Journal of Clinical and Translational Research 2024; 10(5): 307-316

Journal of Clinical and Translational Research

Journal homepage: http://www.jctres.com/en/home

ORIGINAL ARTICLE

Processed microvascular tissue improves healing in a case series of challenging wounds

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(This article belongs to the Special Issue: Innovations in Wound Healing)

ARTICLE INFO

Article history:
Received: August 31, 2024
Accepted: November 2, 2024
Published Online: November 22, 2024

Keywords:
Microvascular tissue
Wound healing
Diabetic foot ulcer
Charcot foot
Venous leg ulcer
Mohs defect
Advanced wound care
Case series

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ABSTRACT

Background: Healthy microvasculature provides nutrient and oxygen delivery and removes waste metabolites critical for sustained tissue viability and function after wound healing. Processed microvascular tissue (PMVT), a novel allograft, aims to directly address the compromised microvasculature found in chronic and complex wounds.

Aim: Building on a Level 1 randomized controlled trial demonstrating improved healing and lower extremity sensation with PMVT in neuropathic diabetic foot ulcers, along with a sub-study demonstrating increased wound area blood flow, this article details the authors' clinical experience with PMVT in a case series of challenging wounds, including diabetic foot ulcer, Charcot foot ulcer, venous leg ulcer, and Mohs surgical wound cases.

Methods: Patients received weekly or semi-weekly topical PMVT treatment until wound sites demonstrated active healing with evidence of good microcirculation and progressing re-epithelialization. In all cases, PMVT was covered with a non-adherent dressing and left untouched between visits. Patients were directed not to change the wound dressing, to comply with standard care guidance appropriate for each of their wounds, and to return weekly for assessment of the wound and (if needed) reapplication of the PMVT product. Wound size was measured using a ruler at each visit.

Results: Closure criteria were 100% epithelialization with no maceration, exudate, or signs of infection. The topical application of PMVT successfully healed all challenging or at-risk wounds evaluated in this clinical case series.

Conclusion: By repairing the deficient local microvasculature within and around the wounds, PMVT was able to facilitate the delivery of oxygen and nutrients to the ulcer and enable healing.

Relevance for Patients: PMVT demonstrates the potential to be a strong advanced wound care technology for the treatment of chronic and complex wounds that are refractory to standard care.

1. Introduction

Normal wound healing involves several sequential yet overlapping steps: hemostasis; inflammation; migration, attachment, and proliferation of responding cells; angiogenesis; re-epithelialization; and tissue remodeling [1-3]. Chronic non-healing wounds generally fail to progress through the normal stages of healing, remaining stuck in the inflammation stage. These affect about 3 – 6 million people in the United States of America (USA), resulting in healthcare expenditures exceeding $3 billion/year [4].

Patients with a compromised blood supply are prone to developing ischemic tissue, especially in the lower extremities furthest from the heart that also bear the burden of supporting the body's weight, creating a dangerous combination that leaves patients susceptible to chronic skin wounds. The lack of vascularity in this tissue limits

DOI: http://doi.org/10.36922/jctr.24.00059

migration of responding cells to the wound site, hindering repair. In addition, the oxygen-deprived environment impairs the healing ability of the cells that do arrive [5]. As in all wounds, a functioning microcirculation that provides adequate tissue oxygenation is essential for healing. Wound healing, microvascular ingrowth into a non-healing site, and general tissue repair all require an effective extracellular matrix (ECM) scaffold.

During normal wound healing, angiogenesis leads to tissue revascularization and the establishment of a functioning microcirculation to deliver oxygen and nutrients required for proper tissue repair, along with the removal of waste metabolites and combating microbial burden [5]. The microvasculature, composed of small blood vessels (arterioles, capillaries, and venules), ECM proteins that form the basement membrane and vessel structure, and inherent cells (multipotent cells, endothelial cells, pericytes, fibroblasts, and smooth muscle cells), serves as the foundation for granulation and remodeling during wound healing [6-8]. Microvascular ECM proteins form the basic structure of blood vessels and provide physical scaffolding, mechanical stability, and biochemical cues necessary for tissue to form and maintain stability [9,10]. The ECM is capable of modulating a whole host of processes, including cell migration, attachment, differentiation, and repair [11].

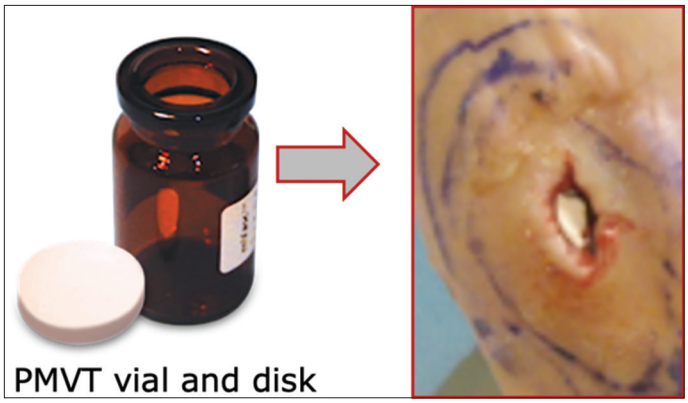

Figure 1. Application of processed microvascular tissue (PMVT). The sterile, lyophilized PMVT disk can be removed from the vial, broken into pieces if desired, and applied topically in dry form to a surface wound site.

