIONS: These data show evidence of a molecular mechanism for the scientific basis of topical oxygen-modulated growth factor expression in chronic diabetic wounds, previously unresponsive to standard wound care. We conclude that topically applied oxygen alters angiogenesis-related growth factor expression in wound fluids from chronic diabetic foot ulcers in a manner consistent with revascularization and renewed healing.