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EPIDERMAL GRAFTING
The Use of ReCell® and Regenerative Epithelial Suspension™ in Effective Treatment of Skin Injuries and Defects

Abstract

Skin regeneration is the physiological process of restoration of normal skin. Regenerative Epithelial Suspension (RES™), naturally features the epithelial elements needed to support the highly regulated cascade of healing events leading to regrowth of healthy skin. RES is autologous and is made entirely at the point of care from a sample of the patient’s skin. The suspension consists of disaggregated skin cells, including keratinocytes, fibroblasts, melanocytes and Langerhans cells. In the disaggregated state, the cells are freed from contact inhibition, and they behave as though at the edge of a wound, signaling and mediating the dynamic processes of new tissue formation.

Keywords: wound healing, re-epithelialisation, suspension, skin graft, regenerative

Introduction

ReCell® Autologous Cell Harvesting Device (Figure 1) is a class III, single use, sterile medical device, including a proprietary enzyme formulation that enables clinicians to produce Regenerative Epithelial Suspension for treatment of a range of skin injuries and defects including acute burn wounds, chronic wounds, scar and dyspigmentation. ReCell is patented, CE-marked, TGA registered in Australia and CFDA cleared in China.

The clinical effectiveness of the Regenerative Epithelial Suspension has been described in a number of published studies (Table 1) and is the subject of a number of ongoing randomised controlled trials: for burns in the United States, for venous leg ulcers in the United Kingdom, for vitiligo in the Netherlands, and for acute and chronic wounds in China.

History and Benefits

There are well-documented advantages, particularly from a safety standpoint, to autologous techniques for epidermal replacement. The use of autologous skin in grafting results in a lower risk of negative outcomes in comparison to allogeneic transplantation. In 1951, Billingham and Medawar noted allogeneic skin triggers a potent reaction by the host’s immune system. Multiple mechanisms contribute to the rapid elimination of the allogeneic cells and subsequent rejection of the graft. Since rejection mechanisms are not triggered with autologous skin, there is no risk of graft failure due to rejection and no requirement for immunosuppressive therapy. In addition, the extensive processing and broad safety testing for infectious disease associated with allogeneic treatments are not needed for autologous therapeutics.

Cell culturing has historically played an important role in patient care, especially as part of the management of extensive skin injuries. While typically autologous, cell culturing techniques involve considerable time and expense. Rheinwald and Green first described serial cultivation of epithelial cells, a technique which has been used in the development of cultured epithelial autografts (CEAs). Cell culture is limited by differences in incubation conditions for the different cell types; fibroblasts and keratinocytes are difficult to co-culture. Melanocytes, which are very sensitive to stress mechanisms, proliferate slowly and die in cell culture resulting in depigmentation after CEA treatment. In contrast to cultured cells, melanocytes contained in RES survive to localize to the epidermal side of the dermal-epidermal junction and evenly distribute melanin throughout the epidermis for normal pigmentation of the new skin. As preparation and delivery of
RES happens at the point of care, within a span of approximately 30 minutes, RES contains viable populations of the skin cell phenotypes that have been shown to be essential in the normal physical and chemical interplay between the different cell types in wound healing.

It is known that skin cells produce many signaling proteins that act on themselves (autocrine) and on other cells around them (paracrine) to produce more than one effect (pleiotropic) on multiple cell types. The cells are inter-dependent and disruption in the concentration or timing of any of these factors may result in failure to heal. In non-healing (chronic) wounds, protein expression and responses to cell factors have become dysfunctional. Further, this process is naturally resource-constrained, as the primary source for cells and their expressed cytokines is limited to the edge of the wound.

While there has been interest in cells of the dermal-epidermal junction, both basal and suprabasal keratinocytes play roles in wound re-epithelialization. In addition to representation of multiple cell phenotypes, the disaggregated RES: a short summary of selected publications describing outcomes associated with the use of RES.

