A Randomized, Controlled Multicenter Clinical Trial of a Novel Processed Microvascular Tissue Graft: Wound Closure and Enhanced Tissue Quality in Nonhealing Diabetic Neuropathic Foot Ulcers *(The HIFLO Trial)*

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Background

Microvascular tissue is composed of small vessels, extracellular matrix proteins and inherent cells. A functioning microvasculature is crucial for closing wounds and re-establishing a normal environment that translates into well-perfused, sensate, high quality tissue.

Processed microvascular tissue (PMVT*), is an off-the-shelf human microvascular tissue graft that has been lyophilized and terminally sterilized, while preserving structural tissue fragments, associated nonviable cells, and inherent biological factors.

PMVT has been shown to enhance angiogenesis and wound healing preclinically, and in clinical case series heals complex wounds and chronic diabetic foot ulcers.[1-3]

Methods

The HIFLO Clinical trial is an IRB-approved, Level 1, prospective, single-blind, RCT conducted at 6 US sites that assessed outcomes on patients with Wagner 1&2 DFUs.

Patients with DFUs of >4 weeks ranging from 0.75–25 cm^2 were eligible for enrollment. Screening included a 2-week run-in period with standard of care (SOC) treatment (sharp debridement, topical collagen and nonadherent dressings, offloading). 127 subjects were screened, with 27 subjects excluded for not meeting study criteria.

Patients were randomized to either SOC, or SOC plus weekly topical PMVT application. Subjects were treated for up to 12 weeks or until confirmed closed. Index wounds were measured using the eKare inSight® system. Wound closure was verified by 3 independent blinded adjudicators employing 4 rigorous, predefined criteria.[4]

The primary endpoint was % of ulcers healed at 12 weeks. Secondary endpoints were percent wound area reduction, time to heal, and local neuropathy. Sub-studies were conducted on wound area perfusion (n=10) and regional peripheral neuropathy (n=21).

Results

Demographics: Over 20 different patient- and wound-related demo-graphics were tracked. There were slight differences between HbA1c, wound location, and wound depth, but all were within the inclusion criteria for the study and did not impact the study outcomes.

Adverse Events: There were no product or procedure related AEs/SAEs. All observed AEs were typical of this diabetic patient population.

Representative Case: Figure 1 shows wound images at the initial visit, treatment visit 3 (80% PAR, new epithelialization and granulation tissue evident), and EOS (closed) of a 57yo female who presented with a 2.5 cm^2 Wagner 2 ulcer, which healed after 7 weekly PMVT treatments.

Figure 1A *Randomization Visit*

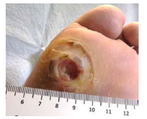


Figure 1B *Treatment Visit 3*

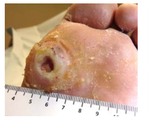


Figure 1C *Healing Visit - Week 7*

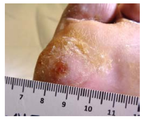


Figure 2: Complete Closure at 12 Weeks

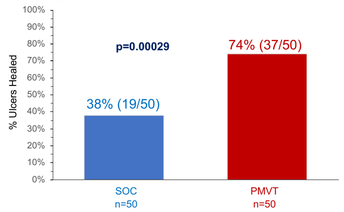


Figure 3: % Wound Area Reduction

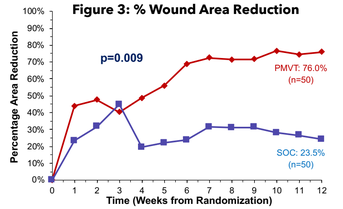
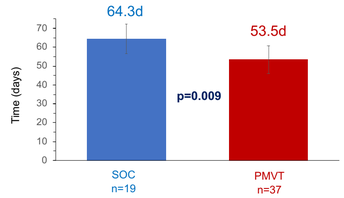


Figure 4: Mean Time To Heal



Primary Endpoint: Unadjusted healing results (Fig. 2) show 74% of ulcers treated with PMVT healed in 12 weeks, compared to 38% in SOC (p=0.00029). In, an adjusted analysis using logistic regression modeling, PMVT was determined to increase the odds of healing by 9 times compared to SOC.

PAR: Percent Wound Area Reduction over time (Fig. 3) was determined using a General Linear Mixed Model. PMVT reduced the wound size by 76%, ~3 times more than SOC alone (p=0.009).

