Progress in Clinical Research on Regenerative Medicine Technologies for the Treatment of Chronic Hard-to-Heal Wounds

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Abstract: Regenerative medicine technologies, which activate the body's intrinsic repair mechanisms to achieve tissue regeneration, are currently regarded as a promising new direction in the treatment of chronic hard-to-heal wounds. This study explores the clinical research progress of regenerative medicine technologies in the treatment of such wounds. Chronic hard-to-heal wounds are increasingly prevalent in China, stemming from trauma, diabetes, pressure ulcers, lower limb venous and arterial diseases, among others. The causes are complex, and treatment is challenging, leading to high disability rates and significant suffering for patients. In recent years, regenerative medicine technologies have been widely applied in the treatment of chronic hard-to-heal wounds. These technologies are capable of non-invasive liquefaction and removal of necrotic tissue, physiological control of bacterial and toxin infections, and creating a physiologically moist environment conducive to skin regeneration. By promoting cell proliferation, tissue remodeling, granulation tissue growth, angiogenesis, and epithelial migration, regenerative medicine accelerates wound healing. In the treatment of chronic hard-to-heal wounds, the application of regenerative medicine technologies helps to establish standardized treatment protocols. These protocols not only reduce the economic burden on patients but also alleviate their suffering, enhancing their quality of life and offering substantial value for clinical promotion.

Keywords: Chronic Hard-to-Heal Wounds; Regenerative Medicine Technologies; Moisture Exposed Burn Ointment; Standardized Procedures

1. Introduction

A chronic hard-to-heal wound is defined as a wound that fails to heal or shows no signs of healing despite receiving proper treatment for one month [1]. Among hospitalized surgical patients, 1.5% to 3.0% of cases involve ulcers induced by diabetes, with an incidence rate of 8.1% [2]. Chronic hard-to-heal wounds inflict significant physical pain on patients, leading to a reduced quality of life and negatively impacting psychological health [3]. Moreover, the prolonged treatment period demands long-term medical care and incurs high treatment costs, resulting in a heavy financial burden on patients and their families. Regenerative medicine technologies, such as Moist Exposed Burn Therapy (MEBT) and Moist Exposed Burn Ointment (MEBO), play a crucial role in the repair process of wounds. These technologies facilitate the resolution of inflammation, promote cell proliferation, and support tissue remodeling during the healing process [4-5]. MEBO, the core therapeutic agent of regenerative medicine [6], offers several key advantages. It can non-invasively liquefy and eliminate necrotic tissue, control bacterial and toxin infections physiologically, create a moist environment conducive to skin regeneration, provide essential nutrients required for wound healing, and serve as an exogenous tissue culture medium for skin regeneration. To further promote the clinical application of regenerative medicine, this paper reviews wound treatment based on the TIME principles: T for Tissue nonviable (necrotic tissue), I for Infection or Inflammation, M for Moisture imbalance, and E for Edge imbalance [7]. These principles guide the systematic approach to wound care, optimizing the chances of healing.

2. Clinical Examples of Chronic Hard-to-Heal Wounds

The treatment of chronic hard-to-heal wounds is now widely facilitated by MEBO, which is commonly used for various conditions, including pressure ulcers, diabetic foot ulcers, lower limb venous ulcers, traumatic ulcers, and residual burn wounds.

2.1 Pressure Ulcers

Pressure ulcers, also known as pressure sores, occur when sustained pressure damages the skin and underlying tissues, restricting blood flow and leading to ischemia and hypoxia. This results in tissue necrosis [8] and ulceration, which, if left untreated, can lead to sepsis and pose a life-threatening risk [9]. Pressure ulcers are most commonly seen in bedridden patients, often affecting areas such as the shoulders, sacrum, hips, and ischial regions.

2.2 Diabetic Foot Ulcers

Diabetic foot ulcers are among the most severe complications of diabetes, resulting from neuropathy and vascular changes in the lower extremities. These ulcers can lead to infection, necrosis, and a high risk of amputation, and in some cases, sepsis [10]. Clinically, diabetic foot ulcers present with purple skin discoloration, increased skin temperature, swelling, pain, gangrene, and ulceration. The healing process is typically prolonged, and recurrence is common after healing [11-12].

2.3 Lower Limb Venous Ulcers

Venous reflux diseases and reflux obstructive diseases of the lower limbs lead to blood stasis and tissue hypoxia in the distal extremities, causing nutritional disorders of the skin. This ultimately results in the formation of skin ulcers, a condition known as lower limb venous ulcers. It is the most severe complication in the progression of chronic lower limb venous insufficiency [13]. These ulcers often occur as a result of lower limb varicosities and are frequently accompanied by swelling, pain, skin pigmentation, ulceration, and prolonged non-healing [14].