Repair of damaged microvascular structure and restoration of adequate blood flow to provide oxygen and nutrients to the site is essential to promote healing and minimize tissue breakdown in the newly epithelialized wound. Formation of a new neurovascular network after tissue injury is critical for wound resolution and maintaining tissue viability and function. Advanced age, diabetes, and radiation treatments are all conditions that manifest in deficient or dysfunctional microvasculature, which can compromise the healing process, leading to poor tissue quality and impaired healing in these patient populations.

Processed microvascular tissue (PMVT) is a microvascular tissue structural allograft (mVASC®; MicroVascular Tissues, Inc., USA) consisting of lyophilized and terminally sterilized allogeneic microvascular tissue ECM harvested from the hypodermal tissue of cadaveric human donors. It is packaged as a lyophilized disk in a sealed glass vial for single-patient

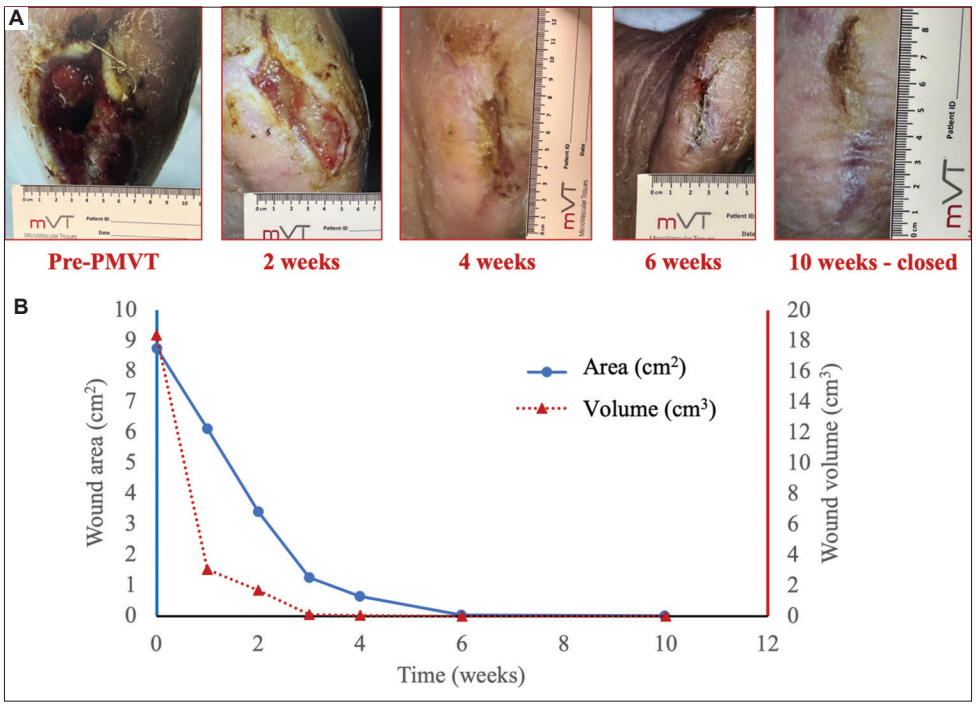

Figure 2. Progression of metatarsal diabetic foot ulcer. (A) Images demonstrating that weekly topical application of processed microvascular tissue through week 6 rapidly healed the ulcer, leading to complete closure by week 10. (B) Graph detailing the healing rate of the closing ulcer by area and volume.

DOI: http://doi.org/10.36922/jctr.24.00059

use and can be topically applied in a dry form to the surface of the wound (Figure 1). PMVT is isolated through a proprietary process that involves cutting, cleaning, isolation, lyophilization, and sterilization of the harvested tissue, and is intended to improve blood flow through the repair and reconstruction of microvascular tissue, by serving as a scaffold for cellular invasion and capillary growth. The benefits of improved microcirculatory blood flow may be particularly impactful on patients with compromised microvasculature.

Preclinical studies of PMVT demonstrated angiogenesis support and significantly increased healing rates in rodent models of pressure injury and ischemia [12,13]. In a robust Level 1, prospective, randomized, controlled, and multicenter clinical trial involving 100 diabetic patients with non-healing Wagner Grades 1 and 2 neuropathic foot ulcers (the "HIFLO Trial"), the weekly topical application of PMVT resulted in significantly increased complete wound closure at 12 weeks compared to the standard-of-care group (74% vs. 38%; P = 0.00029, with a nine-fold increased odds of healing). Sub-studies also demonstrated improved wound area perfusion and increased levels of sensation and tissue quality in this neuropathic patient population [14,15]. Here, we report on real-world clinical experiences with PMVT in a case series of five challenging non-healing wounds.

