Case Reports and Reviews

Original Article

Regenerative Healing of Large Pressure Wounds Using Topical Mesenchymal Stem Cell Conditioned Media Spray: Translational Rationale, Clinical Potential, and Early Case Outcome

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Abstract

Background: *Stage IV pressure injuries are among the most difficult chronic wounds to treat, particularly in patients with type 2 diabetes mellitus (T2D), severe obesity, and prolonged immobility, where impaired angiogenesis, persistent inflammation, and defective tissue remodeling contribute to poor healing. Mesenchymal stromal cell-conditioned media (MSC-CM) is a cell-free regenerative biologic that delivers a bioactive secretome of growth factors, cytokines, and extracellular vesicles capable of modulating multiple pathways involved in tissue repair. We describe the clinical application of an investigational topical MSC-CM spray as adjunctive therapy for extensive refractory Stage IV pressure injuries.*

Case Summary: *A 66-year-old woman with T2D, severe obesity, and complete immobility presented with five chronic Stage IV pressure injuries involving the sacrococcygeal region, bilateral buttocks, and posterior thighs, with a combined baseline wound surface area of 326.0 cm² despite comprehensive standard wound care. An investigational MSC-CM spray was administered weekly as adjunctive therapy for 120 days while conventional wound management was maintained. Early treatment was characterized by progressive granulation tissue formation, reduction in wound depth, and improved wound bed quality preceding measurable wound contraction. By Day 120, total wound surface area had decreased to 205.86 cm², representing a 36.9% reduction from baseline, with the greatest contraction occurring between Days 60 and 90 (42.1% reduction). Patient-reported pain improved from moderate-severe at baseline to 3/10 at Day 120. No local hypersensitivity reactions, treatment-related infections, systemic adverse events, or hospitalizations were observed.*

Conclusion: *Adjunctive topical MSC-CM therapy was associated with progressive wound bed regeneration, substantial wound contraction, pain reduction, and favorable tolerability in a patient with extensive refractory Stage IV pressure injuries and multiple adverse healing comorbidities. Although causality cannot be established from a single uncontrolled case, these findings provide preliminary clinical support for further prospective evaluation of cell-free MSC-derived biologic therapies as adjuncts to standard wound care.*

Introduction

Pressure injuries affect approximately 2.5 million individuals annually in the United States alone and remain among the costliest preventable complications of prolonged hospitalization and immobility, with estimated annual healthcare expenditures exceeding $25 billion [1,2]. Despite advances in multidisciplinary wound care, healing rates for advanced Stage IV pressure injuries (defined by full thickness tissue loss with exposure or direct palpability of fascia, muscle, tendon, ligament cartilage, or bone) [3] remain poor, particularly among patients with diabetes mellitus, obesity, malnutrition, and prolonged immobility, in whom biological mechanisms of tissue repair are profoundly disrupted [4]. Current standard-of-care management for Stage IV pressure ulcers encompasses strict pressure offloading, repositioning protocols, moisture balance management, glycemic optimization, nutritional supplementation, advanced wound

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dressings, debridement, and skilled nursing oversight [5]. Despite adherence to these evidence-based protocols, a substantial proportion of large Stage IV pressure ulcers remain refractory to conventional therapy and progress toward deep tissue infection, osteomyelitis, and systemic sepsis [6]. Consequently, even comprehensive guideline-directed wound management frequently fails to achieve durable closure in extensive Stage IV lesions, underscoring the need for regenerative therapies capable of actively modifying the wound microenvironment rather than solely providing supportive care [7].

Mesenchymal stromal cells (MSCs) have emerged as important mediators of tissue repair, with accumulating evidence indicating that their therapeutic activity is mediated predominantly through paracrine signaling rather than durable cellular engraftment [8,9]. The MSC secretome comprises a complex network of growth factors, cytokines, chemokines, extracellular vesicles (EVs), microRNAs, and matrix-remodeling proteins that act synergistically to regulate multiple phases of wound healing. Rather than targeting a single biological pathway, these bioactive mediators simultaneously promote angiogenesis, modulate inflammation, enhance fibroblast activation and collagen remodeling, stimulate keratinocyte migration and re-epithelialization, reduce oxidative stress and apoptosis, and facilitate restoration of extracellular matrix homeostasis [10,11]. The pathophysiologic abnormalities characteristic of advanced Stage IV pressure injuries, e.g., impaired angiogenesis, persistent inflammation, extracellular matrix degradation, cellular senescence, and dysregulated macrophage activation, closely parallel the regenerative pathways targeted by the MSC secretome [12]. Functionally, proangiogenic mediators such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) promote endothelial proliferation and neovascularization; platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) stimulate fibroblast activation, collagen synthesis, and granulation tissue formation; stromal cell-derived factor-1 (SDF-1) supports endogenous progenitor cell recruitment; and basic fibroblast growth factor (bFGF) enhances cellular proliferation and wound contraction. In parallel, MSC-derived extracellular vesicles facilitate intercellular communication by transferring regulatory proteins and nucleic acids that attenuate chronic inflammation, promote macrophage polarization toward reparative phenotypes, and coordinate tissue regeneration. Collectively, these complementary mechanisms provide a strong biological rationale for evaluating MSC-derived therapies in chronic pressure wounds that have failed conventional management.

