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Autologous Skin Cell Spray-Transplantation as an Innovative Alternative to Autologous Split- Thickness Skin Grafts for Deep Partial Thickness Burn Wounds: An Integrative Literature Review

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By

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Abstract

Burn wounds tend to be a critical problem with a complicated healing process. Although advancements have been made and the treatment of burn wounds has improved significantly, the healing process for deep-partial thickness burn wounds remains problematic. The purpose of this thesis is to review the available literature on an innovate biotechnology, autologous skin cell-spray transplantation, to more effectively treat burn wounds and potentially other injuries in the future. This study was conducted by critically researching and comparing (N=7) peer-reviewed research articles focusing not only on burn wounds using traditional treatments, but also the treatment of burn wounds using revolutionary cell-spray autographing technologies. The findings in this thesis show significant enhancement using this innovative approach for the treatment of burn injuries, and presents pivotal information for future nursing research, clinical practice as well as policy and education.

Dedications

To my dad, mom, sister, brother, fiancé, and daughter. If it weren't for you, I wouldn't be me. I love you.

Acknowledgments

I would like to express my deepest appreciation to my thesis committee chair, Dr. Angeline Bushy. Without your extensive knowledge, valuable time, unwavering support, and patience that cannot be underestimated, this project would not have been possible. I am also extremely grateful for Dr. Leslee D'Amato-Kubiet, my honors in the major coordinator. Your valuable advice and constant encouragement have been instrumental in my success throughout not only this project, but my nursing degree. Lastly, I would like to extend many thanks to my friends and family whose help and support cannot be overestimated. Your endless amount of love and profound belief in my abilities has helped me accomplish my goals and has shaped me into the person I am today. Thank you.

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Introduction

Burns are one of the most common and devastating injuries the human body can experience. In fact, burns are one of the most severe forms of trauma the body can sustain. In 2016 an estimated 400,258 people suffered a fire or burn related injury; of these 3,284 resulted in death (National Center for Injury Prevention and Control, 2016). Not only are burn wounds extremely painful, but also are challenging injuries to treat because they are complex and idiosyncratic. The inability to accurately classify the skin depth and extent during early evaluation makes diagnosis and prognosis very difficult. An uncertain prognosis makes planning for a conservative or non-conservative treatment problematic. Whether a conservative or non-conservative approach is chosen, early diagnosis and prognosis is essential for optimal burn wound healing.

Burn wound healing is a multistep process entails overlapping intervention phases that are essential for successful wound closure. A vital step in the treatment process is re-epithelization, which involves the migration, proliferation, and reconstruction of differentiated epithelial cells. Burn injuries in and of themselves can result in a lifetime of serious and challenging psychological, social, physical and functional outcomes for the affected individual (Stiles, K. 2015). Delayed re-epithelization may not only worsen these outcomes but result in a longer hospital stay with increased risk for complications such as infection, hypertrophic scar formation, delayed wound closure, and poor functional and aesthetic outcomes (Esteban-Vives et al., 2016b).

More severe burn wounds, including deep partial thickness and full thickness burn wounds, require early surgical treatment, such as skin transplantation, in order to avoid delayed re-epithelization. If a more conservative approach is used to treat these types of burn wounds, the risk of delayed wound healing increases. The most common technique used to treat more severe burn injuries utilizes a skin graft. In short, the skin graft procedure involves a section of healthy skin being surgically removed from somewhere on the individual's body (donor site) and transplanted to the affected injured area on the body. Skin grafts can be spilt-thickness skin graft (STSG), consisting of only part of the epidermis and a portion of the dermis, or a full-thickness skin graft, consisting of the epidermis and the entire thickness of the dermis from the donor site (U.S. National Library of Medicine, 2018). In this literature review, only STSGs will be addressed (Esteban-Vives et al., 2017).

The use of STSGs optimizes the expansion of the donor skin by meshing the graph into a “skin lattice.” However, mesh graft expansion continues to be of concern in the healing process. Not only is use of donor skin painful, imposing its own wound-healing burden on the patient, but it requires harvesting a large portion of the donor’s skin (Rowan et al., 2015). Often times, especially for larger burn areas, the available healthy donor skin may be limited. Therefore the there is insufficient healthy donor skin to cover the entire burn wound. In turn, lack of donor skin not only effect the individual’s healing process but frequently limits range of motion at the affected burn site. Furthermore, “take” rates or re-epithelialization of donor tissue, especially when treating the face, joints, hands, or feet, often is unsatisfactory and commonly results in aesthetic challenges. (Esteban-Vives et al., 2017).

Cell-spray autografting is an innovative alternative to traditional mesh autografting for deep partial thickness burn wounds. Cell spray autografting refers to a reconstructive process involving the patient’s own tissue which allows for a safer and faster healing process. This regenerative-based approach achieves rapid burn wound re-epithelialization by using a suspension of enzymatically isolated cells from the individual’s donor site, which are suspended in a saline solution that is transferred onto the wound (Esteban-Vives et al., 2016a). Evidence supports cell-spray autografting can achieve rapid re-epithelization, particularity for large and or deep burn wounds. This technique also requires a significantly smaller donor site compared to traditional mesh autografting proceedures (Esteban-Vives et al., 2017). Not only does the cell-spray autografting procedure aid in rapid, uncomplicated re-epithelialization but also results in more aesthetically and functionally satisfying outcomes, with fewer hospital days, and significant enlargement of the donor-to-graft-area. (Esteban-Vives et al., 2016a).