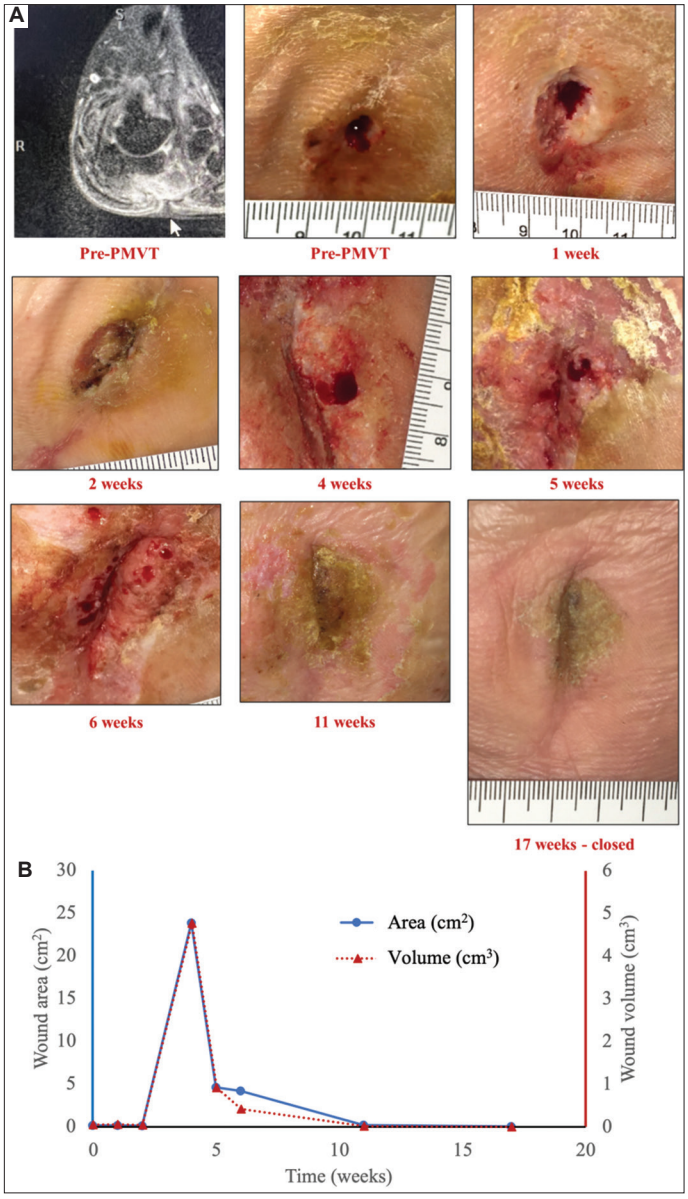

Figure 3. Progression of Charcot diabetic foot ulcer. (A) Images of the defect on initial presentation and progression with topical processed microvascular tissue (PMVT) application, which healed the ulcer, despite off-loading non-compliance during treatment and re-emergence of infection; this led to 99% epithelialization by 11 weeks (seven PMVT applications) and complete closure by 17 weeks. (B) Graph detailing the healing rate of the closing ulcer by area and volume.

2. Methods

All patients received weekly or semi-weekly topical PMVT treatment until wound sites closed or demonstrated active healing with evidence of good microcirculation and progressing re-epithelialization. In all cases within this series, PMVT was covered with a non-adherent dressing and left untouched between visits. Patients were directed not to change the wound dressing, to comply with standard care guidance appropriate for each of their wounds, and to return weekly for assessment of the wound and (if needed) reapplication of the PMVT product. Wound size was measured using a ruler at each visit, and, when appropriate, wound depth was determined using a DM Stick foam-tipped measuring device (Puritan, USA). Closure criteria were 100% epithelialization with no maceration, exudate, or signs of infection.

As this case series was conducted under the standard practice of medicine with a commercial human tissue product for each respective application, no additional ethical regulations or formal research protocol were required, nor were the cases added to a public database. All facility procedures for obtaining patient consent for treatment were followed, and release forms to allow data and image publication were obtained from each patient.

3. Results

3.1. Case 1: Stimulation of perfusion and healing using PMVT in a refractory metatarsal diabetic foot ulcer

Despite growing efforts to adopt a "limb preservation" approach in wound clinics, amputations are an increasingly unwanted complication of non-healing foot ulcers in diabetic patients and are known to have a 50% mortality rate within 5 years [16]. When amputation is necessary, a transmetatarsal amputation (TMA) (as opposed to a below-the-knee amputation) may be justified when macrovascular blood flow to the foot is sufficient. However, patients with TMA are at high risk of skin breakdown or higher amputation, especially when vascular deficiency is present [17,18].

In this case, the patient, a 57-year-old male with poorly controlled type 2 diabetes who had a prior right foot TMA, presented with a DFU on his fifth metatarsal at the TMA site. Following 6 months of unsuccessful treatment with

DOI: http://doi.org/10.36922/jctr.24.00059

standard dressings, collagen, offloading, hyperbaric oxygen, and intravenous (IV) antibiotics, the patient presented with a refractory wound of 7 cm^2 in area and 2 cm deep, with exposed bone and chronic osteomyelitis. He was treated with weekly applications of topical PMVT along with additional IV antibiotics. High-resolution photos of the wound progression and a graph depicting wound area and volume reduction are displayed in Figure 2A and B. After just one treatment with PMVT, over 80% of the wound volume had been replaced with new tissue. After six applications, the wound size had reduced by more than 99%, so PMVT treatment was discontinued. The ulcer fully closed after four additional weeks with standard care and remained healed at his most recent visit 9 months following closure.

