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Putting a Spin on Traditional Skin

Artificial skin is quickly becoming a reliable treatment for burn injuries. My paper examines its benefits and the mechanisms behind its ability to heal burns.

INTRODUCTION:

Ooh, burn! According to the American Burn Association, there are nearly 500,000 burn injuries each year that require medical treatment. Burns can be caused by accidents with fire/flame, scalding, electricity, chemicals, or simply contact with a hot object. The 2016 National Burn Repository Report concluded that the most common burn cases were those of fire/flame, making up 41% of all burn injuries. Due to the widespread prevalence of burn injuries, it is necessary to have treatments that can effectively replace the damaged skin cells of the wound site. An optimal burn treatment does not produce a significant immunogenic response in the patient's body, restores vascularization in the dermis, and maintains functional ability of the skin.

General Overview of Skin and Burns

Damage to the skin can dramatically hinder everyday functions, because the skin acts as a barrier to protect the body's internal fluids from the external environment (Bennett, 2014). The skin consists of two main regions, the epidermis and the dermis. The epidermis consists of four or five layers, depending on the thickness of the skin. There are no blood vessels present in the epidermis; this is because 95% of the cells in the epidermis are keratinocytes that maintain the structure and barrier properties of the skin (Carneiro, 2011). The dermis supports the epidermis, providing nutrients through the dermal blood supply (Bennett, 2014). Consisting mostly of fibroblasts that create collagenous and elastic fibers, the dermis gives skin its elasticity and strength (Bennett, 2014).

Burns can be classified into four types, according to the severity of the wound: epidermal, superficial partial-thickness, deep partial-thickness, and full-thickness (Shevchenko et. al, 2010). Whereas epidermal and superficial partial-thickness burns require little to no medical attention, deep partial-thickness and full-thickness burns can lead to severe functional damage and scarring without the proper treatment (Shevchenko et. al, 2010). Deep partial-thickness and full-thickness burns often require skin grafts, because the significant damage to the dermal tissue disallows the body to epithelialize and properly heal (Shevchenko et. al, 2010).

While there are many studies examining the specifics of burn damage to the body, I will be focusing on the treatment of burns by replacing the damaged skin cells with artificial skin.

Current Usage of Skin Grafts

Currently, the most common treatment for severe burns is the skin graft. Skin grafting is the surgical process of transplanting skin, either with an autologous skin graft (from a different area of the subject's body) or an allograft (from another donor) (Shimizu & Kishi, 2012). Despite its commonality, skin grafting poses many limitations. With autologous skin grafts, the patient is limited by the amount of available tissue in the body; thus, for severe burns that affect multiple

areas of the body, autografts are not a viable option (Shimizu et. al, 2012). Allografts from other donors are a popular option due to their ability to vascularize, which is the process of producing blood vessels; however, the blood vessels present in allografts make the burn susceptible to disease transmission through blood contamination (Wang et. al, 2015). In addition, meshed skin grafts that are stretched for extensive burns form interstices, small spaces that cause a slow epithelialization and the formation of scar tissue (Burke et al., 1981). The build-up of scar tissue in the interstices can negatively hinder the cosmetic and functionality abilities of the burn patient.

The Future of Burn Treatments: Integra, an Artificial Skin

With the limitations of skin grafting in mind, artificial skin is gaining popularity as an excellent candidate for burn treatment. Artificial skin was first invented by John F. Burke and Dr. Ioannis V. Yannas in the 1970s (Burke et. al, 1981). Since then, scientists have constantly been remodeling the bi-layer of artificial skin to create the most effective treatment to mimic skin. A sufficient artificial skin bi-layer must consist of two main regions: a viscous and soft layer to simulate the hypodermis and dermis, and a hydrophilic, moisture-absorbing stiff outer layer to imitate the epidermis (Nachman et. al, 2016).

Throughout this paper, I will be focusing on Integra, one of the most popular artificial skin bi-layers currently used in the field of medicine (Lagus et. al, 2013). Integra is composed of type 1 bovine collagen, chondroitin 6-sulfate from shark cartilage, and a silicon layer (Lagus et. al, 2013). In addition, fibroblasts and various growth factors are often integrated within the bi-layer (Wilcke et. al, 2007). Growth factors incorporated in Integra include vascular endothelial growth factors (VEGF), basic fibroblast growth factors (bFGF), and transforming growth factor beta 3 (TFG- β3) (Wilcke et. al, 2007; Metcalfe et. al, 2007). The addition of these growth factors to the Integra matrix aids in wound-healing by stimulating the faster reconstruction of the neo-dermis (Wilcke et. al, 2007).