Recognition that MSC activity is largely secretome-mediated has shifted regenerative medicine toward cell-free therapeutic platforms. MSC-conditioned media (MSC-CM), which contains the soluble factors and extracellular vesicles responsible for much of this regenerative activity, retains the biological benefits of MSC signaling while avoiding many limitations associated with live-cell therapies, including variable cell viability and engraftment, manufacturing complexity, cryopreservation requirements, immunogenicity, and regulatory challenges [13,14]. These characteristics make repeated topical administration particularly attractive for chronic wound management. Although MSC-derived secretome therapies have demonstrated encouraging regenerative effects in experimental models and early clinical studies of chronic diabetic wounds, published clinical experience in extensive Stage IV pressure injuries remains extremely limited [15]. To our knowledge, reports describing topical application of MSC-CM to multiple large refractory Stage IV pressure ulcers are scarce. We therefore describe the biologic rationale, treatment protocol, longitudinal wound response, and safety profile associated with adjunctive topical administration of an investigational MSC-derived regenerative biologic spray in a medically complex patient presenting with five refractory Stage IV pressure injuries (total baseline wound surface area, 326.0 cm^2). This case provides preliminary clinical evidence supporting the feasibility of this regenerative strategy and informs future prospective evaluation of cell-free MSC therapies for advanced chronic wounds.

The MSC-conditioned media (MSC-CM) Platform

MSC-conditioned media (MSC-CM) is an acellular biologic generated by culturing mesenchymal stromal cells under standardized conditions and harvesting the bioactive secretome released into the culture medium [16]. The resulting formulation contains the soluble growth factors, cytokines, chemokines, extracellular vesicles, exosomes, lipids, and regulatory nucleic acids that mediate the paracrine regenerative effects of MSCs [17]. By delivering these bioactive mediators without viable cells, MSC-CM preserves many of the regenerative properties of MSC therapy while avoiding the need for cellular engraftment. Compared with live-cell therapies, MSC-CM offers several translational advantages, including reduced immunogenic and tumorigenic potential, simplified manufacturing and storage, improved batch standardization, greater scalability, and fewer logistical and regulatory challenges [18]. The acellular formulation is also well suited for repeated topical administration, making it particularly attractive for chronic wound management where sustained local delivery of regenerative signals may be beneficial [19,20]. (Figure 1).

Experimental studies have consistently demonstrated that MSC-CM enhances wound repair by promoting angiogenesis, stimulating fibroblast proliferation and collagen deposition, accelerating keratinocyte migration and re-epithelialization, modulating macrophage polarization toward reparative phenotypes, and reducing oxidative stress, apoptosis, and chronic inflammation. Early clinical studies in chronic wounds, burns, ischemic injury, and other tissue repair applications have similarly reported encouraging safety profiles and signals of therapeutic efficacy [21,22], although prospective controlled clinical data remain limited. Despite this strong mechanistic rationale and growing preclinical evidence, published clinical experience evaluating topical MSC-CM for extensive Stage IV pressure ulcers remains extremely limited. Consequently, important questions regarding feasibility, safety, and clinical effectiveness in medically complex patients with refractory pressure injuries remain unanswered. The present case was undertaken to help address this important translational gap.

Biologic Mechanisms relevant to chronic pressure wound healing

Stage IV pressure injuries are characterized by multiple interacting biological abnormalities, including sustained tissue ischemia, chronic inflammation, impaired angiogenesis, extracellular matrix degradation, cellular senescence, and defective tissue remodeling [4,7,23]. Because these processes occur simultaneously rather than sequentially, successful regenerative therapies must address multiple components of the wound microenvironment. MSC-CM is particularly attractive in this setting due to its diverse secretome acts through complementary pathways that collectively restore the biological processes required for wound healing.

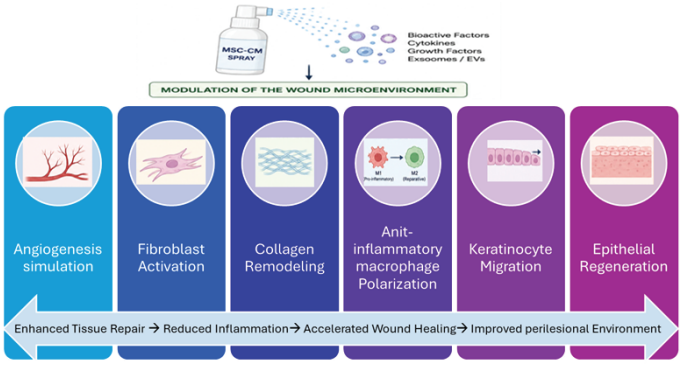

Figure 1. *Proposed Regenerative Mechanisms of Mesenchymal Stromal Cell-Conditioned Media (MSC-CM) Spray in Chronic Pressure Wound Healing*