3.2. Case 2: Stimulation of perfusion and healing using PMVT in a non-healing Charcot diabetic foot ulcer

Diabetic neuropathy is one of the most frequent complications of diabetes, experienced by 50 – 60% of the 389 million diabetic patients worldwide [19,20]. The most common form is peripheral neuropathy, where peripheral nerves are damaged or destroyed, resulting in loss of feeling and/or sensations of pain or paresthesia, primarily in the extremities [21,22]. While the cause of diabetic neuropathy is not fully understood, the combination of vascular and neural components is recognized as important elements in its pathophysiology. Diabetic neuropathy is a progressive disease, in which tissue-level structural changes occur in the patient's peripheral microvascular system [23-25]. The first pathological changes observed are the narrowing of the microvascular vessels and alteration of the normal local microvascular tissue network. As diabetic neuropathy progresses, neuronal dysfunction and reduction in peripheral nerve function have been demonstrated to correlate with the development of blood vessel abnormalities. Neuronal ischemia is a well-established characteristic of diabetic neuropathy [26]. Charcot foot, a severe complication of peripheral neuropathy that can damage the bones, joints, and soft tissue in the foot, is known to result in the formation of non-healing ulcers [27].

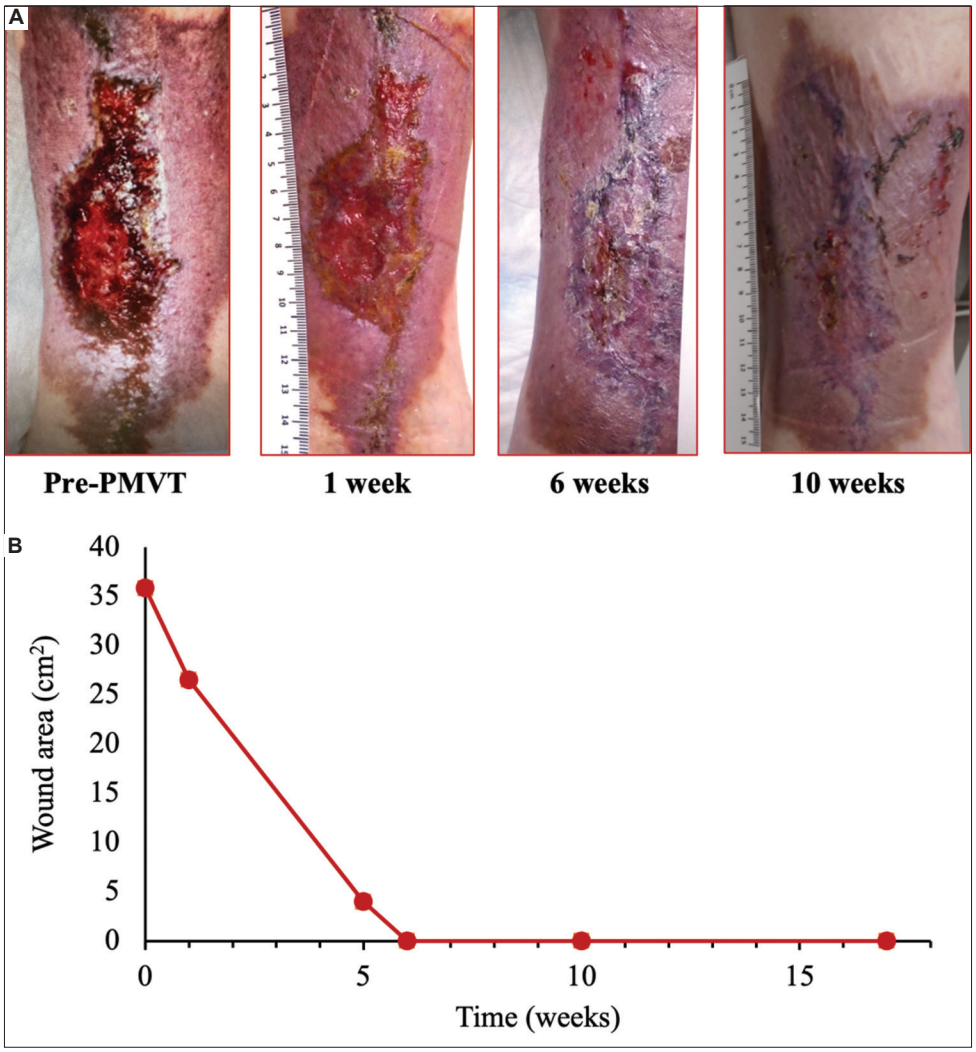

Figure 4. Progression of a venous leg ulcer (VLU). (A) Case images (from left to right): VLU before initial processed microvascular tissue (PMVT) treatment; 1 week after initial treatment; closed 6 weeks after initial treatment (three PMVT applications); healing confirmed 10 and 17 weeks after initial treatment. (B) Graph detailing the healing rate of the closing ulcer by area.