2.4 Traumatic Ulcers

Traumatic ulcers occur as a result of external injury that causes skin breakdown, which does not heal within four weeks of treatment, resulting in a persistent ulceration. These wounds often harbor bacterial contamination, which can further delay the healing process and necessitate medical intervention.

2.5 Residual Burn Wounds

Deep burns, due to their severity, often result in prolonged non-healing wounds. Contributing factors include the depth of the injury, necrosis of skin flaps following grafting, and incomplete debridement during the initial treatment [15]. The compromised local microcirculation and reduced regenerative capacity of tissues further hinder the healing process [16]. Additionally, bacterial invasion, leading to the formation of biofilms, exacerbates the difficulty in wound closure [17]. As a result, these wounds resist healing, requiring clinical intervention to promote faster recovery and resolution.

3. Clinical Standardization of Regenerative Medicine Technology

Regenerative medicine technologies in wound treatment adhere to the “One Attention” principle: During wound care and dressing changes, it is crucial to avoid using disinfectants, desiccants, or astringents on the wound. If the wound exhibits excessive exudation or significant contamination, physiological saline may be used for cleaning to prevent external factors from causing fibroblast death, which can hinder the growth of granulation tissue. The “Three No’s” principle emphasizes the goal of avoiding pain, bleeding, and damage to healthy tissue during necrotic tissue debridement and dressing changes. The aim is to prevent reperfusion injury, which could further exacerbate the wound. Pain can cause capillary constriction and spasms in the wound area, limiting oxygen and nutrient supply. Bleeding indicates the detachment of healthy tissue or ruptured blood vessels, both of which can delay wound healing. The “Four Timeliness” principle stresses the importance of promptly removing liquefied material, exudates, necrotic tissue, and replacing the moist burn ointment in a timely manner. These substances contain toxins, inflammatory mediators, interleukins, metabolic waste products, and other harmful compounds. Failure to remove them promptly may result in direct toxic effects on local tissues and cells, potentially leading to a systemic inflammatory response (SIRS) and even septicemia [18]. Dressing Change Procedure: According to the standardized treatment guidelines for regenerative medicine (the One Attention, Three No’s, and Four Timeliness principles), apply a 1-2mm thick layer of MEBO to the wound. Then, place the MEBO on a sterile gauze pad and gently rub (avoid applying excessive force to prevent damage to the ointment's framework) until the ointment is uniformly absorbed by the gauze. The gauze should cover the wound with 2-4 layers, extending approximately 1 cm beyond the wound margin. Finally, apply a cotton pad of 1.0-3.0cm thickness to cover the wound and secure the dressing. If there is excessive exudate, liquefied material, or necrotic tissue, the dressing should be changed every 8 to 12 hours. Once fresh granulation tissue has formed, the frequency of dressing changes can be reduced to once per day.

4. Mechanism of Action of Regenerative Medicine Technology in Chronic Hard-to-Heal Wounds

4.1 Application in Necrotic Tissue

When MEBO is applied to necrotic tissue, it effectively liquefies and removes the necrotic material without causing damage. During this process, the necrotic tissue is transformed from a solid to a liquid state under the influence of MEBO [19]. The ointment's lipophilic properties enable the drug's liquid components to react and undergo degeneration with the necrotic tissue. This interaction results in a loss of lipophilicity, causing the drug to mix with the wound's exudate and liquefied material. This mixture then undergoes various biochemical reactions such as hydrolysis, enzymatic degradation, rancidification, saponification, and esterification, continually facilitating drainage. Through this repeated process, MEBO plays a crucial role in cleansing the wound [20].