Time to Heal: The Time to Heal analysis (Fig. 4) only included healed PMVT and SOC subjects. Healed SOC ulcers took 64.3 days to close, compared to 53.5 days for PMVT. This 11-day difference translates to PMVT closing 17% faster, and is both statistically and clinically significant, as it means 1-2 fewer clinic visits and treatments.

Perfusion: In fluorescence angiography, lower ingress rates indicate an increase in tissue perfusion. In a subset of 10 subjects, blood flow in the SOC group decreased 67%, while PMVT subjects exhibited a consistent, steady 60% increase in mean perfusion by the end of the study (Fig. 5).

Local Neuropathy: There was an 11% change in the 10-point Semmes-Weinstein score in the SOC group, while PMVT-treated subjects saw a significantly greater average increase of 118% (p=0.028) (Fig. 6). Improvements generally occurred during the first 2-4 weeks of treatment.

Regional Neuropathy: In the stocking glove area assessment, the boundary of sensation was marked at each visit (Fig. 7A), and area of neuropathy at each visit was calculated using image analysis software (Fig. 7B). There was only a 16% change in neuropathy area in the SOC subset by the end of the study, and a significantly greater 62% mean reduction in neuropathy area in the PMVT group (Fig. 8A). There is a clear trend of a rapid reduction of neuropathy area in red-colored PMVT treated subjects when following the change in sensation over time in each of the 21 subjects (Fig. 8B).

Figure 7A

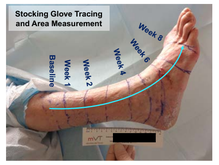


Figure 7B

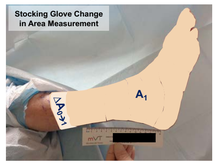
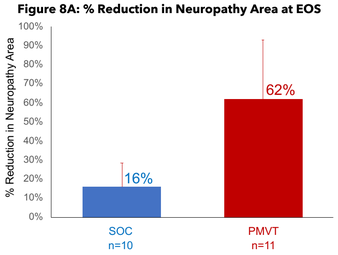


Figure 8A: % Reduction in Neuropathy Area at EOS



IMPROVEMENT **Figure 5: % Change in Mean Perfusion**

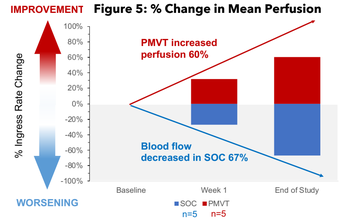


Figure 6: Change in Local Neuropathy

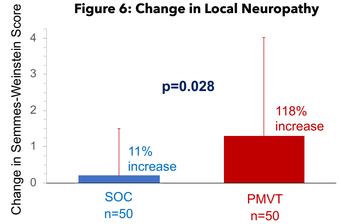
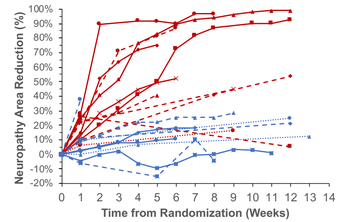


Figure 8B: Individual Change in Regional Neuropathy



Conclusions

- The HIFLO trial sets a new bar for evaluating wound products and is the first RCT using microvascular elements to treat microvascular dysfunction.
- PMVT achieved superior wound closure and a high quality of healing, including increased perfusion and both local and regional neuropathy.
- PMVT is unique among advanced wound products, as it addresses a microvascular deficiency with a microvascular tissue therapy.
- The higher % of closed ulcers, faster time to healing, increased blood flow, and improved sensation with PMVT may mitigate some of the risk factors associated with DFU complications (such as infection, reoccurrence and amputation), though additional studies should be performed.

References:

1) Dobke M, et al., Regen Med, 15(2):1313 (2020).
2) Gimble JM, et al., PRS GO, 6(11):e2010 (2018).
3) Zelen CM, et al., Wounds, 31(4):E29 (2019).
4) Gould L, Li WW, Wound Repair and Regeneration, 27(3):201 (2019).

IRB Approval:

Study conducted in accordance with Western IRB study #1175398 protocol #20171089, and South Shore reference #17-013.

***mVASC®, MicroVascular Tissues, Inc.**

PMVT is marketed in accordance with FDA HCT/P regulations, and is restricted to homologous use for the repair, reconstruction, replacement or supplementation of microvascular tissues.

ML-1025 Rev. 1, Oct. 2020