I will be examining three main areas where Integra shows promise as a developing treatment for burns. The first proposed advantage of Integra is its low immunogenic response in the body, with no reports of immune rejection. In addition, the absence of blood vessels in Integra eliminates the potentiality of the recipient receiving a blood-contaminated disease from a donor skin graft. The second main advantage of Integra is its ability to sufficiently vascularize the wound area. Vascularization is a crucial component of wound-healing in burn injuries, as it allows for the growth of a neo-dermis to replace the damaged cells. The third and final proposed advantage of Integra is its capability to reduce scarring in burn patients. Integra has been proven to dramatically improve the damaged skin's elasticity and cosmetic results, restoring functionality in the wound.

INTEGRA'S DECREASED DISEASE TRANSMISSION AND IMMUNOGENICITY

The first proposed benefit of Integra is its low risk of transmitted disease and low immunogenic response. The epidermal component of Integra prevents bacterial contamination in the wound-site, by acting as a protective barrier against bacterial microbes which could potentially infect the healing skin (Lagus et. al, 2013; Shevchenko et. al, 2010). Integra's synthetic scaffold does not contain any blood vessels, which eliminates the likelihood of disease transmission that often occurs through blood contamination. This demonstrates synthetic skin scaffolds' advantage over natural, donor skin grafts, which can pass infectious diseases through skin transplantation (Kamel et. al, 2013).

In a study conducted in 1989, Gottesdiener examined the risk of transmitting viruses such as human immunodeficiency virus (HIV) and herpes simplex through donor allografts. Gottesdiener concluded that "true donor infection" results from the spread of blood contamination from the infected allograft to the recipient of the skin graft (Gottesdiener, 1989). In another study, Wang et. al (2015) researched the transmission of hepatitis B virus (HBV) through skin allografts. In China, an increased demand for skin grafts led to a greater number of infected donors in skin banks, resulting in the spread of infectious diseases through blood contamination (Wang et. al, 2015). Wang et. al's study detected traces of HBV in host skin cells such as keratinocytes, stromal fibroblasts, and mucosal epithelial cells (Wang et. al, 2015). Thus, in terms of disease infection, Integra's lack of blood vessels makes it superior to donor allografts, which risk spreading blood-contaminated diseases.

Integra's Infection Risk

Although Integra is advantageous for its low risk of disease transmission, its absence of blood vessels makes it more susceptible to infection (Lagus et. al, 2013). A study by L. Bargues et. al (2009) examined the infection risk of Integra, which was noted as one of Integra's main disadvantages. To test Integra's infection possibility, the surgical procedure of its application was deliberately altered; the alteration was a delayed application of the bi-layer to the wound site (Bargues et. al, 2009). Out of the 21 patients in the study, 42% showed signs of infection in response to the the delayed application (Bargues et. al, 2009). However, the studies by L. Bargues et. al (2009) concluded that Integra's infection risk can be avoided by strictly adhering to the precise surgical technique of its application.

Low Antigenicity and Immunogenic Response of Integra

Integra has a low immunogenic response within the body, stimulating the growth of the neo-dermis without inflammation. A comparative study of various burn treatments conducted by Lagus et. al (2013) found no significant immunogenic responses with Integra. After treating the patients' burns with Integra, no foreign body reactions were recorded, such as granulomas or macrophages (Lagus et. al, 2013). In another study, Coulomb et. al (1998) concluded that there were no signs of immune rejection in the patients 4 months after grafting (Coulomb et. al, 1998). The skin substitutes injected with allogeneic fibroblasts were able to stimulate successful epithelialization in all 18 patients. Integra's ability to heal the wound without a significant foreign body reaction or immunogenic response reflects the exceptional biocompatibility of the artificial scaffold (Silverstein, 2006).