The simultaneous use of both spray-skin cell grafting does not however preclude the more traditional mesh autografting for full-thickness burn wounds. However, this more innovative approach could be useful to address challenges accompanying the treatment of deep-partial thicken burn wounds. (Esteban-Vives et al., 2017.). The treatment of burns can be costly both for the human experience as well as the health care system. For those reasons, it is important for nurses to better understand the outcomes of various burn wound healing techniques. This thesis will focus on the literature related to deep partial thickness burn wounds.

Purpose

The purpose of this thesis is to review the literature on the treatment of burn injuries, comparing two interventions, autologous skin cell spray-transplantation with mesh autografting. The findings can enhance nurses understanding regarding the treatment of burn wounds.

Problem Statement

What are the outcomes of burn injuries that are treated with autologous skin cell spray-transplantation compared to mesh autografting.

Literature review

The skin is the body's largest organ covering about 20 square feet of surface area in the average adult. The skin is a waterproof, almost indestructible, organ that protects the body from the external environment. This sensory organ prevents loss of water and electrolytes, regulates temperature, repairs wounds, produces vitamin D and plays a vital role in absorption and excretion. This multifunctional, highly adaptable organ consists of two layers, the epidermis and the dermis. Beneath these two layers is a subcutaneous layer of adipose tissue (Jarvis, 2016).

The epidermis is the superficial waterproof, protective barrier of the skin, composed of tightly bound stratified squamous epithelia. This superficial skin layer contains no blood vessels; cells are nourished via the diffusion of oxygen from surrounding air. Although, epidermis skin is quite thin but rugged, and further subdivided into seven sublayers called *strata*. The deepest layer of the epidermis is called the stratum germinativum, or stratum basale. Here, cells are constantly dividing through mitosis. As cells mature and migrate up the strata, they differentiate and become filled with a fibrous, structural protein called *keratin.* Melanocytes are also dispersed throughout this layer of the skin, producing a pigment called melanin which gives color to the skin. Eventually, the top-most skin cells die associated with the lack of a blood supply; flattening to form the stratum corneum, the outermost layer of the epidermis. Subsequently, the top cells slough off or desquamate through a process called keratinization. The epidermis is constantly shedding and replacing lost cells, completely regenerating itself every four weeks (Jarvis, 2016).

The dermis, lies beneath the epidermis and is the innermost supportive layer of the skin. The dermis is tightly connected to the epidermis by a supporting protein membrane called *collagen* which helps to resist skin tears. The dermis is also made up of elastic tissue that gives skin the unique ability to stretch. Nerves, sensory receptors, blood vessels, and lymphatics exist throughout the dermis. Hair follicles, sebaceous glands, and apocrine glands are embedded throughout the epidermis and dermis (Jarvis, 2016).

The subcutaneous tissue, hypodermis, lies beneath the dermis and is not considered a part of the skin. The hypodermis consists of loose connective tissue, adipose tissue and elastin. Elastin, an elastic protein, allows the body to resume its shape after stretching. This layer of skin is responsible for storing fat for energy; regulating body temperature; serving as a “shock absorber” and protective cushioning for underlying structures; and increasing skin mobility over deeper body structures. The subcutaneous tissue has embedded blood vessels and nerves, and, attaches the skin to underlying bones and muscles (Jarvis, 2016).

Immediately after the skin sustains injury, a survival mechanism known as wound healing commences. This physiological cascade of wound healing is a sequential and well-coordinated process, which, if uninterrupted, results in tissue repair. However, this process can be interrupted by both intrinsic and extrinsic factors. An individual must be nutritionally, hemodynamically and biochemically stable in order for healing to occur (Beldon, 2010). When treating severe injuries, such as burn wounds, all factors and or stressors having the potential to affect the wound healing process must be considered in order to provide an appropriate treatment plan that is tailored to each individual’s injury (Rowan et al., 2015).

The first step in wound healing is hemostasis occurs within seconds after injury. Initially the skin’s vasculature constricts to reduce blood loss. As blood rushes into the wound area, platelets activate numerous pro-inflammatory mediators which leads to clot formation.

Subsequently, the clot seals disrupted blood vessels, preventing further blood loss (Beldon, 2010). This is followed with an inflammatory response which involves both vascular and cellular responses. The blood vessels dilate, and hydrostatic pressure pushes fluid to the extravascular spaces; then, chemotactic factors attract neutrophils and monocytes to the area. Later as the neutrophils decline, macrophages arrive. These cellular changes aid in phagocytosis and the cleaning of the wound (Beldon, 2010).

The proliferative phase is when new tissue begins to form. Neovascularization or angiogenesis occurs, which is the process where vascular endothelial cells form new blood vessels in order to restore oxygen and nutrients to the area. Granulation tissue formation begins, and a new extracellular matrix is formed. Concurrently, re-epithelialization of the epidermis occurs. Myofibroblasts along the edges of the wound aid in wound contraction (Beldon, 2010). Finally, maturation, or the remolding phase, occurs. The final stage of wound healing involves realigning the collagen along tension lines and removal of cells which are no longer needed via a process called apoptosis, or programmed cell death. This slow healing process increases the tensile strength of the wound; however, scar tissue rarely is more than 80% of its uninjured strength (Beldon, P. 2010).

Severe burn injuries elicit specific changes both locally and systemically not encountered in other types of injuries. Such skin injuries require unique care for optimal healing. While skin is a highly adaptable organ and generally heals without complication, severe damage, such as burns, can result in dramatic changes in physiologic body functions; more specifically, life-threatening hypovolemic shock, decreased cardiovascular function, increased evaporative water loss, cellular changes and immunologic disruptions (Heather & McCance, 2017).