DOI: http://doi.org/10.36922/jctr.24.00059

In this case, a 65-year-old male presented with a poorly granulated 1 cm^2 left plantar Charcot DFU. The wound had been open for more than 1 year despite standard care, including serial debridement, negative pressure wound therapy (NPWT), and total contact casting. The lesion extended 0.4 cm deep to devitalized bone, and the patient was being treated concurrently for chronic osteomyelitis on presentation and initiation of PMVT treatment. Between 2 and 4 weeks, offloading non-compliance led to re-emergence of infection, requiring significant debridement and initiation of antibiotics. Following this, the wound area was now 24 cm^2. Despite this setback, after three additional PMVT applications, the wound had become 99% epithelialized, and PMVT treatment was discontinued. The ulcer went on to fully close within 6 additional weeks with standard care and has remained healed 6 months to date following closure. Images of the ulcer progression and the wound area/volume graph are displayed in Figure 3A and B.

3.3. Case 3: Increasing blood flow using PMVT to treat a chronic venous leg ulcer

Venous leg ulcers (VLUs), among the most common types of lower extremity wounds, are open ulcers that frequently occur on the inside of the leg above the ankle. VLUs comprise about

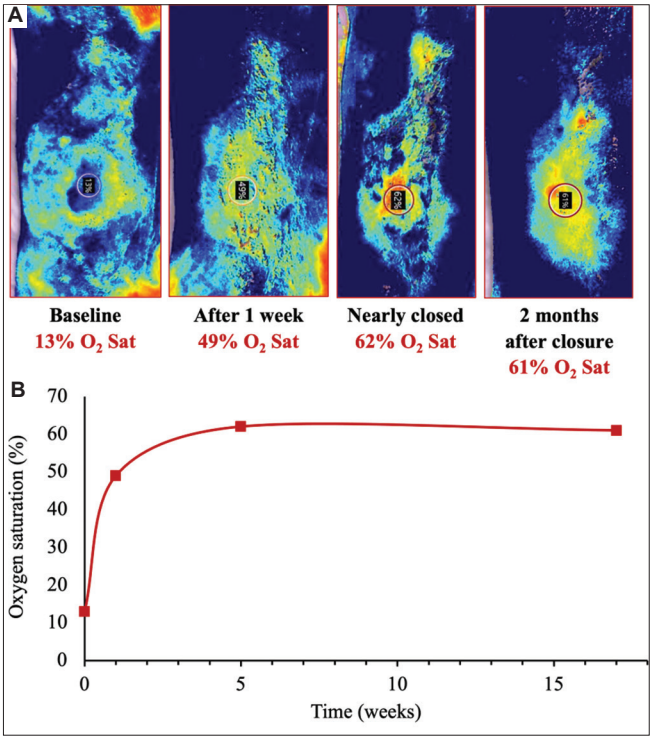

Figure 5. Tissue oxygenation changes within a healing venous leg ulcer. (A) Tissue oxygenation saturation images from historical baseline through processed microvascular tissue treatment and closure. Near-infrared imaging allows for visualization and quantification of oxygen saturation from very low (black/dark blue) to high (yellow and red) levels. Note the relative change in oxygen saturation from the periphery of the wound bed to within the wound bed, indicative of increased local blood flow. (B) Graph detailing the oxygen saturation increase of the closing ulcer over time.

28% of global chronic wounds that require treatment, accounting for nearly $2 billion in annual expenditures, representing an enormous and growing global problem [28]. Up to 60% of VLUs are considered chronic because they persist for more than 6 weeks, usually as a result of blood circulation problems. Obesity, smoking, deep vein thrombosis (DVT), varicose veins, previous leg injury or surgery, age, and diabetes are all risk factors that can contribute to the development of a VLU [28]. As PMVT is intended to improve blood flow through the repair and reconstruction of microvascular tissue by serving as a scaffold for cellular invasion and capillary growth, the benefits of improved microcirculatory blood flow may be particularly impactful on patients with compromised microvasculature, such as patients with increased risk for non-healing VLUs.

The 64-year-old male with a history of chronic kidney disease (Stage 3b), hypertension, chronic DVT, Leiden Factor V, and asthma, who presented with a left VLU in August 2021, is an example of such a patient. The ulcer worsened following DVT in April 2022. No thrombectomy interventions were advisable due to an unacceptably high risk of complications. Multiple topical wound management products, including silver alginate, foam, hydroconductive and other composite dressings, cadexomer iodine, topical antibiotics, and an ECM xenograft, along with compression wraps (the patient's job requires standing 8 h a day), all failed to close the VLU.

