Concomitant Hyperbaric Oxygen and Retention-Processed Placental Grafts for DFU



therapy.

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Diabetes has become a very prevalent disease in the United States. One of the most recent estimates indicates there are about 30 million people who are diagnosed with diabetes melitus, 10 million people who have diabetes melitius but don't know it, and around 115 million people with pre-diabetes.(1) Diabetics are prone to neuropathy and vascular problems which predispose a patient to diabetic foot ulcers (DFUs). The lifetime risk of a diabetic developing a foot ulcer is 19-39% and there are about 1.6 million DFUs treated in the US every year.(2)Infection will develop in over half the ulcers. 20% will get osteomyelitis, and 20% of moderate to severe infections will result in amputations. In diabetics, 85% of amputations are preceded by a DFU.(4) Amputations above the ankle lead to increased expenditures associated with the surgery and post op care, the prosthesis, training/rehabilitation, and potential conversion to non-independent status with its associated costs.(3) I feel a useful approach to DFUs is to aggressively heal them as soon as possible. There are unfortunately shortsighted insurance regulations that prevent a more expedient push to heal DFUs, but I think in the long run, all out efforts to heal these ulcers will be cost effective. The following is a recent case I treated which is demonstrative of a more aggressive approach.

DFU CASE 72 year old white male with a PMHx+ for HTN, HLD, DM2, obesity (BMI=42.1), CKD3, Tricuspid Regurgitation, OSA, DFU. lymphedema (R greater than L). Pulmonary HTN. In early Feb 2024, he was admitted to a tertiary referral center hospital in Cleveland by a DPM with R heel ulcer. He underwent multiple debridements and usage of 4 artificial (Integra) grafts over the next several months. After no progress in the wound, he was offered a calcaneal resection to help cure the ulcer. At this point, he asked me to assume care for the wound on 5/3/24.

METHODS The patient was seen at least 3 times/week by a CWCS certified wound care nurse. A CWSP certified wound care physician saw the patient every 1 - 2 weeks. Wound was regularly cleansed with VASCHE and curetting with a 7 mm curette was done as deemed necessary by the physician. The patient was started on Hyperbaric Oxygen treatments (HBO) using the following protocol: HyperTec Sea Long Multiplace Chamber with oxygen delivery headgear - 2.4 ATA X 120 minutes with one 5 minute air break. Ascent time – 3.0 psi/min 1 week after starting HBO, the first Retention-Processed Placental Graft (AmnioWrap2) was placed. BlastX was placed for 3 days prior to graft application. Other than that time, the usual dressing consisted of Revyve, silver alginate, Drawtex, ABDs, Kerlix and Ace Wraps. A total of 3 grafts were used, spaced about 2 weeks apart.

Air = 0.21 O2 X 760mmHg = inhaled pO2 159.6 mmHg Yields a pO2 in tissues of 23 – 70 mmHG. HBO = 1.0 O2 X 2.4 X 760mmHg = inhaled pO2 1824 mmHg Yields pO2 in tissues of 200 – 500 mmHg.

2nd graft was placed on day 20.



DISCUSSION Approximately 40-60% of all lower limb amputations are in patients with diabetes.(3). As noted earlier, 85% of amputations are preceded by a foot ulcer. Aggressive treatment of foot ulcers can result in a 50% decrease in the amputation rate (3). Lifetime cost of an amputation is around \$750,000* (4). In part, that is lowered by the fact that the 5 year survival after a major amputation is only 20 per cent. People with DFUs often require repeated hospitalizations and ongoing treatment for months or even years. Prevention of DFUs and aggressive attempts to heal them when they occur is the most effective way to reduce costs of care in this population. Hyperbaric oxygen (HBO) is a well-established adjunctive modality for healing difficult wounds. Oxygen acts as the final electron acceptor in the electron transport chain and so it is intimately related to cellular energy. Hence, it accelerates fibroblast proliferation, angiogenesis, collagen formation. In vitro, fibroblast proliferation is maximized at about 1900mmHg, which is what a 2.5 ATA dive delivers(7). The excessive amounts of oxygen dissolved in the tissues helps overcome the microvascular damage caused by diabetes. There is an 8 fold increase in the diffusion distance of oxygen from small vessels(7). HBO also helps to stimulate production of multiple growth factors.

It is fascinating that the first use of placental membrane in wound healing was in 1910 at Johns Hopkins Hospital. Over a century later, I am not sure we use it to its fullest potential. Human amniotic membrane sheets contain, extracellular matrix (ECM), and key bioactive molecules, such as fibronectin, laminin, growth factors, glycosaminoglycans, and elastin. In addition, studies have shown that placental grafts modulate macrophages to evolve into the M2 phenotype encouraging wounds to progress through the normal stages of wound healing (8,9,10,11). Multiple studies have shown increased healing of DFUs with use of placental membranes.

In the case presented, the patient had a grouping of comorbid factors that made his DFU very difficult to heal. Previous attempts by other caregivers had been unsuccessful for several months before I assumed care for this wound. The combination of hyperoxygenation of tissues available through HBO and the co-stimulation with the collection of growth factors and other mediators delivered with the placental graft create a wound environment that is highly conducive to healing compromised tissues. Clearly, we need randomized controlled studies to see if the combination therapy exceeds the healing potential of either modality alone. However, until that is available, I think patients with DFUs deserve the most aggressive approach to heal the ulcer before it creates the devastating complication of limb loss. Placental grafts are processed differently by different companies. AmnioWrap2 has shown the highest levels of multiple growth factors, anti-inflammatory cytokines and other mediators of wound healing. This product was successful in the treatment of this recalcitrant wound. *converted to 2024 dollar equivalent

this recalcitrant wound.