In conjunction with its low immunogenic response, Integra has a low antigenicity, which is the capacity of a substance to produce an immune response (Polley et. al, 2014). Basic fibroblast growth factors (bFGF) integrated into Integra's matrix induce fibroblast growth in the wound; fibroblasts are non-antigenic, because the body does not recognize the fibroblasts as foreign cells (AccessScience, 2015). Thus, it is unlikely for the body to produce an immune response against the artificial scaffold (Polley et. al, 2014). A reduced risk of disease transmission and low immunogenic response are critical properties for wound-healing, making Integra an excellent treatment for burn injuries.

INTEGRA'S INCREASED VASCULARIZATION

Another hypothesized advantage of artificial skin is its ability to stimulate neovascularization in the surrounding endothelial cells of the burn injury. Vascular development

is a critical component of wound-healing, because the growth of new blood vessels supplies the surrounding damaged tissue with nutrients and oxygen (Bondke Persson, 2013). One method to induce vascularization in artificial skin is to stimulate internal angiogenetic responses at the wound site with the aid of growth factors such as basic fibroblast growth factors (bFGF) or vascular endothelial growth factors (VEGF) (Kamel et. al, 2013). bFGF and VEGF are often integrated into the dermal template of Integra (Wilcke et. al, 2007). In a study by Wilcke et. al (2007), bFGF and VEGF were incorporated into the Integra matrix by a fibrin sealant, which allowed a prolonged release of growth factors in the wound.

Inducing Vascularization with Incorporation of bFGF and VEGF

The incorporation of bFGF and VEGF in the Integra matrix facilitates the degradation of surrounding endothelial cells, which creates a new scaffold for neo-vessels to form (Cassell et. al, 2002). The bFGF and VEGF in the artificial skin stimulate neighboring endothelial cells to increase the production of collagenase and protease (Cassell et. al, 2002). Collagenase breaks down the peptide bonds in collagen, a structural protein of the extracellular matrix, whereas protease breaks down proteins of the extracellular matrix through the hydrolysis of peptide bonds. The subsequent breakdown of the extracellular matrix by collagenase and protease reduces mechanical tension within the endothelial cells (Cassell et. al, 2002). The subsequent lack of tensile stress allows the extracellular matrices to reorganize into a new scaffold for increased neo-vessel growth (Cassell et. al, 2002). With a restructured scaffold, neo-vessels are then able to mature and grow (Cassell et. al, 2002).

Shaterian et. al (2009) conducted a study to examine the kinetics of revascularization in wound-healing. A non-invasive imaging method was used to study the vascular permeability of the dermal construct with immunohistochemical analyses. The analyses revealed that the Integra grafts in patients were well-vascularized, and Integra stimulated extensive and thorough vascularization in the wound (Shaterian et. al, 2009). According to Shaterian et. al (2009), Integra's formation of a capillary bed in the wound site was caused by the production of angiogenetic blood vessels and the recruitment of endothelial progenitor cells (EPCs), which aid in the reconstruction of the epidermal lining (Shaterian et. al, 2009). In addition, a study conducted by Silverstein et. al concluded that a well-vascularized neo-dermis grew in all patients treated with Integra. The study revealed that angiogenesis had occurred in the wound site—new blood vessels formed from a nearby blood supply, because the addition of growth factors bFGF and VEGF in Integra had induced vascularization in the dermal tissue (Silverstein et. al, 2006).

Downside: Integra's Slow Vascularization

Although many studies reveal Integra's superior vascularization capacity, a setback of Integra is its long period of vascularization in the burn site. In a demonstration by Greenwood et. al, a confocal laser scanning microscopy method was used to observe the vascularization mechanism of Integra. The microscopy method examined that neovascularization in the wound took up to 4 or 5 weeks (Greenwood et. al, 2009). From the study, Greenwood et. al (2009) concluded that Integra's vascularization tardiness can be attributed to the absence of existing blood vessels in its synthetic bi-layer matrix. Thus, it takes longer for the wound to vascularize because the vascularization must first occur in the wound bed itself (Greenwood et. al, 2009). As discussed earlier, wound bed vascularization occurs from the addition of growth factors, which restructure the scaffold for new blood vessels to grow (Kamel et. al, 2013).