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<th>INDICATION</th>
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<td>Burns</td>
<td>A randomized trial comparing ReCell® system of epidermal cells delivery versus classic skin grafts for the treatment of deep partial thickness burns. A prospective randomised clinical pilot study to compare the effectiveness of Biobrane® synthetic wound dressing, with or without autologous cell suspension, to the local standard treatment regimen in paediatric scald injuries. Healing of widely meshed autografts using freshly isolated autologous epidermal cells and acellular Xe-Derma xenodermis.</td>
<td>2-cohort RCT (n=82). Use of RES for effective healing with reduced donor area and less postoperative pain (p=0.03) were observed vs skin grafting. 3-cohort pilot RCT (n=13). Early intervention with Biobrane® + RES was associated with effective healing (without grafting), less pain and better scar outcomes. Use within 4 days of injury saved on nursing time, dressing, analgesic and scar management costs. Within-subject comparative study (n=14). Healing of wound areas treated with RES and XeDerma was of superior quality to XeDerma alone, reducing the development of early and late onset complications in the extensive burns patient.</td>
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<td>Chronic Wounds</td>
<td>Autologous skin cells: a new technique for skin regeneration in diabetic and vascular ulcers. Preliminary results with the use of a non-cultured autologous cell suspension to repair non-healing vascular leg ulcers. Randomized clinical trial of autologous skin cell suspension combined with skin grafting for chronic wounds.</td>
<td>Four patients (diabetic, n=3; non-diabetic, n=1) were treated using RES. Effective epithelialization with no signs of infection was observed by 4, 6 or 8 months. No further clinical intervention of these ulcers was required. Treatment of 12 ulcers (11 venous and 1 vasculitic) with RES resulted in a 55% mean reduction of the surface area of 10 ulcers and a complete healing of the remaining 2. These preliminary results demonstrate RES was effective in restarting the repair process of non-healing ulcers and in reducing pain. STSG + RES v STSG RCT (n=88). Combination of RES with STSG grafting in chronic wounds demonstrated improved healing rates over STSG alone, together with a decrease in wound recurrence and complications.</td>
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<td>Scar reconstruction</td>
<td>Combination of Medical Needling and ReCell® for Repigmentation of Hypopigmented Burn Scars. Use of a novel autologous cell-harvesting device to promote epithelialization and enhance appropriate pigmentation in scar reconstruction.</td>
<td>Patients with 1 year old hypopigmented scars treated with RES (n=20). The combination of medical needling and RES resulted in statistically significant objectively measured repigmentation vs within-subject control scar. RES treatment of post-traumatic scars (n=30) resulted in excellent or good aesthetic and functional outcomes (80%) and normal pigmentation (60%) of the patients.</td>
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<td>Repigmentation</td>
<td>Evaluation for performance of ReCell for repigmentation. Treatment of vitiligo lesions by ReCell® vs conventional melanocyte-keratinocyte transplantation(MKT): a pilot study.</td>
<td>RES+ CO2 laser with UVA within-subject pilot RCT (n=10) for patients with stable segmental vitiligo. Median re-pigmentation was 78% for RES treated areas, 0 % for CO2 control or no treatment areas (in press, personal communication). Within-subject comparative study (n=5, MKT vs RES). Comparable pigmentation was observed between RES and MKT, but without specialised laboratory facilities.</td>
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Table 1. A short summary of selected publications describing outcomes associated with the use of RES.
skin cells in RES are in the “free edge” state, and thereby introduce a cascade of signals that regulate and promote the sequence of healing.\textsuperscript{27} Injured keratinocytes rapidly release Interleukin 1 (IL-1),\textsuperscript{28,29,30} acting as a paracrine signal to lymphocytes and fibroblasts\textsuperscript{31,32}, and as an autocrine signal to activate other keratinocytes, causing them to become proliferative and migratory.\textsuperscript{29,33,34} High Mobility Group box protein 1 (HMGB1) is also released early in the injury by damaged keratinocytes to initiate a positive feedback autocrine loop to maintain the inflammatory cascade and is critical for signaling skin repair mechanisms and dysfunction of this signal results in impaired wound healing.\textsuperscript{35} Master regulator proteins such as Heat Shock Protein 90 (HSP90), are rapidly secreted by injured and “free edge” keratinocytes and fibroblasts and orchestrate the cell signaling cascade of cell migration, angiogenesis and matrix re-modelling essential for skin regeneration.\textsuperscript{22,36,37,38} Use of RES introduces disaggregated epithelial cells and the associated signaling across the surface of the skin to regenerate the skin and function. Application of RES overcomes the usual limitation of availability of healthy cells.
wound, overcoming the usual limitations of the wound edge.  

(Figure 3)  

The absence of “neighbour” cells initiates the cascade of cell signals that brings about cell migration and proliferation to heal the wound. This contrasts with the contact inhibited cell signals that brings about cell migration and proliferation (Figure 3) 

In 1975, Rheinwald and Green first described disaggregated skin cells and the independence of the cell types by demonstrating that keratinocytes proliferate and migrate but require the presence and products of fibroblasts. In 1999, Singer and Clark reviewed the importance of all the skin cell types in wound healing. It has been shown that melanocytes, fibroblasts and keratinocytes are highly interactive and communicate with each other via secreted factors, their receptors and via cell/cell contacts to regulate the function and phenotype of the skin. For normal tissue regeneration and pigmentation, multiple cell types and processes are required and cellular responses to inflammatory mediators, growth factors and cytokines must be appropriate and precisely timed.

Conclusion

Avita Medical’s technology can be used at the point of care to produce Regenerative Epithelial Suspension, which is a safe, rapid, and physiologically relevant means for restoration of normal skin. Since RES is autologous in origin, the suspension is non-antigenic with a low risk of negative side-effects. It is readily available with the economic benefits of low-cost and simple logistics. While understanding of the detailed roles of each skin cell type and their interplay during skin regeneration continues to develop, it is apparent that disaggregated populations of cells in suspension are activated in the process of separation from confluent tissue. The physiologically relevant and complete nature of RES underpins its potential for restoration of normal skin characteristics. ■

References