Burn wounds can be caused by thermal and non-thermal sources including friction, chemical, electrical, or radioactive sources. Friction burns are abrasions associated with the skin rubbing against another surface. Thermal burns are caused by heat sources that raise the temperature of the skin, damaging tissues leading to tissue charring and cell death. Chemical burns occur when a strong acidic or alkaline substance is in contact with skin leading to tissue damage. Electrical burns occur from electrical currents and radiation exposure such as occurs with prolonged ultraviolet rays of the sun as well as other radiation sources. Regardless of cause, all burns are classified based on the extent and depth of damage to the skin organ. The extent of a burn injury is determined by calculating the total affected body surface area (TBSA) and the depth of the injury on the skin based on four categories, and expressed as a degree of injury (Heather & McCance, 2017).

Estimating the extent of a burn injury is the first step in assessing the severity of a burn and is described as the percent of TBSA that is affected. The percent of burn injure can be calculated using three different methods. The Rule of Nines is a rapid method for estimating the extent of body surface burned. This technique divides the surface area of the body into areas of 9% or multiples of 9%. However, the Rule of Nines is not the most accurate in calculating the TBSA in patients under 15 years of age. A more accurate diagnostic approach to assess burn injury utilizes the Lund and Browder Chart. This method subdivides the body area and assigns a proportionate percentage of body surface area based on an individual's age. The TBSA can also be estimated by using the affected person's hand size; that is, assuming the hand's palmer surface equates to about 1% of the body (Johnson, & Richard, 2003). Burns exceeding 20% of TBSA are classified as a major injury, and associated with massive systemic physiologic consequences within a few minutes following the initial injury.

The second step in assessing the severity of a burn is determining the depth of the skin injury. First-degree (superficial) burns affect only the epidermis and present as a red, painful, and dry injury with no blistering. These types of burns typically require minimal if any treatment;

healing within 3 to 5 days without scarring. Second-degree (partial thickness) burns involve the epidermis and a portion of the dermis. The burn site generally appears red, swollen and blistered within a few minutes after injury. With 2nd degree burns tactile pain sensors remain intact throughout the healing process, resulting in extreme pain. These types of wounds heal within 3 to 4 weeks if the individual receives adequate nutrition and if no other complications arise. However, a burn that is deep, takes more time to heal. Often, deeper burns result in severe scarring, and sometimes reopens, which may require skin grafting from a donor site. Third-degree burns, or full-thickness burns, destroy the epidermis. Upon assessment, with this type of burn injury, the dermis has a dry, leathery appearance; and, typically have less pain or even may be painless since nerve endings have been destroyed. A third-degree burn usually requires skin grafting in order to heal. When bones, muscles, or tendons are also burned, this is referred to as a fourth-degree burn (John Hopkins Medicine, 2018).

The plan of care for burn wounds cannot be developed until severity of the burn is determined, specifically the extent and depth of the injury. However, the assessment process can be difficult since estimation of extent and depth is a subjective process, resulting in a wide margin of discrepancy. Some burns, particularly partial-thickness wounds, are problematic to accurately diagnose associated with the initial confusing presentation of clinical characteristics. Surprisingly, surgeons incorrectly diagnosis burn depth approximately one-third of the time (Johnson, & Richard, 2003). On the one hand, a more conservative approach of routine local wound care often is implemented by surgeons to avoid scar formation. On the other hand, misdiagnosing a burn wound that should have a surgical intervention ultimately can delay wound closure. Which, in turn, may result in a longer hospital stay, infections, poor aesthetic and functional outcomes including hypertrophic scarring, contracture, reduced range of motion, and unsatisfactory psychosocial adjustment. For these reasons, an accurate early diagnosis is essential with appropriate interventions which may involve skin grafting for optimal wound recovery, functionality, and aesthetic outcome (Esteban-Vives et al., 2017).

For decades, early excision of burnt eschar (damaged tissue) and grafting have been the standard of care for extensive burn injuries. The excision of eschar within the first two days of injury not only increases graft take rates but decreased blood loss, infections, length of hospital stays, and mortality rates. Excising and covering the wound as early as possible remains a critical aspect in preventing infections in a burn wound (Rowan et al., 2015). Although there are numerous biologically and synthetically derived skin substitutions available to cover burn injuries, for the purpose of this literature review only autologous split-thickness skin grafts and autologous cell spray transplantation will be considered.

A skin graft is often utilized when a wound is too large to heal on its own or cannot be directly closed. A skin graft may also be used to prevent infection, hasten healing, improve physical functioning, or for improved cosmetic outcomes (Tasmanian Health Service, 2013). Autologous skin grafting involves taking a portion of uninjured skin from the individual and securing it to the injury site (Tasmanian Health Service, 2013). More specifically, autologous split-thickness skin grafts (STSG) involve harvesting a portion of donor skin from the epidermis and a small portion of the dermis, which is then meshed into a “skin lattice” to facilitate optimal expansion of the donor skin. Mesh incisions also provide a route of drainage and increase the flexibility of the graft, so it can conform to uneven wound beds. Such grafting techniques provide sufficient coverage of a burned area with minimal risk of rejection and are less damaging to the donor site compared to traditional grafting procedures (Gerlach et al., 2011).

Currently, the STSG is the most widely used technique for the treatment of extensive burns. However, this “gold standard” intervention has some inherent challenges that impact burn wound healing. For example, the retrieval of the donor skin can be a painful process and become a chronic wound (Rowan et al., 2015). Although this technique attempts to effectively utilize the donor skin via a skin lattice, the technique itself not only limits the range of motion for the individual but produces a “fish net” aesthetic appearance upon healing. Especially when larger body areas are burned, available healthy donor skin may be limited; therefore, insufficient to cover the entire wound if a STSG is used. Furthermore, because the deep dermal structures such as sweat glands and hair follicles are not involved, the STSGs may be aesthetically and functionally abnormal. Aesthetic outcomes and ‘take rates’ commonly are unsatisfactory when treating the face, joints, hands or feet, especially when over-grafting has occurred (Gerlach et al., 2011). Regardless of the graft location and size, with STSG multiple reconstructive surgeries may be required to address complications such as scarring and contractures. One study focusing on the patient experience of living with split thickness skin grafts found participants reported problematic symptoms and unsatisfactory perceptions associated with their grafts. Yet, all the participants said they would be willing to participate in future clinical trials to improve their outcomes (Burnett et al., 2014).