Figure Legend. Proposed regenerative mechanisms of mesenchymal stromal cell-conditioned media (MSC-CM) spray in chronic pressure wound healing. Following topical application, the MSC-derived secretome modulates the chronic wound microenvironment through multiple complementary regenerative pathways. These include stimulation of angiogenesis, activation of fibroblasts, enhancement of collagen synthesis and extracellular matrix remodeling, polarization of macrophages from a pro-inflammatory (M1) to reparative (M2) phenotype, promotion of keratinocyte migration, and acceleration of epithelial regeneration. Collectively, these coordinated mechanisms improve tissue perfusion, attenuate chronic inflammation, restore extracellular matrix integrity, and promote wound closure, providing the biological rationale for the use of topical MSC-CM as an adjunctive regenerative therapy for refractory Stage IV pressure injuries.

Brief Description: Chronic Stage IV pressure injuries are characterized by persistent inflammation, impaired angiogenesis, defective extracellular matrix remodeling, and failure of normal tissue regeneration, particularly in patients with diabetes mellitus, obesity, and prolonged immobility. Rather than targeting a single biological pathway, MSC-CM delivers a complex secretome of bioactive growth factors, cytokines, and extracellular vesicles that acts simultaneously on multiple components of the wound-healing cascade. As illustrated, topical MSC-CM is proposed to stimulate angiogenesis and improve tissue perfusion, activate fibroblasts responsible for granulation tissue formation and collagen deposition, enhance extracellular matrix remodeling, promote polarization of macrophages toward a reparative anti-inflammatory phenotype, accelerate keratinocyte migration, and facilitate epithelial regeneration. Together, these complementary mechanisms restore a regenerative wound microenvironment that supports tissue repair and wound closure. Although individual signaling pathways continue to be investigated, this multimodal mechanism provides a strong biological rationale for evaluating cell-free MSC-derived therapies as adjunctive treatment for chronic refractory pressure injuries.

Key Clinical Message

- MSC-conditioned media provides a multimodal regenerative therapy that targets several fundamental biological defects responsible for chronic non-healing pressure injuries rather than a single molecular pathway.
- Coordinated enhancement of angiogenesis, extracellular matrix remodeling, inflammation resolution, and epithelial regeneration provides a biologically plausible mechanism for improved wound healing observed in refractory Stage IV pressure injuries.
- Cell-free MSC-derived biologics represent a promising adjunct to standard wound care and warrant prospective clinical evaluation in patients with complex chronic wounds.
- **Restoration of tissue perfusion:** Pro-angiogenic mediators within the MSC secretome promote endothelial proliferation, neovascularization, and microvascular remodeling, improving oxygen and nutrient delivery to ischemic tissue [24].
- **Resolution of chronic inflammation:** MSC-derived cytokines and EVs suppress excessive pro-inflammatory signaling, promote macrophage polarization toward reparative phenotypes, and reduce matrix metalloproteinase activity, facilitating progression from chronic inflammation to tissue repair [25].
- **Extracellular matrix reconstruction:** Growth factors stimulate fibroblast recruitment, collagen synthesis, granulation tissue formation, and controlled matrix remodeling, restoring structural support necessary for wound closure [26].
- **Cellular regeneration:** The secretome enhances keratinocyte migration, re-epithelialization, mitochondrial function, and resistance to oxidative stress while reducing cellular senescence and apoptosis [27].
- MSC-derived neurotrophic factors may additionally support peripheral nerve repair, although their contribution to pressure ulcer healing remains incompletely understood [28].

Collectively, these complementary mechanisms suggest that MSC-CM has the potential to modify the chronic wound microenvironment rather than simply support wound coverage. By simultaneously improving perfusion, attenuating persistent inflammation, restoring extracellular matrix homeostasis, and promoting tissue regeneration, MSC-CM may address several of the fundamental biological barriers that limit healing of advanced Stage IV pressure injuries.

Case Presentation

Investigational Product (IP)

The IP evaluated in this report is a proprietary topical MSC-derived regenerative biologic spray formulated around concentrated MSC-CM. The active component consists of the acellular secretome harvested from cultured human MSCs under standardized manufacturing conditions and subjected to predefined quality-control procedures before incorporation into the final topical formulation. Rather than delivering viable cells, the spray provides the bioactive soluble factors and EVs responsible for MSC-mediated regenerative signaling. The spray delivery platform was specifically developed for extensive chronic wounds with large, irregular surface areas that are difficult to treat using conventional topical preparations. Non-contact application enables uniform distribution of the regenerative biologic across fragile wound beds while minimizing mechanical disruption of newly formed granulation tissue and reducing patient discomfort during repeated administration. The formulation was designed to optimize local bioavailability of regenerative signaling molecules while maintaining a moist wound environment conducive to epithelialization and tissue remodeling. Given the extensive wound burden, prolonged failure of conventional therapy, and multiple comorbidities present in this patient, spontaneous wound closure was considered unlikely. Consequently, adjunctive treatment with an investigational MSC-derived biologic spray was initiated with the objective of modifying the

wound microenvironment and facilitating progression toward tissue repair.

