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Cell-spray auto-grafting technology for deep partial-thickness burns: Problems and solutions during clinical implementation

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ABSTRACT

Cell-spray autografting is an innovative early treatment option for deep partial-thickness burn wounds. As an alternative to non-operative management, cell-spray autografting can achieve rapid wound re-epithelialization, particularly in large wounds. When compared to traditional mesh autografting for deep partial-thickness burn wounds, cell-spray autografting can accomplish re-epithelialization with a much smaller donor site. In this review, we describe the development of a biomedical engineering method for isolation and immediate distribution of autologous, non-cultured, adult epidermis-, and adult dermis-derived stem cells. We present data on cell isolation procedures in 44 patients with deep partial-thickness burns performed over five years under an innovative practice IRB. Treated patients presented with a variety of burn wound etiologies and a wide range of TBSA. Overall clinical results were very satisfying. The average hospital length of stay following treatment was seven days. Over the time period, the donor-site to burn-wound surface area ratio was enhanced from 1:80 to 1:100. A detailed analysis of all process-related biotechnology and operative problems, pitfalls, and solutions was performed and is reported herein. Strategies for future clinical studies are discussed.

1. Introduction

Skin transplantation has evolved from autologous full-thickness grafts to split-thickness skin grafts (STSG), to mesh expansion of STSGs into a "skin lattice" [1–3]. The most widely used technique limits the typical expansion of a STSG donor area to 1:3, as larger ratios are often associated with unsatisfactory results and complications [4–6]. The Meek technique [7] cuts the STSG into small tissue cubes, enabling a donor site to wound ratio from 1:3 to 1:9 [8]. For large burn wounds, however, the lack of available donor site remains a

Abbreviations: BMI, body mass index; DSST, donor site skin tissue; IRB, Institutional Review Board; LR, Ringer's lactate; STSG, split-thickness skin grafts; TBSA, total body surface area.

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problem. Additional challenges exist when treating the face, joints, hands, or feet, where take rates and aesthetic outcomes are sometimes not satisfactory [9].

Deep partial-thickness burn wounds present a difficult diagnostic and prognostic challenge [10]. A conservative treatment strategy [11] of daily local wound care is often chosen by surgeons to avoid the donor site scar formation that accompanies mesh grafting [12]. However, the associated delay in re-epithelialization [13] may extend the patient's hospitalization period, increase the risk of infection, and lead to poor functional and aesthetic outcomes, as hypertrophic scar formation can complicate delayed wound closure [14]. Early surgical intervention shortens healing time and hospital length of stay, improves functional outcomes, and limits scar formation [15].

Autologous cell-spray grafting of non-cultured epidermal cells is an innovative dermis-derived, stem cell-based therapy [16] that can be applied early using a small donor site and thus presents an alternative to conservative treatment for large deep partial-thickness burns [17]. By employing epidermal and dermal progenitor cells and using the patient's wound as a "bioreactor" for cell expansion *in situ,* re-epithelialization can occur with a relatively small number of cells (as compared to STSG or cultured epidermal autografting) [18]. This method provides an on-site cell isolation process followed by the immediate application of autologous stem and progenitor cells to a freshly debrided wound bed. Cells in a saline suspension are sprayed uniformly across the wound bed to proliferate and accelerate the re-epithelialization process [17–19].

Cell-spray autografting does not preclude traditional mesh autografting, if used subsequently, and therefore could be a good early solution to address the therapeutic dilemmas attendant to deep partial-thickness burns. Furthermore, early re-epithelialization may reduce complications such as hypertrophic scarring, contracture with reduced range of motion, and poor aesthetic outcome, all of which could result in unsatisfactory psychological adjustment after therapy [20]. Our experience indicates that cell-spray autografting can enlarge the ratio of donor area to graft area from a routine 1:3 mesh to 1:100, thus facilitating operative therapy for the larger deep partial-thickness burn areas, while preserving donor area for full-thickness injuries [5]. Finally, the deposition achieved by spraying a cellular solution may improve autografting over contoured surfaces such as face and hands.

We present our experience with implementing a biomedical engineering approach in the treatment of 44 patients under innovative-practice IRB with overall very satisfactory clinical results (Table 4, online addendum). We performed a thorough analysis of all the problems that occurred; pitfalls and remedies are shared herein. Seven of the 44 patients treated were also reported previously in case reports, which include photographs of pre- and post-procedure wounds with follow-up information [17,19].

2. Material and methods

We worked as a multidisciplinary team of cell biologists, experimental surgeons, bioengineers at the University of Pittsburgh and clinical experts in burn care (University of Pittsburgh Medical Center [UPMC] Mercy Hospital). The original developer of the technology (StemCell Systems, Berlin, Germany) and an industry partner (RenovaCare, NY) were also involved to enable commercialization and marketing.

2.1. Patient criteria for cell-spray treatment inclusion

The Institutional Review Board (IRB) from UPMC Mercy Hospital, through its Technology and Innovative Practice Assessment Committee, approved the cell-based grafting procedures under an innovative practice approach. Data collection on 44 patients and retrospective analysis was performed under authorization of the Institutional Review Board (IRB# PRO14010023, 23-01). Patient selection was based on the physician team's best judgment but was limited to deep partial-thickness burn wounds.

2.2. Patient inclusion in cell isolation method analysis

Cell isolation was performed on 47 skin donor samples from 44 patients. Two patients had two and three cell isolation processes carried out on different days. The skin donor sample was harvested under local anesthesia using lidocaine either with or without epinephrine.

2.3. Patient inclusion in wound healing studies analysis

Change to: Forty-four patients were selected for cell-spray autografting treatment of deep partial-thickness burn wounds. Forty-three patients were treated and one patient did not have enough cells to undergo treatment. Only 27 patients, however, were included in the autologous cell-spray effects and the healing time analysis section, and 11 patients with mixed partial and full-thickness burn wounds were analyzed separately. Eight patients were excluded from data analysis for a variety of reasons including poor cell recovery due to significant comorbidities (4), >80% TBSA full-thickness burn (2), and cell isolates distributed on donor sites following STSG to full-thickness wounds (2), leaving 36 patients for analysis (see Table 1).

2.4. Cell-isolation process

The process of cell isolation has been previously described and published [16–19]. The donor site skin tissue area (DSST) is calculated using the formula that combines patient's biometric data like weight and height with the percentage of burned area to be treated. The total treatable burned area is combined with the desired seeded cell density that will be sprayed over the burn wound and divided by the constant that includes the number of isolated cells per skin square centimeter.

$$\mathrm{DSST}(\mathrm{cm}^2) = \left[\frac{0.007184 * \mathrm{W}^{(0.425)*}\mathrm{h}^{(0.725)*}\mathrm{TBSA}^{*}\mathrm{C}_1}{\mathrm{C}_2}\right]$$

DSST=donor site skin tissue (cm^2); w=weight (kg); h=height (cm); TBSA=total body surface area (%); C_1=cell density constant (10^4cells/cm^2); C_2=isolated cells per donor site skin tissue area (1,070,000cells/cm^2).

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