The main goal for burn wound care management is to provide a treatment that enhances early wound closure by re-epithelialization and avoids delayed re-epithelialization with its associated complications. However, this process is complicated due to the confusing clinical presentation of most burn wounds during early evaluation. Often times a conservative approach leads to delay wound healing while an invasive approach could lead to a donor area burden and or overtreatment (Johnson, & Richard, 2003). Cell-spray autografting technologies are an innovative alternative treatment option for treating partial- and deep partial-thickness burn wounds.

The cell-spray autografting technique is a revolutionary epidermis- and dermis-derived stem cell-based therapy that uses a suspension of isolated cells, from an individual’s donor site skin tissue; which are then mixed into a solution to be sprayed onto the donor’s burn area. Cell-spray autografting can be utilized independently to treat partial-thickness burns, or in combination with skin grafting during early or delayed wound healing. The procedure itself can be done either in an inpatient or outpatient setting and has several advantages when compare to traditional mesh autografting (Esteban-Vives et al., 2016).

The skin cell isolation process for cell-spray grafting begins with harvesting tissue from the individual's donor site skin. This tissue is divided into multiple sections and the epidermis and dermis are separated. Specific tissue enzymatic digestions are used to select appropriate cells, such as epidermal stem cells, transit amplifying cells, and dermal derived cells. After the isolation process, the cells are mixed in a solution and prepared for spray deposition on the burn wound sits. Since this process is performed immediately after skin harvest, spaying to the burn site takes place during the same operative session thereby not only reducing the patient's time under anesthesia but health care costs as well (Esteban-Vives et al., 2016).

Cell-spray grafting has been found to aid in rapid wound re-epithelization by using a relatively small number of cells. This procedure also improves long term functionality with a decreased risk of delayed wound healing and other complications. Cell-spray grafting also improves ratio of donor site to covering the wound site; in other words, a little goes a long way. A gentle, homogenous distribution is achieved by (spraying) autografting over affected contoured surfaces such as the face, hands, feet and joints and avoids over grafting. This approach compared to traditional mesh autografting, results in shorter hospital stays, reduced risk for infection, and improved aesthetic and functional outcomes specifically, hypertrophic scarring, contractures, range of motion, and psychosocial adjustment (Esteban-Vives et al., 2016).

Methodology

This integrative literature review analyzing and synthesizing of peer reviewed research articles published in professional journals. Databases searched included EZproxy, National Center for Injury Prevention and Control, Google Scholar, PubMED, the Cumulative Index to Nursing and Allied Health Literature (CINAHL Plus), Medline, ScienceDirect, Elton B. Stephens Co. (EBSCO), BioMed, and Directory of Open Access Journals. Search terms included cell-spray grafting, skin cell spray transplantation, and autologous skin cell spray grafts. Inclusion criteria included articles written in the English language and published from 2010 to 2018. International studies will be included in this review process. Exclusion criteria will include articles published in a language other than English and outside of the specified publication date.

In the initial search using key terms yielded 132 results. However, after applying the inclusion and exclusion criteria the search was narrowed down to 6 peer reviewed research-based articles. An additional 8 studies were acquired from the reference section of the previously gathered articles. A total of 14 studies were reviewed for this thesis; of which 7 studies focused on specific interventions for enhancing deep partial thickness burn wounds. The article selection process for this review can be found in in the appendices (See Appendices Figure 1: Consort Chart; Table 1; Table of Evidence)

Findings & Discussion

Burn wounds treated with split thickness skin grafts present with challenging and unsatisfying outcomes. Burnett et al. (2014) utilized an interpretive description qualitative methodology (N=12) to investigate the experiences of patients living with traditional split thickness skin grafts. They collected data by recording and transcribing a two-part single patient interview with participants who had been treated with a traditional split thickness skin graft due to an acute illness such as burns, polytrauma or necrotizing fasciitis. The interviews focused on questions that were relevant to living with a split thickness skin graft; and, attributes the respondents would like to change associated with the resulting scar. The researcher's findings showed all the participants had at least one physical symptom they found bothersome including fragility, mechanical abnormalities, itching, altered sensation, pain, satisfaction with appearance, and poor coping strategies. Furthermore, all participants reported the abnormalities associated with their spilt- thickness skin grafts were significant enough so they would be willing to participate in future clinical trials investigating alternative therapies.

Cell-spray autographing biotechnology is an alternative burn would treatment that addresses many of the complications associated with traditional mesh autographing. (Esteban-Vives et al., 2016a) conducted a retrospective chart analysis (N=6) focusing on six individuals with second-degree burns that were treated with autologous cell-spray technology. Each burn had a different etiology and total body surface area affected. The healing process was measured by clinical observation including photographic documentation. Consistently mostly favorable outcomes were noted focusing on rapid and complete re-epithelization, hyper- and hypopigmentation, range of motion, hypertrophic scarring, physical functioning, and esthetic outcomes. However, in some cases with more extensive burn injuries, the investigators found impaired range of motion, hypertrophic scarring and hypo- and hyperpigmentation remained a concern.