In January 2024, after nearly 2.5 years of not healing, the patient received his first treatment of PMVT. The PMVT disk was removed from the vial and applied directly onto the surface of the ulcer after very minimal selective debridement. On contact with blood at the wound site, the PMVT graft was quickly absorbed into the surrounding tissue. Two additional PMVT applications were made at weeks 1 and 5 after the initial treatment. A non-adherent dressing (Mepitel; Mölnlycke Health Care, USA) was used to cover 1 – 2 cm beyond the ulcer's edges after each PMVT application. The VLU was covered further by a compression bandage (initially an alginate-based absorbent compress for the first two treatments, then Coban 2 Lite [3M Healthcare, USA] for the final application). The patient suffered a right hip fracture requiring surgery and hospitalization 2 weeks after initial treatment and had limited transportation means for further follow-up visits until week 6, resulting in a gap between the second and third PMVT applications. As with the other cases, the VLU was visually examined and photographed at each visit, and the wound size was measured using a ruler. In addition, tissue oxygenation was assessed using a point-of-care near-infrared (NIR) imaging device (Snapshot NIR; Kent Imaging, Canada).

The ulcer closed after just three applications of PMVT. Images of the VLU's progression are displayed in Figure 4A, with evident wound closure at the 6-week visit. Wound size over time is presented in Figure 4B. A confirmation visit at 10 weeks demonstrated the wound had remained healed and the surrounding erythema had noticeably subsided, and remained so at 17 weeks, even after the patient had returned to work with significant time on his feet.

The sequential oxygenation saturation images (Figure 5A) and corresponding graph (Figure 5B) depict increased tissue

DOI: http://doi.org/10.36922/jctr.24.00059

oxygenation within the center region of the wound area from the historical baseline (13%), after initial PMVT treatment (49%), through healing just before closure (62%), and maintained following closure (61%). Although these numbers are relative, the increased oxygen saturation represents improved blood flow and is indicative of the transition to the proliferative and remodeling phases of healing within the wound area.

By repairing the deficient local microvasculature around the VLU, PMVT was able to assist with the delivery of oxygen and nutrients to the ulcer. With just three topical applications, it successfully healed a challenging ulcer that had not closed after over 2.5 years of conventional wound management.

3.4. Cases 4 and 5: Stimulation of healing using PMVT in a challenging at-risk Mohs surgical defect

Mohs surgery is the gold standard technique to remove cancerous lesions from the skin [29]. Risk factors, such as ongoing chemotherapy and/or radiation treatment, diabetes, or peripheral vascular disease, may lead to a dysfunctional local microcirculation, which, along with the size and depth of the defect, patient age, and other factors, may cause the post-surgical skin defect to be at greater risk for not healing. In such cases, proactive use of an advanced wound care treatment may be warranted.

The first Mohs patient, a 51-year-old male with coronary artery disease, hypertension, nicotine dependence, and post-COVID pulmonary issues, had undergone Mohs excision of a basal cell carcinoma on his right scapula. Initial attempts to close the defect using standard treatment and negative pressure wound therapy were unsuccessful, and he presented 5 weeks post-excision with a defect 13 cm^2 in area and 0.4 cm deep. After just one treatment of topical PMVT, over 50% of the wound volume had been replaced with new tissue. After 5 weekly applications, the defect had closed, and PMVT treatment was discontinued. Wound progression during PMVT treatment is presented in the images and graph in Figure 6A and B.

The second Mohs patient was a non-compliant 84-year-old female former smoker with prior breast cancer who presented with a 6 cm^2 defect on her left leg following squamous cell carcinoma excision. Despite the patient's non-compliance in maintaining compression on her leg, as evidenced by the staggered progress in the wound size graph on the right, after

