Potential Application of Wharton's Jelly-derived Mesenchymal Stem Cells Conditioned Medium (WJMSCs-CM) on Delayed Wound Healing: A Case Report

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Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Delayed wound healing refers to wounds that do not repair the wounded tissue’s integrity in a timely manner, prolonging the inflammatory, proliferative, and remodelling phases of healing. Delayed wound healing increases the chance of infection, causing discomfort, lowering the quality of life, and increasing healthcare costs. One of the newest techniques to heal wounds is to use the conditioned medium (secretome) of mesenchymal stem cells. One case was reported, a seventeen-year-old man appeared with a one-month history of wound in his left neck that had not healed after a keloid removal surgery. The wound was treated with a 10% Wharton's Jelly-derived Mesenchymal Stem Cells Conditioned Medium (WJMSCs-CM) topical gel. During the two weeks of the intervention, the results are encouraging. The lesion has reduced in size and turned into a closed wound.

Keywords: Delayed wound healing; Wharton’s jelly; conditioned medium; mesenchymal stem cell.
1. INTRODUCTION
When the skin is wounded, a biological process called wound healing takes place. For effective wound healing, the four steps of hemostasis, inflammation, proliferation, and remodelling must all be accomplished. Wound healing will be hampered if one or more of these stages are interrupted, and the process will likely stall at the inflammatory stage. In wounds that are not healing properly, there is a lot of neutrophil infiltration, infection, and unusual biofilm production. Wound healing can be influenced by genetic abnormalities, age, stress, smoking, alcohol intake, diet (obesity or malnutrition), diabetes, immunocompromise conditions, and other factors. Cancer is more likely to grow in wounds that do not heal [1,2]. Wound healing remains a difficulty, despite the extensive use of debridement procedures, wound dressings, and topical medicines in wound care regimens, particularly in patients with triggering factors such as diabetes, elderly individuals, smokers, and others. To improve wound healing, a more holistic technique is required [3,4]. The effect of stem cell therapy on wound healing is currently being researched extensively. Stem cells work through a paracrine effect that produces various molecules and biological factors (growth factors, cytokines, and chemokines) that are contained in conditioned medium (secretome). Wharton's Jelly-derived Mesenchymal Stem Cells (WJMSCs) are a type of stem cell that is commonly used in research. The usage of the WJMSCs conditioned medium in wound healing has been shown to boost the rate of re-epithelialization, revascularization and wound healing in both in vivo and in vitro investigations. The potential advantage of using WJMSCs conditioned medium to treat delayed wound healing is discussed in this report [3,5].

2. PRESENTATION OF CASE
A seventeen-year-old man presented with a one-month history of lesions in his left neck that had not healed after keloid removal surgery. One week after surgery, the surgical suture broke and became an open wound, then exudate developed over time. The patient had no prior history of immune system dysfunction and was not on any immunosuppressive medications, although he was a chain smoker. The patient was hemodynamically stable and had a normal body temperature when examined. A red open wound approximately 15 x 5 cm was discovered on the left neck during a dermatological check, along with exudate, scabs, and pain (Fig. 1). The patient was given antibiotics intravenously first. After cleaning the lesion with NaCl, one fingertip unit of 10% Wharton's Jelly-derived Mesenchymal Stem Cells Conditioned Medium (WJMSCs-CM) topical gel was applied. The patient was also given WJMSCs-CM topical gel to be applied at home with the same dosage twice daily for two weeks. The patient was monitored online during home care. Seven days after the intervention, the regeneration and healing had begun. The lesion appeared to be clean, with reduced erythema, scabs, and pain (Fig. 2). After two weeks, the lesion was improved. The size of the lesion has reduced and turned into a closed wound. The patient was really pleased with the outcome (Fig. 3).
Fig. 3. Two weeks later, the lesion was improved. The size of the lesion has reduced and turned into a closed wound.

3. DISCUSSION

Wound healing is a complicated biological process that includes hemostasis, inflammation, neoangiogenesis, granulation tissue formation, and re-epithelization, as well as changes in the extracellular matrix [1,6,7]. A wide range of cell types, including neutrophils, macrophages, lymphocytes, keratinocytes, fibroblasts, and endothelial cells, are implicated in skin injury [8]. The healing process is mediated by local wound factors and systemic factors. Local wound factors are infection, oxygenation, venous sufficiency, and foreign body. Systemic factors are age and gender, sex, hormones, stress, ischemia diseases, obesity, medications, alcoholism, smoking, immunocompromised conditions and nutrition [1,6].

Delayed wound healing refers to a wound that does not repair the integrity of the injured tissue in a timely manner within three months or that has gone through a repair process without showing supportive anatomical and functional results with prolongation of the inflammatory, proliferative, and remodeling phases of healing [1,9,10]. Delayed wound healing is often seen in vascular ulcers (such as venous and arterial ulcers), diabetic ulcers, and pressure ulcers [8]. Prolonged or excessive inflammatory phase, overabundant neutrophil infiltration, persistent infections, and frequent production of tissue/organ atypical biofilms are all characteristics of chronic wound, resulting from delayed wound healing [1].

Conventional wound management techniques such as debridement, topical antibiotics, and compression bandages are used to promote natural wound healing by addressing the wound's underlying cause (e.g., infection, ischemia, etc.). Advanced wound therapies, such as skin grafting and the use of growth factors, are gaining significant attention at the moment. However, clinical findings indicate that more than half of the chronic wounds are resistant to conventional therapy. Meanwhile, the use of growth factors has been shown to increase the risk of developing malignancy. Treatment with tissue-engineered skin grafts has limitations and disadvantages due to the risk of rejection, the short half-life, and the high cost. Therefore, a more effective chronic wound care strategy is needed [11,12].