Esteban-Vives et al. (2016b) performed an experimental retrospective analysis (N=21) to develop a systematic rational approach that standardized clinical study protocols for a reproducible cell application process that minimized patient' donor site area burden. Data were collected via clinical observation including case reports and photographic documentation. The researches adapted a clinical protocol routine that included a standardized approach to calculate donor site skin tissue. Satisfying results were occurred in all 21 subjects, including an increased ratio of skin donor site to treatment surface area. The researchers proposed their procedure could be redefined for harvesting processes and spray technology; thus, be applied to any clinical cell-spray grafting technique independent of available technology.

Esteban-Vives et al. (2017) conducted a more recent retrospective analysis (N=44) focusing on problems and solutions during clinical implementation of cell spray autografting. Subjects wounds were deep partial-thickness burn wounds, of various etiologies and affected total body surface areas. Data included comprehensive documentation of the treatment and outcomes. In the data analysis, the researchers noted the autologous cell-spray grafting consistently had the advantage of being immediately available, requiring minimal cell manipulation along with an ability to use the patient's body as a bioreactor. This, in turn, resulted in minimal loss of progenitor and epidermal stem cells. Initially obtaining donor skin under local anesthesia and sterile conditions prior to patients' entering the operating room, minimized length of time under general anesthesia; ultimately, reducing post-operative complications and health care cost. The most satisfying results occurred when donor site skin tissue was harvested with an electrical dermatome with a 0.02 cm guard setting. However, burn wound size, tobacco use, and age were factors that were correlated with hospital length of stay.

Cell spray autographing has been shown to be more convenient and beneficial when treating mores serious burns compared with traditional mesh autographing. Gerlach et al. (2011) focused on a single burn case (N=1) to study the application and outcomes of autologous skin cell spray transplantation in ambulant treatment room setting. The patient presented at the ambulant center five days after suffering a deep partial-thickness burn. He had been conservatively self-treating the injury with various lotions and ointments. The investigators treated the burn using cell autographing techniques; progress was monitored and data were collected by clinical observations with photographs to document baseline and subsequent physical changes. The researchers noted that cell spray technology effectively expanded the ratio of skin donor site to treatment surface area; and, re-epithelialization without the use of dressings. Using the Vancouver Scar Scale the burn wound was evaluated healing at 3 months, 6 months and 12 months to assess aesthetic and functional quality of re-epithelialization. Other than discoloration that had almost disappeared by 12 months, no infections, inflammation or complications were observe.

Johnson and Richard (2003) conducted another case report (N=1) evaluating the use of Vivostat®, a co-delivery system, in conjunction with ReCell®, an autologous keratinocyte suspension to treat a 29- year old female with burns covering 27% total body surface area. Data were collected via clinical observation including photographic documentation. Previously the woman received a skin graft on the burn site but experienced significant graft loss. The patient received four additional grafts prior to the application of a cell-spray solution. Subsequent to receiving the cell-spray solution no further surgical skin grafts were required. The findings supported that ReCell®, delivered via Vivostat®, has the potential to effectively improve burn wound healing by anchoring of keratinocytes to challenging burn wounds.

Although the findings related to cell spray autographing have shown significant advancements in the treatment of burn wounds, uniform guidelines and standards of practice are less than optimal. Allouni, Papini, and Lewis (2013) conducted a qualitative study (N=25) focusing on current indications for autograft use, culture techniques, cell spray techniques and other intraoperative and postoperative considerations. Data were collected via an online survey comprising of 23 items. They found cell spray autographing to be a common practice, however there was no standard treatment protocol. Of respondents, 78% reported having no formal guidelines regarding patient selection criteria or when the cell spray should be applied to a burn. Half of the respondents managed burns using the same approach as with mare traditional autografting and the remaining half reported having no use restrictions. Fewer than 45% of respondents had or used guidelines for follow up care, evaluation criteria, or the type of dressing to be used throughout the healing process. The majority of respondents admitted they do not use a formal consent process prior to treating a burn. The indications for use of cell spray autographing o varied among respondents. However, there was consensus that sterile recipient site was paramount for optimal results. While a majority of respondents concurred the importance of diluting donor cells before spraying, there was no agreement on the spray cell-dilution ratio.

Consistent Findings

Consistent findings in the literature review included Burnett et al. (2014); Esteban-Vives et al. (2016a); Gerlach et al. (2011); Johnson and Richard (2003) consistently reported unsatisfying burn wound healing outcomes associated with traditional treatment approaches including mesh autographing, creams and ointments. Whereas Esteban-Vives et al. (2016a); Esteban-Vives et al. (2016b); Esteban-Vives et al. (2017); Gerlach et al. (2011); Johnson and Richard (2003) had favorable outcomes with autologous cell skin spray technology including rapid and complete would re-epithelization, minimal hyper- and hypopigmentation, improved range of motion, less hypertrophic and aesthetic scarring. There was an increased ratio of skin donor site to treatment surface with limited or no infections. Cell spray autographing technology also has an ability to treat challenging burns especially difficult to graft areas such as parts of the face, joints, hands, back and feet. Other than discoloration that had almost disappeared by 12 months, no infections, inflammation or complications were observed.

Inconsistent Findings

Only one inconsistent finding was noted in the literature review. Specifically, Esteban-Vives et al. (2016a) found minimal hypopigmentation and hyperpigmentation in one patient treated with autologous cell spray technology and hypertrophic scarring in another. However, when comparing the two methods, traditional mesh autographing and cell spray autographing, cell spray autographing results in more satisfying results and less complications.