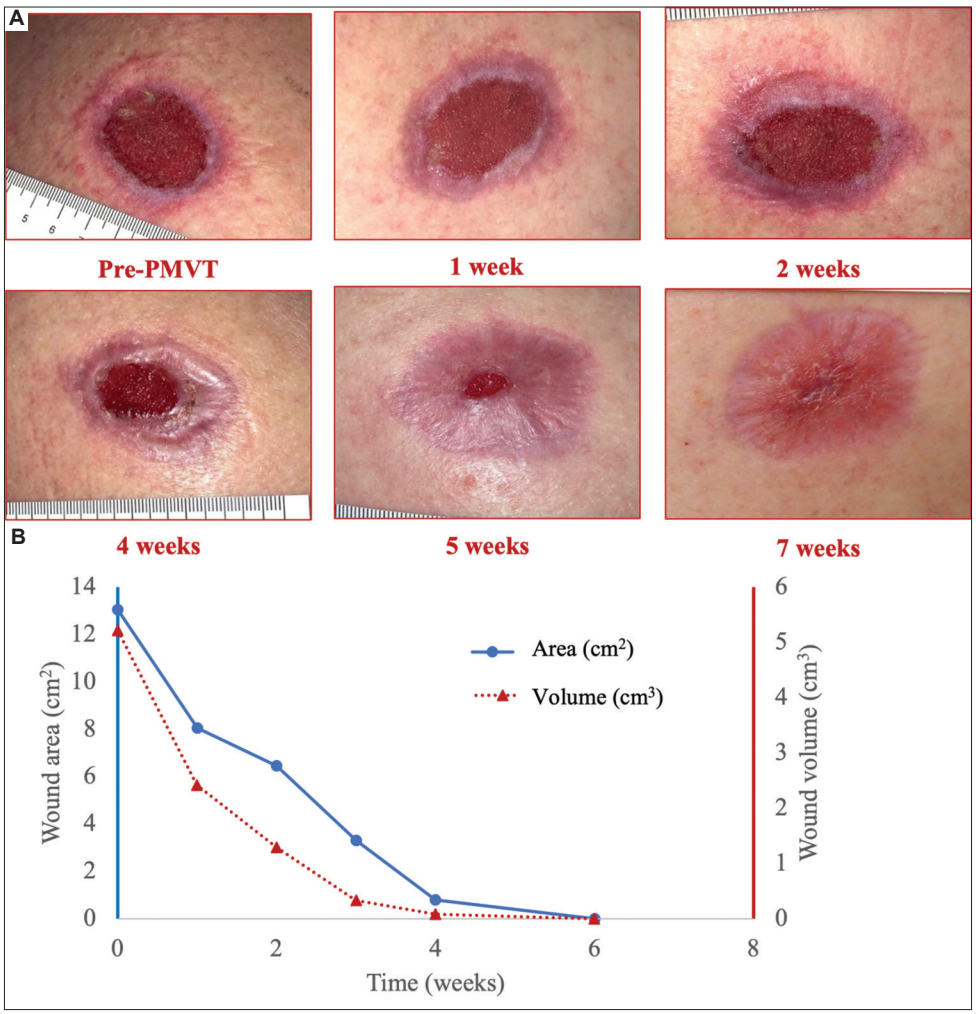

Figure 6. Progression of at-risk Mohs surgical defect. (A) Images demonstrating that weekly topical application of processed microvascular tissue healed the wound in 7 weeks. (B) Graph detailing the healing rate of the closing defect by area and volume.

DOI: http://doi.org/10.36922/jctr.24.00059

8 weeks of weekly topical PMVT treatments, the defect was completely filled and 99% epithelialized. After 10 weeks, the defect was closed, and PMVT treatment was discontinued. Wound progression during PMVT treatment is presented in the images and graph in Figure 7A and B.

4. Discussion

Repairing damaged microvascular structures and restoring blood flow to provide oxygen and nutrients to the site and remove waste metabolites is essential to promote healing and minimize tissue breakdown in a newly epithelialized wound. Reversing the stalled wound environment, restoring blood flow, and changing the trajectory of healing toward wound resolution have been previously reported as hallmarks of PMVT treatment, including within a Level 1 randomized controlled trial (RCT) on diabetic patients with neuropathic DFUs [12,14,30,31]. PMVT's microvascular ECM composition drives host cell attachment and supports angiogenesis, important modes of action in the treatment of wounds with deficient microvascular tissue.

Two of the most common complications of diabetes that lead to ulceration are microvascular dysfunction and peripheral neuropathy. Vascular changes, including endothelial dysfunction, hyperpermeability, decreased blood flow, and tissue hypoxia, can directly result from hyperglycemia. Vascular defects involving the vasa nervorum contribute to diabetic neuropathy [23,26,32-35], which can lead to undetected ulcers at greater risk of delayed healing [36-39]. Formation of a new vascular and neural network beneath complete epithelialization of the skin enables the functionality of the healed tissue. Microvascular tissue therapy, with documented evidence of improved perfusion and improvement in neuropathy, can be effective in healing chronic wounds and achieving complete wound closure in diabetic ulcers, Charcot foot ulcers, VLU, and at-risk surgical wounds, as demonstrated in the PMVT case series reported here. No other advanced wound care technologies have been reported to directly address the microcirculatory defects or neuropathy present in chronic or refractory wounds.

The structure of PMVT serves as an ECM scaffold for revascularization, positioning it as a viable option to address conditions of compromised vascularity. The increase in local tissue perfusion documented by the increased tissue oxygen

