Case report

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

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 increasing the chance of infection, causing discomfort, lowering 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 17-year-old male appeared with a 1-month history of wound in his left neck that had not healed after a keloid surgery. The wound was treated with a topical Wharton's Jelly-derived Mesenchymal Stem Cells Conditioned Medium (WJMSCs-CM). During the 2 weeks of the intervention, the results are encouraging. The lesion has reduced in size and has scarred 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

Seventeen-year-old man presented with a one month history of lesions in his left neck that had not healed after keloid 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 at first. After cleaning the lesion with NaCl, a topical Wharton's Jelly-derived Mesenchymal Stem Cells Conditioned Medium (WJMSCs-CM) was applied. The patient was also given WJMSCs-CM gel to apply at home on a daily basis. The patient regained control seven days later. 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 improving. The lesion has reduced in size and has scarred into a closed wound. The patient was really pleased with the outcome. (fig 3).

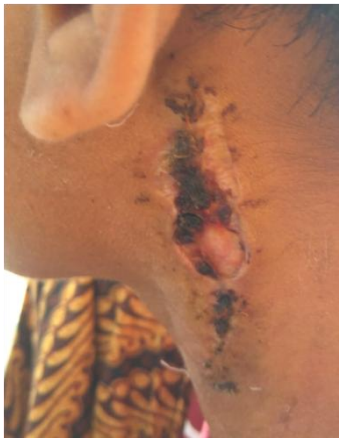

Fig 1: A red open wound, measuring 15 x 5 cm, accompanied by exudate, scabs and pain.

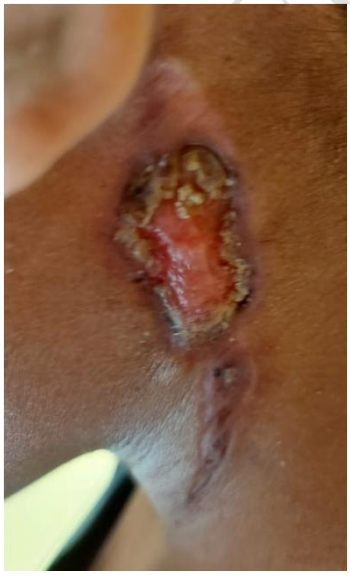

Fig 2: After seven days later by applying topical Wharton's Jelly-derived Mesenchymal Stem Cell Conditioned Medium (WJMSCs-CM).

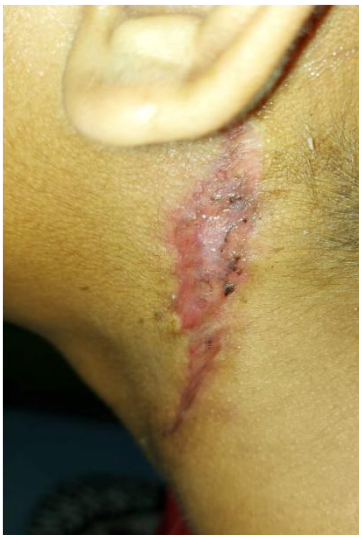

Fig 3: Two weeks later, the lesion was improving. The lesion has reduced in size and has scarred into a closed wound.

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 systemc 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 wounds that do not repair the wounded tissue's integrity in a timely manner, prolonging the inflammatory, proliferative, and remodelling phases of healing[1] 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]

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.[9] The use of MSCs in the treatment of delayed wound healing has demonstrated to be effective.[10] MSCs aid in the healing of cutaneous wounds by speeding wound closure, enhancing tissue granulation, promoting angiogenesis, lowering inflammation, and increasing ECM remodeling.[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.[11] 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 amniotic fluid, umbilical cord blood, peripheral blood, urine, and menstrual blood.[12,13]

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.[3,9,11,13] 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.[14,15] The survival pathway, PI3K/Akt or FAK-ERK1/2 controls cell proliferation, differentiation, apoptosis, and migration. Many cell types rely on this route for their physiology and pathology.[11,14] 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.[14]

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 SPD (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.[10,16-18]

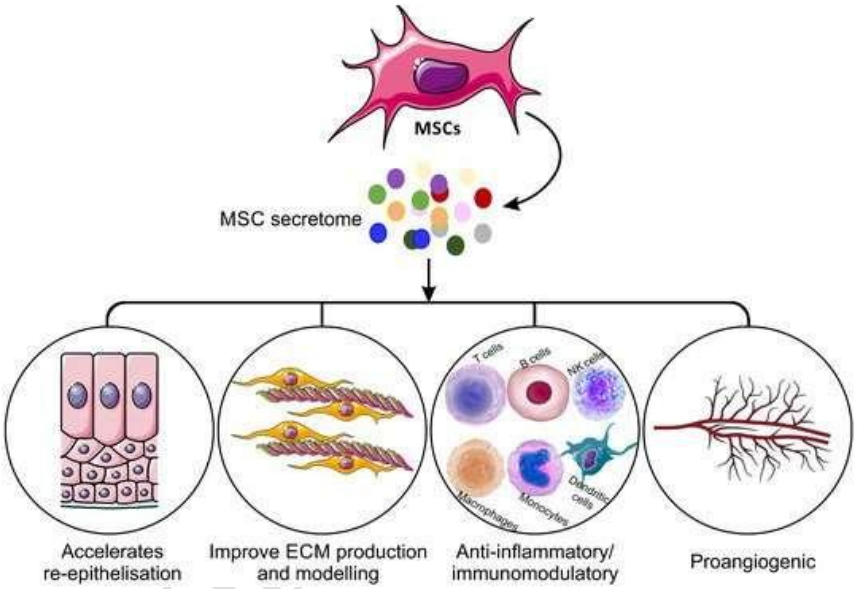

Fig. 4: The role of MSCs in wound healing[5]

MSCs are derived from the umbilical cord's wharton's jelly region and have higher proliferation, immunomodulatory activity, plasticity, and self-renewal capability than other mesenchymal stem cells.[7,19] 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.[7,20]

WJMSCs secrete anti-inflammatory factors (TGF β, IDO, IL-10, PGE2, and TSG-6)[7,20], 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.[5,12,20,21]

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.[3,7,22,23]

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 infection, causes discomfort, reduces quality of life, and become a burden of the healthcare system. Mesenchymal Stem Cells derived from conditioned medium of Wharton's Jelly could be a potential therapy for wound healing that has been delayed. The wound healing process of a 17-year-old man treated with 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.

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