4.2 Regulation of Local Inflammatory Response

In most chronic hard-to-heal wounds, bacterial biofilms are present. Bacteria utilize extracellular matrix components such as secreted proteins, extracellular polysaccharides, and extracellular DNA to encase themselves, thus forming a biofilm [21-22]. In other cases, once the immune barrier of the wound is compromised, bacteria easily invade the wound, leading to infection [23]. The overuse of antibiotics has led to bacterial resistance, making the control of wound infections less effective [24]. Chronic wound infections are primarily caused by Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and enterobacter cloacae [25]. The ingredients in MEBO such as Coptis chinensis, Phellodendron amurense, and Scutellaria baicalensis exhibit a range of antimicrobial effects. From a modern pharmacological perspective, Coptis chinensis possesses antibacterial properties, as it reduces the number of pili on the bacterial surface, preventing the bacteria from adhering to human cells, thus achieving antimicrobial action [26]. The berberine alkaloid in Phellodendron amurense has inhibitory effects on both Gram-positive and Gram-negative bacteria. Furthermore, both Coptis chinensis and Phellodendron amurense exert anti-inflammatory effects by enhancing antioxidant enzyme activity and reducing lipid peroxidation [27]. Scutellaria baicalensis, containing baicalin, is known for its potent antibacterial activity [28]. Research indicates that baicalin is an immune modulator with strong antibacterial and bactericidal effects against Methicillin-resistant Staphylococcus aureus (MRSA) in vitro. This action may occur through the mediation of reactive oxygen species (ROS) clearance, leukocyte adhesion, inhibition of leukotriene synthesis, and reduced release of arachidonic acid, all contributing to its anti-inflammatory effect [29]. By inducing non-heritable mutations in bacteria, MEBO reduces their toxicity and invasiveness, thereby decreasing the local bacterial count in the wound and achieving antimicrobial and bacteriostatic effects [30]. Consequently, the burn ointment helps control bacterial and toxin infections physiologically, alleviates the persistent abnormal inflammatory response in the wound, reduces lymphocyte infiltration, promotes angiogenesis, and stimulates granulation tissue formation.

4.3 Maintenance of a Physiological Moist Environment in Wounds

The theory of wound moisture balance has been widely recognized. The discovery that a moist environment promotes healing reactions underscores the critical importance of maintaining optimal moisture levels for effective wound healing [31]. Research by XIAO et al. [32] conducted on animal models concluded that the ideal moisture level for wound healing is approximately 25%, with moisture-balanced dressings considered to provide the appropriate humidity to prevent bacterial infections. MEBO creates a physiological moist environment for wounds by forming a protective film. This film effectively isolates the wound from the external environment, reducing direct exposure to air and slowing the rate of moisture evaporation. This helps maintain a relatively moist environment around the wound. Additionally, MEBO contains linoleic acid, which supplies essential nutrients to the wound and enhances the activity of epidermal growth factors. It also promotes the migration and proliferation of epithelial cells, further supporting the healing process.

4.4 Promotion of Granulation Tissue Growth and Epithelialization

Once necrotic tissue is removed and infection is controlled, the wound enters the phases of granulation tissue formation and epithelialization. MEBO has been shown to enhance the levels of vascular endothelial growth factor (VEGF) in granulation tissue, which increases vascular permeability, alters extracellular matrix components, and induces neovascularization. Basic fibroblast growth factor (bFGF) promotes granulation tissue growth and accelerates capillary regeneration. Epidermal growth factor (EGF) induces or directly regulates cell proliferation, initiating the wound healing process and stimulating epithelial cell growth [33]. Research by Tang Qianli et al [34]. found that in rats with acute wounds, treatments such as MEBT/MEBO significantly elevated the expression levels of VEGF, bFGF, and EGF mRNA in granulation tissue. In rats with chronic hard-to-heal wounds, MEBO increased the protein levels of VEGFR-2, EGF, and its receptor, as well as the expression of VEGFR-2 mRNA. These effects aid in the proliferation of fibroblasts and new capillaries, accelerating the growth of epithelial cells and thereby promoting wound healing.

In summary, the application of regenerative medical technologies in the treatment of chronic hard-to-heal wounds should adhere to standardized treatment protocols. The core drug in these regenerative therapies, MEBO, effectively and non-traumatically liquefies and removes necrotic tissue, physiologically controls bacterial and toxin infections, activates the regenerative potential of wound cells, and promotes the proliferation of fibroblasts and new capillaries. This accelerates granulation tissue growth and epithelialization. Under the contemporary Enhanced Recovery After Surgery (ERAS) model, these treatments expedite wound healing, improve patients’ quality of life, reduce their suffering, and alleviate the economic burden on families.

5. Conclusion

In the field of medicine, wound repair holds a critical position, intricately linked to the treatment of various conditions such as burns, trauma, and ulcers. With the continuous advancement of science and technology, the field of wound repair is also in a state of ongoing development and innovation. As this field evolves, regenerative medicine technologies require further exploration of new methods in basic research to propose novel therapeutic strategies. This exploration occurs across both macroscopic and microscopic levels. As society progresses and the standard of living improves, the public’s demand for medical services has steadily increased. Regenerative medicine, having been proven as an ideal therapeutic approach, holds significant clinical guidance value and societal practical significance. Consequently, its clinical applications have been increasingly promoted and adopted across various medical settings.

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