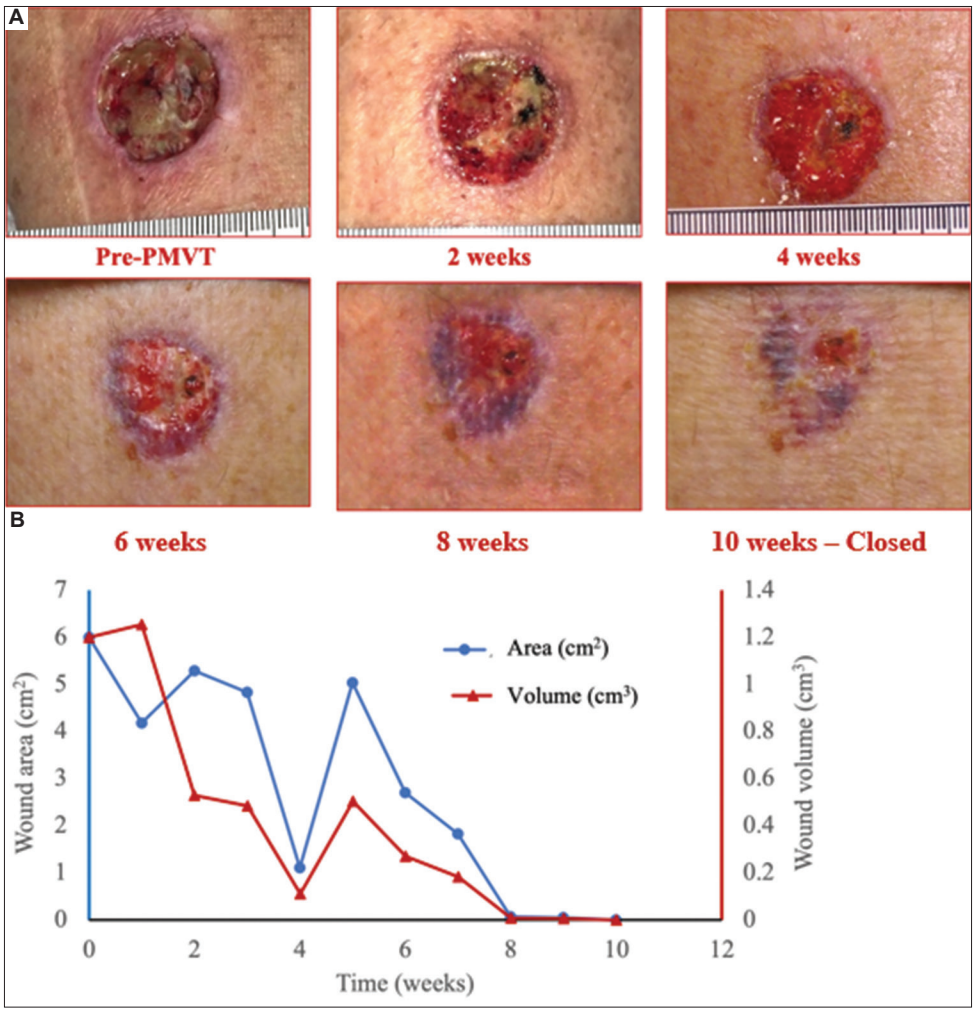

Figure 7. Progression of Mohs surgical defect in a non-compliant patient. (A) Images demonstrating weekly topical application of processed microvascular tissue healed the wound in 10 weeks. (B) Graph detailing the healing rate of the closing defect by area and volume.

DOI: http://doi.org/10.36922/jctr.24.00059

saturation with NIR imaging in the VLU case presented here supports the use of PMVT and addresses a key risk factor for non-healing. The restoration of the microcirculation enables increased oxygen and nutrient delivery to the wound, which promotes granulation and wound epithelialization [40].

This case series demonstrates the breadth of potential applications for PMVT in real-world clinical experience, beyond the previously published Level 1 RCT data neuropathic DFUs. Podiatrists, plastic and reconstructive surgeons, and wound care practitioners may all benefit from learning about the outcomes in this series for their own hard-to-heal wounds and skin defects in patients with damaged or deficient microvasculature. The authors recognize that the number of patients treated within each wound category reported here is limited, and that ideally a more formal protocol-driven case series or clinical trial would provide additional insight into PMVT's effectiveness in these different types of wounds. PMVT is limited to local applications only; intravascular or other systemic delivery is contraindicated.

5. Conclusion

While the broad conclusions that can be drawn from this series of challenging wound cases are limited, it is evident that the use of PMVT can benefit patients with non-healing or at-risk tissue defects of different types caused by microvascular insufficiencies. All defects fully healed in the five cases presented in this series, with patients requiring 3 – 8 topical PMVT applications before closure. Tissue in the healing defect sites became progressively more granulated during PMVT treatment, as assessed through visual observation and NIR spectroscopy images of tissue oxygenation. This is indicative of PMVT's ability to support the repair and reconstruction of microvascular tissue, which, in turn, drove complete wound healing. Successful closure of these refractory and challenging cases across the spectrum of non-healing and at-risk wounds demonstrates both the broad importance of repairing and reconstructing damaged or deficient microvascular tissue and the use of PMVT to improve healing in multiple complex wound environments.

Acknowledgments

The PMVT product used in this case series was provided by MicroVascular Tissues, Inc.

Funding

None.

Conflict of Interest

J.F.A. reports no conflict of interest. D.M.A. is an employee of MicroVascular Tissues, Inc., the company that provided the product for this case series.

Ethics Approval and Consent to Participate

As this case series was conducted under standard practice of medicine with a commercial human tissue product for each respective application, no additional ethical regulations or formal research protocol were required, nor were the cases added to a public database. All facility procedures for obtaining patient consent for treatment were followed, and release forms to allow data and image publication were obtained from each patient.

Consent for Publication

As this case series was conducted under standard practice of medicine with a commercial human tissue product for each respective application, no additional ethical regulations or formal research protocol were required, nor were the cases added to a public database. All facility procedures for obtaining patient consent for treatment were followed, and release forms to allow data and image publication were obtained from each patient.

Availability of Data

Due to commercial reasons, access to the data that support the findings of this case series is restricted.

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DOI: http://doi.org/10.36922/jctr.24.00059