Mesenchymal stem cells (MSCs) have emerged as a technique with tremendous therapeutic potential in the treatment of multifactorial diseases such as heart, lung, kidney, liver, brain, and skin damage after injury in recent years [13]. The use of MSCs in the treatment of chronic wounds in vascular ulcers (such as venous and arterial ulcers) diabetic ulcers, and pressure ulcers, has been demonstrated to be effective [14]. MSCs aid in the healing of cutaneous wounds by speeding wound closure, enhancing tissue granulation, promoting angiogenesis, lowering inflammation, and increasing ECM remodelling [3,5]. MSCs are multipotent adult stem cells with a defined capability for self-renewal and differentiation into cell types from all three germ layers, depending on their origin [15]. MSCs come from a variety of tissues and organs, including bone marrow, umbilical cord, fat, placenta, dermis, hair follicles, dental pulp, limbal tissue, and body fluids such as amniotic fluid, umbilical cord blood, peripheral blood, urine, and menstrual blood [16,17].

MSCs with pericytes, adventitial cells, fibroblasts, marrow adipocytes, endothelial cells, hematopoietic, and immunological cells create a dynamic compartment by forging cell-to-cell contacts and generating soluble compounds with autocrine and paracrine qualities [3,13,15,17]. The secretome contained in the conditioned medium of MSCs is a collection of physiologically active substances released by MSCs, including cytokines, growth factors like EGF (Epidermal Growth Factor), bFGF (Basic Fibroblast growth factor), and HGF (hepatocyte growth factor), and chemokines [18,19]. MSC-conditioned medium (secretome) is economically valuable and
advantageous for processing, storage, packaging, and transportation. It can be used for an extended period of time without reducing its efficacy or becoming toxic. It is constantly monitored for safety, dosage, and efficacy [7,20,21].

EGF, bFGF, and HGF are three well-known secretory factors that can stimulate dermal fibroblasts, keratinocytes, and vascular endothelial cells to migrate and proliferate. By boosting fibroblast migration and proliferation, EGF-producing stem cells hasten wound healing. HGF-secreting stem cells stimulate wound healing in the nasal epithelium in vitro and in vivo, but not by growing directly into the target tissues. bFGF is also commonly used to speed up skin regeneration, which helps to reduce scarring in poorly healed wounds [18].

MSCs have antimicrobial activity that is mediated by two pathways that increase bacterial death and immune cell phagocytosis. Direct antimicrobial activity is mediated by the secretion of antimicrobial factors such as cathelicidin, LL-37, hepcidin, hBD-2 (Human Defensin 2), Lcn (Lipocalin), and SP (Surfactant Protein D). Indirect antimicrobial activity is mediated by the secretion of immune-modulating factors. Secreting antimicrobial peptides (AMPs) and expressing molecules (3-dioxygenase (IDO), interleukin (IL)-17, and indoleamine-2) can provide antimicrobial action [13,22-24].

One of the MSCs is derived from the wharton’s jelly region of the umbilical cord (WJMSCs) and has higher proliferation, immunomodulatory activity, plasticity, and self-renewal capability than other mesenchymal stem cells. WJMSCs have an extracellular matrix made up of collagen, proteoglycans, and hyaluronic acid that has been demonstrated to create a healing environment and a connective tissue matrix to replace or supplement injured or deficient integumental tissue. WJMSCs secrete anti-inflammatory factors (TGF β, IDO, IL-10, PGE2, and TSG-6) [7,25], angiogenic factors (VEGF (Vascular Endothelial Growth Factor), EGF, HGF, PDGF (Platelet Derived Growth Factor), bFGF), PGF (Placental Growth Factor), IL-6, Ang-1 (Angiopoietin-1), Ang-2, angiostatin, CXCL16, GM-CSF (Granulocyte Macrophage-Colony Stimulating Factor, MCP-1 (Monocyte Chemotactic Protein-1), MMP-8 (Matrix Metalloproteinase-8) and MMP-9) as well as other substances that aid in the healing of wounds [5,16,25,26].

MSCs administration is not risk-free so that numerous critical points should be considered, including cell malignancy, the risk of inducing tumor growth in vivo, and the possibility of cell maldifferentiation. In comparison to direct MSCs transplantation in vivo, MSC-conditioned medium eliminates the risk of grafted cells maldifferentiating or transforming malignantly, making it a much safer approach. Nevertheless, because of its immunosuppressive properties, the use of MSC-conditioned medium may impair the immune system, increasing the risk of infection and immunodeficiency in treated patients. Therefore, additional preclinical and clinical studies are required in the future, particularly clinical evaluations of the safety and efficacy of MSC-conditioned medium [5,11].

![Fig. 4. The role of MSCs in wound healing [5]](image-url)
In numerous studies, WJMScs have been proven to be particularly effective at treating delayed wound healing with minimal scarring including hypertrophic scar or keloid. Hypertrophic scars are formed by a disruption in the ECM as well as a disruption in the balance between collagen production and breakdown (large levels of immature type III collagen and mature type I collagen). WJMSCs is a treatment that overcomes the limits of current surgical procedures like debridement or medication therapy [3,7,27,28].

4. CONCLUSION

Delayed wound healing refers to wounds that do not repair the wounded tissue’s integrity in a timely manner, prolonging the inflammatory, proliferative, and remodelling phases of healing. Delayed wound healing increases the risk of infection, causes discomfort, reduces the quality of life, and becomes a burden on the healthcare system. Wharton’s Jelly-derived MSCs conditioned medium could be a potential therapy for delayed healing wounds. The wound healing process of a seventeen-year-old man treated with one fingertip unit of 10% Wharton’s Jelly-derived MSCs conditioned medium (WJMSCs-CM) topical gel improved significantly, and the patient was pleased with the outcome.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard, patient’s consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