Patient Demographics and Medical History

A 66-year-old woman receiving home-based physician-directed advanced wound care presented with multiple chronic Stage IV pressure injuries involving the sacrococcygeal region, bilateral buttocks, and posterior thighs. Her medical history was significant for T2D, obesity, and severe immobility, all recognized risk factors for impaired wound healing. Despite prolonged treatment with comprehensive guideline-based wound care, including pressure offloading, advanced dressings, nutritional optimization, and regular physician-directed wound management, the ulcers remained non-healing and were considered refractory to conventional therapy.

Baseline Wound Assessment

Baseline wound dimensions were measured (Day 1) using standardized clinical wound assessment techniques, including maximal length, maximal width, and deepest measurable cavity depth following routine wound cleansing (Figure 1A).

Application Protocol

Following routine wound cleansing and standard dressing changes, the investigational MSC-derived biologic spray was applied directly to the wound bed using a non-contact spray delivery system to achieve uniform coverage of all viable tissue surfaces. A total of 6 mL was administered weekly and distributed proportionally across the five active wounds according to wound size and surface area. Standard wound dressings were subsequently applied in accordance with the existing wound care protocol.

Standard of Care Co-Interventions

The following evidence-based standard wound care measures were maintained throughout the entire 120-day observation period:

- Strict pressure offloading and patient repositioning every two hours
- Moisture balance management with advanced wound dressings
- Glycemic control optimization
- Nutritional supplementation
- Skilled nursing wound oversight with weekly physician-directed assessments
- Photographic documentation at each interval with written and verbal patient consent

Clinical Course

Day 1 to Day 30

During the first 30 days of treatment, total wound surface area remained unchanged (326.0 cm²). However, serial clinical assessments and photographic documentation demonstrated clear evidence of biologic wound improvement (Figure 2A). Wound beds exhibited progressive formation of healthy granulation tissue, reduction in fibrinous debris, improved tissue quality, and decreased cavitary depth without evidence of local infection. These findings suggest early regenerative remodeling preceding measurable planar wound contraction. No treatment-related adverse events (AEs) were observed.

Day 30 to Day 60: Between Days 30 and 60, wound surface area remained stable, while continued maturation of granulation tissue, progressive reduction in wound depth, and improved wound bed architecture were observed clinically

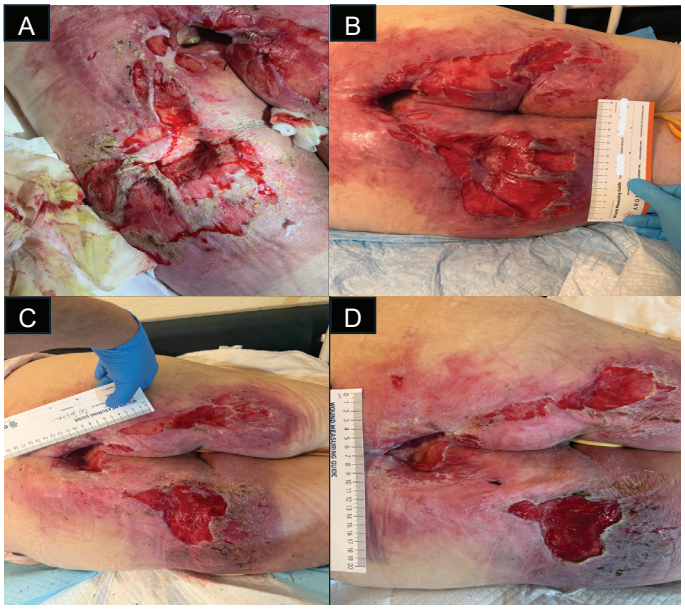

Figure 2. Serial photographic documentation of wound healing following adjunctive treatment with investigational MSC-CM biologic spray.

Brief Description: A 66-year-old woman with type 2 diabetes mellitus (T2D), severe obesity, and prolonged immobility presented with five chronic Stage IV pressure injuries involving the sacrococcygeal region, bilateral buttocks, and posterior thighs despite comprehensive guideline-directed wound care. The combined baseline wound surface area was 326.0 cm², with deep cavitary defects and extensive soft tissue involvement. Because the wounds remained refractory to conventional management, an investigational topical mesenchymal stromal cell-conditioned media (MSC-CM) biologic spray was initiated as adjunctive therapy while all standard wound care measures, including pressure offloading, advanced dressings, nutritional optimization, glycemic management, and physician-directed wound surveillance, were maintained. Serial clinical photographs obtained over a 120-day treatment period demonstrate the temporal progression of wound healing. Panel A (Day 1) illustrates extensive tissue loss with deep cavitary wounds, fibrin deposition, and exposed granulation tissue. Panel B (Day 30) demonstrates early biologic improvement characterized by increased healthy granulation tissue, reduced fibrin burden, and decreased wound depth despite minimal change in overall wound surface area. Panel C (Day 90) shows substantial wound contraction with consolidation of wound margins and progressive re-epithelialization. Panel D (Day 120) demonstrates sustained wound closure with continued epithelial advancement, mature granulation tissue, and maintenance of a marked reduction in total wound burden. Overall wound surface area decreased by 36.9% (326.0 to 205.86 cm²) during the observation period. No treatment-related adverse events, wound infections, or systemic complications were observed.