Gaps in the literature

Cell-spray autographing is a rather new biotechnology. Thus, standard protocols were not found to optimize the cell isolation process, calculating the expansion ratio, method of delivery and associated wound care management for optimal healing outcomes. Use of cell spray autographing for injuries other than deep partial thickness burn wounds was not addressed such as with decubiti, ulcerations and other complex wounds. Demographic factors and burn healing processes and outcomes using cell-spray autographing based on clinical evidence were not noted in the literature that was reviewed, including lifestyle habits, age, and co-morbidities.

Implications for Nursing

Education

Staff education, training, and quality management are critical factors for successful treatment of burn wounds in general and cell spray autographing in particular. Continuing education is essential that focuses on quantitative objective assessment of burn injuries along with appropriate mathematical calculations. Education is needed on the importance of early on initiating therapeutic rehabilitation interventions that can improve healing outcomes, enhance quality of life and reduce health care costs.

Practice

Evidence-based guidelines and procedures are needed to ensure consistent practice patterns when using cell spray technologies to treat burn wounds. Standards of professional practice should address indications of use, harvesting donor graft techniques, cell preparation processes, and implementation delivery guidelines, including initial application, subsequent applications and evaluation criteria. Guidelines also are need to guide the practitioner about the inclusion of other graphing methods along with use and application of adjunctive therapies such as ointments, lotions for wound care management. A clinical pathway to treat and manage burn wounds that includes the use of cell spray technologies could prevent inconsistences of patient care and optimize clinical outcomes.

Policy

A health care institution should establishing protocols to effectively standardize cell spray autographing practice in the treatment of burns and other types of wounds. Guidelines must be established regarding patient selection, evaluation criteria, timing and indications of use on various types of wounds, consent protocols, follow-up and wound care management. Protocols for mathematical equations to calculate needed donor site skin tissue, proper cell-dilution ratio for the spray solution for therapeutic treatment options for burn wounds.

Research

Further studies are needed for evidence supporting consistent protocols and guidelines when using cell spray autografting that optimize outcomes and cost effectiveness. Studies also are needed to measure outcomes of cell spray autographing when combined with other surgical and adjunctive therapies. Studies are needed including more diverse populations especially race and ethnicity along with “skin harvesting techniques” that reduce the time a patient is under general anesthesia. Finally, studies are needed for the most effective nursing interventions to manage the physicological and emotional needs of patients with burn wounds of varying severity and extent.

Limitations

This review was limited to peer-reviewed research articles written in English and published between the years of 2010 to 2018. Since, cell spray technology is a relatively new approach there were limited publications; most of which consisted of a very small sample size and two studies consisted of a case study with one subject. Most of the studies also focused on the initial uses of a particular biopharmaceutical product; thus, long term use and outcomes could not be determined in this review.

Summary

In conclusion, while significant advancements in the treatment of burns over the past several decades, treating such wounds, especially extensive burns, remains a clinical challenge. Cell spray autographing has the potential to enhance burn wound treatment with improved a patient's long term outcomes, quality of life and also reduce health care costs. Although further studies are needed to standardize care, cell spray autographing could make a significant impact for nurses who care for patients with burns and other kinds of wounds.

Appendices

Figure 1: Consort Chart

Searched databases:
EZproxy, National Center for Injury Prevention and Control, Google Scholar, PubMED, the Cumulative Index to Nursing and Allied Health Literature (CINAHL Plus), Medline, ScienceDirect, Elton B. Stephens Co. (EBSCO), BioMed, and Directory of Open Access Journals

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Using Key terms:
Cell-spray grafting, skin cell spray transplantation, and autologous skin cell spray grafts n=132.

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Inclusion criteria:
- Peer reviewed research-based articles published in professional journals
- Articles written in the English language
- Published from 2010 to 2018
- International studies will be included in this review process.

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Exclusion:
- Articles published in a language other than English
- Articles outside of the specified publication date.

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Studies that did not fit inclusion criteria or were unattainable n=126.

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After further review of studies n=6.

↓

Additional studies acquired from references n=8.

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Total studies to be reviewed n=14.

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After further review, studies pertaining to specific interventions enhancing deep partial thickness burn wounds n=7.

Table II: Table of Evidence

Last Name of First Author/ Location/ Year	**Study Design**	**Sample Size/Data Collection Method**	**Diagnosis of Wound Severity**	**Participant(s)/Study Characteristic**	**Skin Cell Isolation/Grafting Process Used**	**Key Findings/Conclusions Using Autologous Skin-Cell Spray Transplantation**
▪ Allouni ▪ Birmingham, England ▪ 2013	▪ Qualitative Study	▪ N= 25 ▪ Online survey comprising 23 questions	▪ No burn wounds were evaluated to conduct this research study.	▪ Burn consultants in the UK, who are member of the British Burn Association ▪ The questionnaire evaluated current indications for cultured epithelial autograft use, culture techniques, cell spray techniques as well as other intra-operative and postoperative considerations.	▪ No skin cells were isolated to conduct this research study. ▪ No skin grafts were used to conduct this study.	▪ Seventy eight percent of respondents reported having informal guidelines regarding patient selection criteria and the timing chosen to spray cells. ▪ Less than 45% had guideline with regards to follow up, evaluation criteria, and type of dressing used. ▪ Majority of respondents reported that they have no formal consent process prior to harvesting skin for cell culture and spraying. ▪ There were variations in the indications for cell culture and a broad consensus that sterility of the recipient bed was paramount. ▪ Majority of respondents advocated diluting the cells when preparing the cultured cells for spraying; however, there was no agreement on the optimal dilution ratio. ▪ Half of respondents managed the areas in the same way as traditionally autografted areas, with immobilization of affected area. The remaining respondents did not place any restrictions. ▪ Setting protocols to standardize a practice that is agreed among burn consultants throughout the UK, will ensure optimum results and cost effectiveness.

