

Accelerated Wound Healing: Harnessing the Power of Platelets, Biomaterials, Stem Cells and Gene Therapy

The goal of accelerated wound healing is reduced morbidity and less scarring, that can result in tremendous savings of time and money, besides improving the quality of life. Various techniques are being introduced to improve wound care and hasten wound closure. Any injury or break in the skin sets into motion a sequence of events to repair the wound that is characterised by the movement of specialised cells into the wound site. This process of wound healing has four distinct phases that overlap with each other; haemostasis, inflammation, proliferation and remodelling.^[1] Wound healing begins as soon as the tissue is injured. As blood spills into the site of injury, the platelets come into contact with exposed collagen and extracellular matrix, releasing clotting factors, to achieve haemostasis as well as essential growth factors (GFs) and cytokines to repair the wound. These GFs include platelet-derived GF, transforming GF beta, vascular endothelial GF (VEGF), platelet-derived epidermal GF, insulin-like GF-I and basic fibroblast GF (bFGF) to name a few. Neutrophils followed by the macrophages then begin to phagocytose bacteria, damaged tissue and other foreign materials, as part of the inflammatory phase. Following this, fibroblasts migrate and begin the proliferative phase which deposits new extracellular matrix and collagen. During the final remodelling phase, the newly laid collagen matrix becomes organised and cross-linked. Numerous cell-signalling events and cytokines are required to orchestrate these events, and there is a constant endeavour to accelerate wound healing when it is lagging or is deficient. This can be achieved using various regenerative techniques.

Regenerative medicine in dermatology is a newer interdisciplinary branch that focuses on the repair and regeneration of cells and tissue of the skin to restore defects resulting from congenital disorders, disease, trauma, burns or ageing skin.^[2] It requires a combination of several technological approaches and biomaterials including, the use of soluble molecules such as GFs, stem cells, gene therapy, tissue engineering and reprogramming of cell and tissue types.^[2]

The goal of accelerated wound healing is less scar formation. In recent times, this has fuelled the exponential rise of autologous platelet-derived products such as platelet-rich plasma (PRP) and platelet-rich fibrin matrix (PRFM), which provide several GFs to accelerate wound healing. Platelet-derived products have become popular because of their simpler techniques. This issue of the journal reports on the successful use of PRFM for chronic ulcers. Nagaraju *et al.*^[3] report on the use of autologous PRFM in non-healing trophic ulcers in Hansen's patients, which are challenging to treat because of trophic changes and repeated

trauma due to loss of sensations. In their small study of seven patients, they observed 93.52% healing as early as completion of two sessions done at weekly intervals and complete healing by a maximum of five sessions in all patients. Similarly, Somani and Rai^[4] compared the efficacy of PRF versus saline as a control in chronic venous leg ulcers. They found a statistically significant difference in the healing rates in the PRF group as compared to controls. The easy availability and simple techniques for preparation of PRP and PRF have led to its use in a myriad of conditions for regeneration such as atrophic acne scars to increase collagen, androgenetic alopecia for hair regrowth and accelerated wound healing for chronic non-healing ulcers. However, standardisation, methodology and protocols are still lacking.

Another approach to accelerate wound healing is through the use of biomaterials and tissue engineering.^[5] Most of the biomaterials are based on natural polymers such as hyaluronic acid. Mohammadi *et al.* reported on the use of amniotic membrane to reduce post-burn hypertrophic scar formation in this issue.^[6] In their comparative study, extremities of each patient with burn wounds were randomly divided into two groups. One limb was treated with a meshed skin graft and traditionally fixed with skin staples (control group), while the other limb was treated with a similar meshed skin graft and then covered with an amniotic membrane. They found accelerated healing with reduced hypertrophic post-burn scars and decreased itching in the amnion group as compared to the control group. In another study, Ramesh *et al.*^[7] found that application of a collagen sheet reduces pain and induces faster wound healing at skin graft donor site as compared to petrolatum dressing. Collagen is a commonly used biomaterial that promotes wound healing by creating a moist wound environment and organisation of freshly formed collagen fibres in the wound bed. Other biomaterials being used are genipin-crosslinked gelatin and collagen sheets, microbial cellulose and electrospun nanofibrous dressings.^[5]

Currently, biomaterials incorporated with drugs and bioactive compounds are being developed to enhance wound healing and reduce scarring. Some biomembranes specialised in scar prevention application include ginsenoside Rg3-loaded electrospun poly (lactic-co-glycolic acid) fibrous membranes as cutaneous wound cover.^[8] It has been shown that on using the biomembranes, the expression of VEGF, mRNA and collagen type I was found to decrease significantly, leading to accelerated wound healing and consequently, inhibiting hypertrophic scar formation.^[8] Norfloxacin-loaded collagen/chitosan scaffold was recently reported to enhance the rate of wound healing, new cell growth and faster wound closure.^[9]

Cell therapy combined with scaffolding biomaterials is another promising biomaterial to enhance wound healing. Apligraf, a bi-layered bioengineered skin substitute, is widely used. The graft is developed from neonatal cells and may stimulate a more foetal-like scarless wound healing, therefore may result in better cosmetic appearance. The direct application of GFs has led to modest results. Stem cell therapy is another application, waiting to take off. The use of mesenchymal stem cells derived from bone marrow, umbilical cord, adipose tissue and epidermal stem cells that can differentiate into other cells that can accelerate the wound healing response has also been documented.^[10] These cells after differentiation and activation in the wound have been shown to produce a variety of GFs including VEGF, platelet-derived GF, bFGF and matrix metalloproteinase-9 that accelerates wound healing.

Recent advances in molecular biology, nanotechnology and an increased understanding of the pathophysiology of chronic wounds have resulted in the development of many novel therapies to accelerate wound healing. In addition, promising developments in the areas of stem cells and gene therapy have given rise to new hope in modulating non-healing wounds. To attain the goal of scarless wound healing, future research should aim to identify critical factors in tissue repair and regeneration that can tackle the problem of scarring.

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