Figure Legend: Serial photographic documentation of wound healing following adjunctive treatment with investigational MSC-CM biologic spray. Representative clinical photographs demonstrate the evolution of multiple Stage IV pressure injuries over the 120-day observation period. (A) Baseline (Day 1): extensive sacrococcygeal, bilateral gluteal, and posterior thigh Stage IV pressure injuries characterized by large wound burden, deep cavitary defects, fibrin deposition, and exposed granulation tissue. (B) Day 30: early improvement in wound bed quality with increased healthy granulation tissue, reduced fibrin burden, and decreased wound depth despite minimal change in planar wound surface area. (C) Day 90: marked wound contraction with consolidation of wound margins, substantial reduction in total wound surface area, and progressive re-epithelialization. (D) Day 120: sustained wound closure

characterized by continued epithelial advancement, mature granulation tissue, and maintenance of the overall reduction in wound burden. All photographs were obtained during routine physician-directed wound assessments.

Key Clinical Message

- Biologic wound bed improvement, including increased granulation tissue and reduced wound depth, preceded measurable wound contraction, highlighting the limitations of surface area measurements alone in advanced pressure injuries.
- Adjunctive topical MSC-conditioned media therapy was associated with substantial wound healing and an excellent safety profile in a patient with extensive refractory Stage IV pressure injuries and multiple adverse healing comorbidities.
- This case supports further prospective investigation of cell-free MSC-derived regenerative therapies as adjuncts to standard care for complex chronic wounds.

Patient Consent: Written informed consent was obtained from the patient for publication of the clinical information and accompanying images. All identifying information has been removed to protect patient confidentiality.

***Table 1**. Baseline Wound Inventory (Day 1 — September 25, 2025)*

Wound Location	Length (cm)	Width (cm)	Surface Area (cm²)	Depth (cm)
Sacrococcygeal	12.0	7.0	84.0	3.5
Right Buttock	15.0	6.0	90.0	3.0
Left Buttock	14.0	5.0	70.0	2.5
Right Post. Thigh	10.0	5.0	50.0	2.0
Left Post. Thigh	8.0	4.0	32.0	2.0
TOTAL			326.0	—

(Figure 2B). Healing responses were particularly evident within the posterior thigh wounds, consistent with ongoing tissue remodeling despite the absence of significant changes in two-dimensional wound measurements. No local or systemic AEs occurred.

Day 60 to Day 90

By Day 90, early biologic improvements translated into substantial measurable wound contraction (Figure 2C). Total wound surface area decreased to 188.76 cm², representing a 42.1% reduction from baseline. Progressive epithelial advancement and consolidation of wound margins resulted in documentation transitioning from five discrete wounds to three primary wound sites, reflecting interval healing rather than development of new ulcers. Throughout this period, healthy granulation tissue remained prominent, and no wound infection, systemic infection, or treatment-related complications were documented.

Day 90 to Day 120

At Day 120 (Figure 2D), total wound surface area measured 205.86 cm², representing a modest increase relative to Day 90 but maintaining an overall 36.9% reduction from baseline. Given the irregular wound geometry, gluteal contour, patient positioning, and consolidation of previously separate wounds, this small interval difference was considered consistent with expected measurement variability rather than biological deterioration. Notably, serial photographs demonstrated continued epithelial advancement, maturation of granulation tissue, and sustained improvement in overall wound quality without evidence of recurrent infection or wound breakdown (Table 2).

***Table 2.** Wound Surface Area Trajectory Over 120 Days*

Timepoint	Total Area (cm²)	% Reduction	Principal Clinical Findings
Day 1	326.0	—	Extensive Stage IV pressure injuries with deep cavitary defects
Day 30	326.0	0%	Improved granulation tissue, reduced fibrin burden, decreased wound depth
Day 60	326.0	0%	Continued wound bed maturation and progressive tissue remodeling
Day 90	188.76	42.1%	Marked wound contraction, epithelial advancement, wound consolidation
Day 120	205.86	36.9%	Sustained net wound reduction with continued epithelialization and mature granulation tissue

Discussion

This case demonstrates the feasibility of adjunctive topical administration of an investigational MSC-derived biologic spray in a patient with extensive refractory Stage IV pressure injuries complicated by T2D, severe obesity, and immobility, which profoundly impaired wound healing. Over the 120-day observation period, treatment was associated with a sustained 36.9% reduction in total wound surface area, progressive wound bed maturation, substantial pain reduction, and an excellent safety profile. These findings suggest that cell-free MSC-derived biologics warrant further investigation as adjunctive regenerative therapies for complex chronic wounds. An important observation was that qualitative improvement in wound bed biology preceded measurable changes in wound surface area. Serial photographic documentation demonstrated progressive granulation tissue formation, reduction in fibrin burden, decreased cavitary depth, and maturation of the wound bed during the first 60 days despite stable planar wound measurements. This sequence is consistent with established wound-healing biology, in which restoration of tissue viability and extracellular matrix organization commonly precedes macroscopic wound contraction.