Despite its lengthy vascularization time, Integra is advantageous for its thorough vascular development in the wound site. This is critical for burns, because vascularization allows blood vessels to transport nutrients to damaged cells for a healthy recovery.

INTEGRA'S REDUCED SCARRING

The third proposed benefit of artificial skin is its capability to reduce scarring with the production of a new tissue matrix at the wound site. In comparison to the first two advantages, which are crucial for full recovery and survival, reduced scarring is more of an aesthetic and cosmetic advantage. As described earlier, the degradation of Integra allows for vascularization as well as the growth of a normal host collagen matrix in its place (Chou et. al, 2001). The growth of a normal collagen matrix effectively replaces the damaged tissue, resulting in lessened scarring (Chou et. al, 2001).

In addition, the bovine collagen structure of Integra allows for the integration of fibroblasts and myofibroblasts in its matrix (Chou et. al, 2001). Fibroblasts and myofibroblasts produce collagen precursors and other proteins that provide structural support, strength, and elasticity to the tissue. Thus, the addition of fibroblasts and myofibroblasts in the Integra template facilitates the growth of the new collagen matrix, or neo-dermis (Chou et. al, 2001). In Lagus et. al's study (2013), the neo-dermis of the patients was initially thicker than the normal dermis directly after application. However, over the following few months, the neo-dermis matured and thinned, eventually becoming structurally indistinguishable from the normal skin's dermis (Lagus et. al, 2013). This reflects Integra's capability to biodegrade and mimic the skin's natural dermis to a certain extent. Currently, Integra is not capable of imitating the exact complexity of natural skin (Metcalfe et. al, 2007).

Normal Collagenous Growth with TFG- β3

Along with fibroblasts and myofibroblasts, transforming growth factor beta 3 (TGF-β3) is also added to the scaffolds of Integra (Metcalfe et. al, 2007). TGF-β3 enhances normal collagenous growth by inducing the development of fibroblasts at the wound site. Fibroblasts aid in preventing scar formation by reconstructing a normal collagen matrix at the wound site (Kamel et. al, 2013). In the intracellular TGF-β pathway, growth factor TGF-β binds with an inactive receptor protein attached to the extracellular matrix, forming the receptor-complex TGF-βR (Walraven et. al, 2015). The subsequent formation of TGF-βR induces the phosphorylation of R-Smads, which are intracellular proteins (Walraven et. al, 2015). The phosphorylated Smad complex travels to the nucleus of the endothelial cell, where it activates the transcription of growth factors that increase fibroblast production (Walraven et. al, 2015; Kamel et. al, 2013). Thus, the addition of TGF-β3 in artificial skin allows for the development of fibroblasts, which create a new collagen matrix that reduces scarring.

Integra's Reduced Wound Contracture

Integra lessens the scarring of burn injuries by controlling wound contraction, thereby reducing wound contracture. Wound contracture is an abnormal excess of contraction that results in abnormal deformities such as scar tissue (Hori et. al, 2016). In contrast to wound contracture, wound contraction is a healthy, normal process that reduces wound size (Hori et. al, 2016). One type of cells involved with wound contraction is keratinocytes, which produce keratin, one of the proteins that structurally composes the outer layer of the skin (Lagus et. al, 2013). The epidermal component of Integra transfers keratinocytes to the wound site, stimulating rapid

epithelialization, a necessary process of wound-healing (Monteiro et. al, 2014). The other cells involved with wound contraction are myofibroblasts, which enhance wound contraction by stimulating matrix growth (Lagus et. al, 2013). Integra binds myofibroblasts to its dermal matrix, promoting increased wound contraction (Lagus et. al, 2013).

In addition, the collagen scaffold structure of Integra itself reduces wound contracture and scarring (Hori et. al, 2016). The porous collagen scaffold controls ligand density, which determines how many myofibroblasts can bind to the surface of the scaffold (Hori et. al, 2013). The larger the pore in the scaffold, the more myofibroblasts can bind to the surface (Hori et. al, 2013). The greater number of bound myofibroblasts stimulates normal matrix growth and thus reduces scarring (Hori et. al, 2013). Because Integra controls the amount of bound myofibroblasts on its surface, it can regulate the amount of contraction that occurs in the wound, preventing the occurrence of wound contracture (Hori et. al, 2013).