▪ Burnett ▪ Calgary, Canada ▪ 2014	▪ Interpretive description qualitative methodology	▪ N= 12 ▪ Two-part single patient interview that was recorded and transcribed	▪ All participants were previously treated with a split thickness skin graft as a result of acute illness such as burns, polytrauma or necrotizing fasciitis	▪ Interviews were geared towards answering the complex and contextually embedded questions that are relevant to living with a spilt thickness skin graft and furthermore, what attribute patients would most like to change about the resulting scars. **Exclusion criteria:** ▪ Primary skin disorders that may affect skin graft such as pemphigus, etc. ▪ Major psychiatric or other communication disorders that would preclude the patient from participating in recorded interview **Inclusion criteria:** ▪ 18-65 years old ▪ English speaking ▪ Treated with a split thickness skin graft as a result of acute	▪ All participants were previously treated with a split thickness skin graft as a result of acute illness such as burns, polytrauma or necrotizing fasciitis	▪ All of the participants in this study described at least one physical symptom they found bothersome in their split thickness skin grafts including fragility, mechanical abnormalities, itching, and an altered sensation. ▪ Pain, satisfaction with appearance, and coping strategies were also common areas of concern among the participants. ▪ All participants reported that the abnormalities related to their split thickness skin grafts were significant enough that they would be willing to participate in a future clinical trial investigating new cell-based therapies.

				illness such as burns, polytrauma or necrotizing fasciitis		
▪ Esteban-Vives, Choi et al. ▪ Pennsylvania, United states ▪ 2016	▪ Retrospective analysis	▪ N= 6 patients with different burn etiology ▪ Clinical observation including photographic documentation.	1. 43-year-old male obtaining a deep partial thickness injury comprising 13% total body surface area on his upper right extremity and right flank, and a superficial burn on his right face and neck caused by a paint can explosion 2. 37-year-old male obtaining deep partial-thickness injuries compromising 12.5% total body surface area of his upper extremities and hands caused by potassium nitrate explosion 3. 35-year-old male obtaining a deep partial thickness burn injury comprising 36.5% total body surface area of his head,	**Exclusion criteria:** ▪ Age < 18 years ▪ Pre-existing infection ▪ Hypersensitivity to trypsin or other enzymatic wound treatments ▪ Risks associated with anesthesia **Inclusion criteria:** ▪ Deep partial-thickness burn wound	1. Skin biopsies obtained 2. Chemical and mechanical separation of the dermis and epidermis followed by cell washing and transfer to sterile disposable syringes for cell deposition by spraying 3. Prior to cell-spray grafting, wounds were debrided or excised depending on their depth	1. Patient one: Small re-epithelialization was observed on POD#4. The wound became dry and the patient was discharged on POD#6. Complete epithelialization and some hypopigmentation were noted on POD#14. Full range of motion with some limitations in wrist motion were noted on POD#13. At the five-month follow-up, minimal hyperpigmentation on the right side of the face and very slight hypopigmentation on the right shoulder and upper extremity were noted. There was no evidence of hypertrophic scarring and the only functional impairment was due to a wrist injury. 2. POD#3 the dressings were changed, and it was noted that the wounds were still open. On POD#5, all wound areas were mostly dry. On POD7# the patient underwent additional split thickness skin grafting. The patient was discharged on POD#9. POD#14, small open areas on left forearm and difficulty with full flexion of right fingers were noted.

			chest, abdomen, upper extremities, and back caused by an electrical burn. 4. 18-year-old male with a history of poor wound healing in the right foot with split-thickness skin grafting and now presenting 3 months after the injury with 14% total body surface area affected in his right foot from a gasoline flame burn. 5. 43-year-old male presenting partial-thickness burns comprising 10% total body surface area on his left upper extremity, shoulder and back cause by a hot water scalding. 6. 43-year-old male obtaining a partial-thickness burn comprising 15% total body surface area on his right			POD#25 full range of motion was observed. POD#55, minimal hypertrophic scarring was noted. POD#607 the areas of autografts were noted to be almost indiscernible and the patient maintained full range of motion without restrictions. 3. Patient three: On POD#4 re-epithelialization of the chest and the arms were observed with few open areas. POD#5 the arms were noted as “healed”, but the hands were still open and were treated accordingly. On POD#6 the right hand and foot were still open and, again, treated accordingly. POD#13 eschar was noted on the right arm and treated, and the left foot was treated with wet-to-dry dressing changed. On POD#20 all areas treated with cell-spray grafting were noted as completely healed and re-epithelialized. There was no evidence of hypertrophic scars or wound contracture, and the patient had a functional range of motion in all extremities. 4. Patient four: Wound areas started showing signs of re-epithelialization on POD#3. Majority of the wounds were healed by POD#6. Wounds were completely healed by POD#12 and there was no evidence of

			arm, hand, and anterior trunk.			hypertrophic scarring or contractures, and the patient demonstrated a full range of motion in all extremities. 5. Patient five: The dressings were changed on POD#3, and the areas of cell grafting were noted to have good re-epithelialization with only a small amount of open areas. POD#6 100% re-epithelialization was noted, and the patient was discharged. POD#46 the patient was noted to have full range of motion in extremities. On POD#136 a very small area of hypertrophic scarring was noted. However, the area was very small and was not causing any functional deficits. The patient was noted to have an excellent aesthetic outcome. 6. Patient six: POD#3 the patient's right arm and hand were noted to be nearly healed, but other spots remained open. POD#5 re-epithelialization was noted in all areas except for small areas at the central chest and abdomen. The patient was also noted to have full range of motion. POD#7 all areas were noted to be healed and re-epithelialized and the patient was discharged. POD#14 hyperpigmentation was noted, no hypertrophic scarring was noted. POD#66 the patient's