The biological response observed in this case is consistent with the proposed mechanisms of MSC-derived secretome therapy. Rather than acting through a single pathway, MSC-CM simultaneously promotes angiogenesis, modulates chronic inflammation, supports extracellular matrix remodeling, enhances re-epithelialization, and restores cellular communication through soluble mediators and EVs [14,17–19,22]. Such multimodal activity is particularly relevant in advanced pressure injuries, where multiple components of the wound-healing cascade are disrupted simultaneously. Large, multi-site pressure wound burdens present delivery challenges

for conventional topical biologics [29]. The spray formulation utilized in this case offers important advantages: it enables rapid, uniform distribution of the bioactive secretome across large, irregular wound surfaces spanning multiple anatomical sites simultaneously. The non-contact application mechanism minimizes mechanical trauma to fragile granulation tissue, reduces procedural burden for home-based administration, and supports consistent weekly dosing without product wastage. In addition to the biologic activity of MSC-CM, the spray delivery platform may offer practical clinical advantages. Uniform, non-contact application facilitates treatment of large irregular wound surfaces while minimizing mechanical disruption of fragile granulation tissue. Such characteristics may be particularly advantageous for home-based management of patients with extensive multifocal pressure injuries.

The safety profile of the investigational MSC spray was excellent across all documented applications. No local hypersensitivity reactions, wound infections, systemic AEs, uncontrolled bleeding, or treatment-related complications were observed during the 120-day treatment period. Although conclusions regarding safety cannot be drawn from a single case, these observations are consistent with the favorable tolerability reported for cell-free MSC-derived biologics in early clinical investigations.

Several limitations should be considered when interpreting these findings. First, this report describes a single patient and therefore cannot establish treatment efficacy or causality. Second, the investigational therapy was administered concurrently with comprehensive guideline-based wound care, precluding determination of the independent contribution of MSC-CM. Third, wound assessment relied primarily on clinical measurements and photography without histologic confirmation or molecular biomarker analyses. Finally, the irregular geometry of large Stage IV pressure injuries introduces unavoidable variability in surface-area measurements despite standardized assessment techniques. Although clinical evidence remains limited, these findings align with growing preclinical and early clinical literature demonstrating that MSC-CM and EVs enhance angiogenesis, modulate inflammation, and accelerate tissue repair in chronic wounds. The present case extends these observations to an unusually extensive burden of Stage IV pressure injuries managed in the home-care setting, supporting the feasibility of this therapeutic approach in medically complex patients. Future studies should prioritize prospective controlled clinical trials incorporating standardized digital planimetry, validated wound-healing endpoints, patient-reported outcomes, serial biomarker analyses, and long-term follow-up. Mechanistic investigations incorporating tissue histology, inflammatory profiling, and extracellular vesicle characterization may further clarify the biological basis of clinical response. Comparative studies evaluating integration of MSC-CM with established wound therapies, including negative-pressure wound therapy and hyperbaric oxygen therapy, will also be important for defining its role in multidisciplinary wound management.

Conclusions, Limitations, and Recommendations

This case provides preliminary clinical evidence supporting the feasibility and favorable tolerability of adjunctive topical MSC-CM therapy for extensive refractory Stage IV pressure injuries with multiple adverse healing comorbidities. Early improvements in wound bed quality preceded substantial wound contraction, consistent with the proposed regenerative mechanisms of MSC-derived secretome therapy. An important methodological observation is that conventional two-dimensional wound measurements underestimated early therapeutic response. During the first 60 days, wound surface area remained unchanged despite clear improvements in granulation tissue, cavity depth, tissue quality, and wound bed architecture evident on serial clinical examination and photography. These findings highlight the limitations of planimetric measurements for assessing complex Stage IV pressure injuries and support incorporation of multidimensional wound assessment in future regenerative wound-healing trials. Although efficacy cannot be inferred from a single uncontrolled observation, these findings support continued clinical investigation of cell-free MSC therapeutics as a potential adjunctive strategy for patients with complex chronic wounds who have failed conventional management.

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Conflict of Interest Statement

The authors (Fernando Iglesia, MD Victor Knutzen, MD, FRCS; Jonathan RT Lakey) declare potential commercial affiliations related to the development of MSC-CM-based therapeutic products.