Comparing Scar Formation of Integra and Skin Grafts

Many reports show that artificial skin produces more elastic and functional results than normal skin grafts. In Lagus et. al's study (2013), the resulting skin after the use of Integra was more elastic and had a better range of motion than the tradition split-thickness skin graft (STSG) (Lagus et. al, 2013). To objectively measure the capability of Integra to reduce scarring, Lagus et. al (2013) used the Vancouver Scar Scale (VSS), which evaluates scars on a scale from 0-14, 0 being the least scarred and 14 being the most. In the study, Integra scored an exceptional 1.3 (Lagus et. al, 2013).

The wound sites of donor skin grafts tend to heal with major scarring issues, especially in the case of meshed skin grafts that are used for extensive burns (Shevchenko et. al, 2010). Meshed skin grafts are donor grafts that have been stretched to fit the wound, resulting in interstices, or spaces within the graft (Shevchenko et. al, 2010). The interstices result in a slow epithelialization, due to the lack of present dermis (Shevchenko et. al, 2010). Thus, meshed skin grafts have a slower recovery time and ultimately form scar tissue from the interstices (Shevchenko et. al, 2010). In another study, Burke et. al (1981) examined the comparison between the cosmetic results of artificial skin and donor skin grafts. Whereas the burn injuries treated with artificial skin showed no signs of hypertrophic scarring, the donor skin grafts revealed severe pliability issues because of the interstices in the grafts (Burke et. al, 1981). Thus, the absence of interstices in Integra leads to a more elastic and functional healing site in the burn.

Although it is not crucial for wound recovery, lessened scarring can lead to cosmetic and functional improvements for the burn patient. Integra significantly reduces scarring through the construction of a new tissue matrix, with the aid of fibroblasts, myofibroblasts, keratinocytes, and the TGF-β3 growth factor.

CONCLUSION

Various forms of artificial skin, such as Integra, are becoming increasingly popular burn treatments. As discussed in the paper, the three main advantages of Integra are its low risk of disease transmission and low immunogenic response, increased vascularization in the wound site, and reduced scarring to improve functional and cosmetic results.

Despite Integra's numerous benefits, there are minor setbacks with its use. Integra's lack of blood vessels makes it highly susceptible to infection, as there are no immunogenic defenses present; to avoid infection, the application of Integra must be followed exactly according to procedure. In addition, although Integra's vascularization is extensive and thorough, it is notably

slow, taking up to 4 or 5 weeks (Greenwood et. al, 2009). This process significantly lengthens the recovery period of the patient, although after recovery, the wound remains fully healed and vascularized in the patient (Silverstein et. al, 2006). Lastly, although Integra serves as an excellent replacement for the normal skin, it cannot fully replace the normal skin's anatomical and functional capabilities. These setbacks are not severe, and do not trivialize Integra's excellent proficiency as a burn treatment.

The Future of Artificial Skin

As of now, there are no current models of artificial skin that fully replace the anatomical and functional complexities of normal skin. To address this issue, bioengineers have been trying to implement other skin appendages to the scaffold of artificial skin (Shevchenko et. al, 2010). These appendages include hair follicles and sebaceous glands, which can restore the functionality of the wound back to its natural capacity (Shevchenko et. al, 2010). Another main setback that remains is artificial skin's limited availability to burn patients across the world. Synthetic skin substitutes such as Integra are often expensive and difficult to obtain due to their limited supply (Shevchenko et. al, 2010). In the future, having a widespread supply of artificial skin across skin banks can eliminate the likelihood of disease transmission through allografts of infected donors.

Artificial skin changes the lives of thousands of burn patients. It facilitates vital wound-healing processes in the burn, with only minor setbacks and risks. Many burn patients are conscious of choosing a treatment that fully heals and restores the functionality of the wound site. Thus, artificial skin has become a popular choice of burn treatment, due to its reliability for patient survival and favorable functional and cosmetic results. Its advantages make it a superior candidate for burn treatment compared to skin grafts, which are currently the most popular method of treating burns. The massive growth in the usage of artificial skin as a burn treatment shows its promise of development in the near future. To continue the advancement of artificial skin, researchers will need to conduct more studies to develop its complexity and ability to mimic normal skin.

People Consulted:

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