						skin pigmentation appeared to be returning to normal without hypertrophic scarring or contractures.
▪ Esteban-Vives ▪ Pennsylvania, Unitied States ▪ 2017	▪ Retrospective analysis	▪ N= 44 ▪ Case report data collection with comprehensive documentation of the treatments, outcome and recovery process for subsequent data analysis.	▪ All wounds were deep partial-thickness burns with a variety of burn wound etiologies and a wide range of total body surface area.	▪ Patient selection was based on the physician team's best judgment but was limited to deep partial-thickness burn wounds.	▪ Skin biopsies obtained ▪ Chemical and mechanical separation of the dermis and epidermis followed by cell washing and transfer to sterile disposable syringes for cell deposition by spraying ▪ Suspended cells immediately spray-transplanted onto burn site	▪ All technical issues were identified during the clinical implementation of the procedure to enable burn surgeons to learn from the researcher's experiences. ▪ Autologous cell-spray grafting has the advantages of being immediately available, requiring minimal cell manipulation, using the patient's body as a "bioreactor" for cell expansion, and limiting the loss of progenitor cells and epidermal stem cells. ▪ Obtaining the donor skin under local anesthesia and sterile conditions in the burn unit procedure suite prior to patients' entering the OR and undergoing general anesthesia proved to minimize time spent in the operating room under general anesthesia and reduced medical costs ▪ The best results were obtained when an electrical dermatome with a 0.02cm guard setting was used to harvest the donor site skin tissue ▪ Burn wound size, tobacco use, and age all showed correlations with an increased hospital stay

▪ Esteban-Vives, Young et al. ▪ Pennsylvania, United States ▪ 2016	▪ Experimental retrospective analysis	▪ N= 21 ▪ Clinical observation including case reports and photographic documentation .	▪ Before starting the treatment, the damaged area was defined by estimating the body surface area of the patient, the percentage of wounded skin, and they depth of the injury.	▪ The calculations presented in this study were intended to provide information for developing a rational approach and standardizing future clinical study protocols towards reproducible cell applications while reducing the patient's donor site area burden.	▪ The cell isolation protocol starts with the donor site skin tissue harvesting, which is calculated directly related to the burned area, and the seeded cell density required to cover the wounded area. ▪ The epidermis and dermis were both digested, sieved, washed, and centrifuged to be mixed into a solution for spraying. ▪ The saline solution in which the cells are suspended is calculated to distribute the cells homogeneously over the wound surface and is proportional to the burned area.	▪ The researchers adapted the clinical protocol routine, to include the equation to calculate the necessary donor site skin tissue and employed the demonstrated method in up to 21 patient treatments with satisfying results. ▪ The researchers also found that the proposed equations and constants can be redefined for any particular cell procurement and deposition technology so that they apply for any clinical skin cell-spray grafting independent of spray technology platforms. ▪ The mathematical calculations presented in this study may be useful in defining clinical study protocols while investing innovative therapeutic options for large partial- and deep partial-thickness skin conditions requiring re-epithelization.
▪ Johnstone ▪ New South Wales, Australia ▪ 2016	▪ Case Report	▪ N=1 ▪ Clinical observation including photographic documentation	▪ 27% total body surface area full thickness burns to right side of torso, right side of abdomen, right	▪ 29-year-old female presenting with 27% total body surface area	▪ ReCell®, an autologous keratinocyte suspension preparatory kit, was applied with fibrin	▪ The patient underwent no further surgeries after the application. ▪ ReCell® shows the potential to improve healing in acute burns and is believed to assist with the anchoring of keratinocytes to the

			forearm, right upper arm, the back, both shoulders and the inner aspects of both legs. ▪ There was also a suspected inhalation injury.	flame burns to her back. ▪ Multiple previous hospital admissions related to excess alcohol intake associated with liver diseases and portal hypertension. Patient also had a significant history of depression and deliberate self-harm. ▪ Patient previously grafted with the sandwich autograft/allograf t technique on day four after injury. ▪ Patient experienced significant graft loss due to the challenging location of the burn. ▪ The patient underwent four more grafting session before a cell-spray solution was	using the co-delivery Vivostat® system, an autologous platelet rich fibrin preparation device.	wound surface and thus aiding in the treatment of challenging areas when delivered with Vivostat®.

				applied on day 12 after injury.		
▪ Gerlach ▪ Pennsylvania, United States ▪ 2011	▪ Case Report	▪ N= 1 Clinical observation including pictures at outpatient clinic	▪ Deep partial-thickness burns to the shoulder and arm with an inflammatory eschar. ▪ Superficial wounds on the face and neck. ▪ Total body surface area was 7%	▪ 43-year-old male patient presenting to the burn center 5 days after injury. ▪ Patient initially treated in an outside facility using a conservative approach including creams and ointments	1. Skin biopsies obtained 2. Chemical and mechanical separation of the dermis and epidermis followed by cell washing and transfer to sterile disposable syringes for cell deposition by spraying 3. Suspended cells immediately spray-transplanted onto burn site	▪ Expansion in the ratio of skin donor site to treatment surface area to approximately 1:20 ▪ The patient was noted to have complete re-epithelialization ▪ Wound dressings were not required ▪ No infections, inflammation or any adverse effects or complications were seen ▪ Aesthetic and functional quality of re-epithelialization at three-, six-, and twelve-month follow-up were considered excellent. ▪ Discoloration was observed but had almost disappeared at month twelve. ▪ Vancouver Scar Scale of 1 point after twelve months

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