Data Availability

De-identified clinical data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval and Patient Consent

Photographic documentation and clinical data were obtained at each interval with written and verbal patient consent. This case report was conducted in accordance with ethical principles consistent with the Declaration of Helsinki.

References

1. Roderman N, Wilcox S, Beal A. Effectively addressing hospital-acquired pressure injuries with a multidisciplinary approach. HCA Healthc J Med. 2024;5(5):577-586. doi:10.36518/2689-0216.1922
2. Aloweni F, Ang SY, Fook-Chong S, Agus N, Yong P, Goh MM, et al. A prediction tool for hospital-acquired pressure ulcers among surgical patients: Surgical Pressure Ulcer Risk Score. Int Wound J. 2019;16(1):164-175. doi:10.1111/iwj.13007
3. Haesler E, Cuddigan J, Carville K, Moore Z, Kottner J, Ayello EA, et al. Protocol for the development of the fourth edition of the Prevention and Treatment of Pressure Ulcers/Injuries: Clinical Practice Guideline using GRADE methods. Adv Skin Wound Care. 2024;37(3):136-146. doi:10.1097/ASW.0000000000000079
4. Monaco D, Zaghini F, Fiorini J, Venturini G, Iovino P, Vellone E, et al. Effect of a wound healing protocol on patients with stage III and IV pressure ulcers: A preliminary observational study. J Wound Care. 2022;31(4):322-328. doi:10.12968/jowc.2022.31.4.322
5. Gould LJ, Alderden J, Aslam R, et al. WHS guidelines for the treatment of pressure ulcers—2023 update. Wound Repair Regen. 2024;32(1):6-33. doi:10.1111/wrr.13130
6. Wong D, Holtom P, Spellberg B. Osteomyelitis complicating sacral pressure ulcers: Whether or not to treat with antibiotic therapy. Clin Infect Dis. 2019;68(2):338-342. doi:10.1093/cid/

ciy559

7. Zaidi S, Sharma S. Pressure ulcer. In: StatPearls [Internet]. StatPearls Publishing; 2024. Accessed January 3, 2024. https://www.ncbi.nlm.nih.gov/books/NBK553107/
8. Patel JC, Shukla M, Shukla M. From bench to bedside: Translating mesenchymal stem cell therapies through preclinical and clinical evidence. Front Bioeng Biotechnol. 2025;13:1639439. doi:10.3389/fbioe.2025.1639439
9. Riedl J, Popp C, Eide C, Ebens C, Tolar J. Mesenchymal stromal cells in wound healing applications: Role of the secretome, targeted delivery and impact on recessive dystrophic epidermolysis bullosa treatment. Cytotherapy. 2021;23(11):961-973. doi:10.1016/j.jcyt.2021.06.004
10. Grogan SP, Stinebaugh G, D'Lima DD. Anti-inflammatory and angiogenic effects of stem cell secretome. Int J Mol Sci. 2026;27(5):2325. doi:10.3390/ijms27052325
11. González-González A, García-Sánchez D, Dotta M, Rodríguez-Rey JC, Pérez-Campo FM. Mesenchymal stem cells secretome: The cornerstone of cell-free regenerative medicine. World J Stem Cells. 2020;12(12):1529-1552. doi:10.4252/wjsc.v12.i12.1529
12. Vizoso FJ, Eiro N, Cid S, Schneider J, Perez-Fernandez R. Mesenchymal stem cell secretome: Toward cell-free therapeutic strategies in regenerative medicine. Int J Mol Sci. 2017;18(9):1852. doi:10.3390/ijms18091852
13. Wong RSY, Tan EW, Goh BH. Mesenchymal stem cell-based therapies: Challenges and enhancement strategies. Cell Biochem Biophys. 2026;84(1):131-147. doi:10.1007/s12013-025-01895-z
14. Karimian A, Khoshnazar SM, Kazemi T, Asadi A, Abdolmaleki A. Role of secretomes in cell-free therapeutic strategies in regenerative medicine. Cell Tissue Bank. 2024;25(2):411-426. doi:10.1007/s10561-023-10073-5
15. Lakey JR, Whaley D, Alfiere T, Alexander M, Drummond C III. Improvements in diabetic neuropathy with topical human mesenchymal stem cell conditioned media. Am J Biomed Sci Res. 2024;21(1). doi:10.34297/AJBSR.2024.21.002792
16. Sagaradze G, Grigorieva O, Nimiritsky P, Basalova N, Kalinina N, Akopyan Z, et al. Conditioned medium from human mesenchymal stromal cells: Towards the clinical translation. Int J Mol Sci. 2019;20(7):1656. doi:10.3390/ijms20071656
17. Negrete-Diaz F, Martinez-Rodriguez S, Guedan-Duran A, Romero-Lopez A, Panetsos F. MSC secretomes as a cell-free therapeutic platform: Molecular heterogeneity, disease-specific bioactivity, delivery strategies, and regulatory translation across six major disease areas. Pharmacol Res. 2026;230:108245. doi:10.1016/j.phrs.2026.108245
18. Musiał-Wysocka A, Kot M, Majka M. The pros and cons of mesenchymal stem cell-based therapies. Cell Transplant. 2019;28(7):801-812. doi:10.1177/0963689719837897
19. Toh WS, Lai RC, Hui JHP, Lim SK. MSC exosome as a cell-free MSC therapy for cartilage regeneration: Implications for osteoarthritis treatment. Semin Cell Dev Biol. 2017;67:56-64. doi:10.1016/j.semcdb.2016.11.008
20. Petrie K, Cox CT, Becker BC, MacKay BJ. Clinical applications of acellular dermal matrices: A review. Scars Burns Heal. 2022;8:20595131211038313. doi:10.1177/20595131211038313
21. Kim N, Cho SG. Clinical applications of mesenchymal stem cells. Korean J Intern Med. 2013;28(4):387-402. doi:10.3904/kjim.2013.28.4.387
22. Rhatomy S, Sumarwoto T, Romaniyanto PT. Role of mesenchymal stem cell-conditioned medium (MSC-CM) in ligament or tendon healing: A systematic review from 1998-2018. Orthop J Sports Med. 2020;8(5). doi:10.1177/2325967120S00109
23. Pastar I, Balukoff NC, Marjanovic J, Chen VY, Stone RC, Tomic-Canic M. Molecular pathophysiology of chronic wounds: Current state and future directions. Cold Spring Harb Perspect Biol. 2023;15(4). doi:10.1101/cshperspect.a041243
24. Nazari-Shafti TZ, Neuber S, Garcia Duran A, Xu Z, Beltsios E, Seifert M, et al. Human mesenchymal stromal cells and derived extracellular vesicles: Translational strategies to increase their proangiogenic potential for the treatment of cardiovascular disease. Stem Cells Transl Med. 2020;9(12):1558-1569. doi:10.1002/sctm.19-0432
25. Klyucherev TO, Yurkanova MD, Revokatova DP, Chevalier DA, Shishkov VV, Vlasova II, et al. Mesenchymal stem cell-derived extracellular vesicles attenuate pro-inflammatory macrophage polarization: Comparison of matrix-bound and small extracellular vesicles. Cells. 2026;15(2):93. doi:10.3390/cells15020093
26. Smith J, Rai V. Novel factors regulating proliferation, migration, and differentiation of fibroblasts, keratinocytes, and vascular smooth muscle cells during wound healing. Biomedicines. 2024;12(9):1939. doi:10.3390/biomedicines12091939
27. Trigo CM, Rodrigues JS, Camões SP, Solá S, Miranda JP. Mesenchymal stem cell secretome for regenerative medicine: Where do we stand? J Adv Res. 2025;70:103-124. doi:10.1016/j.jare.2024.05.004
28. Wei S, Dong J, Hu Q, Bai J, Gao X, Shan H, et al. Advances in mesenchymal stem cells and their derivatives for promoting peripheral nerve regeneration. Burns Trauma. 2025;13. doi:10.1093/burnst/tkaf027
29. Rembe JD, Garabet W, Lackmann JW, Alizadehrahrouei S, Augustin M, Dissemond J, et al. Assessment and monitoring of the wound micro-environment in chronic wounds using standardized wound swabbing for individualized diagnostics and targeted interventions. Biomedicines. 2024;12(10):2187. doi:10.3390/biomedicines12102187.

Supplementary Tables

***Table 3**. Key Growth Factors and Cytokines Present in MSC-Conditioned Media Relevant to Pressure Wound Healing*

Factor	Primary Function in Wound Healing
VEGF	Angiogenesis and neovascularization in ischemic tissue
HGF	Epithelial repair, endothelial cell activation, angiogenesis
PDGF	Fibroblast activation, collagen synthesis, granulation tissue formation
TGF-β	Extracellular matrix remodeling, wound contraction
bFGF	Cellular proliferation, migration, and wound contraction
SDF-1	Progenitor cell recruitment and homing to wound site
IL-10	Anti-inflammatory modulation; macrophage M2 polarization
IGF-1	Cellular growth, tissue regeneration, anti-apoptotic activity
BDNF / NGF	Peripheral nerve repair; relevant to diabetic neuropathy
Exosomes / EVs	microRNA delivery, anti-senescence, macrophage reprogramming

***Table 4**. Advantages of MSC-Conditioned Media Compared with Live Stem Cell Therapy*

MSC-Conditioned Media (Spray)	Live Stem Cell Therapy
Cell-free formulation	Cellular product
Lower immunogenic risk	Potential immune concerns
Simplified storage and transport	Complex storage requirements
Topical spray delivery — non-invasive	Often requires injection or implantation
Reduced tumorigenic concern	Theoretical tumorigenic risk
Scalable manufacturing	Complex cellular expansion processes
Suitable for large wound surfaces	Limited by delivery volume constraints
Home-based administration feasible	Typically requires clinical setting