REVIEW

Burn wound covers, pretreatments, and immunological and microbial concerns

Laura Ortiz [1]

Surgeons can compare three pre-graft methods for treating burn wounds. When using the split-thickness skin graft procedure, many different wound bed covers can be used. The lack of available donor sites can delay skin grafting. During this time, priming the wound bed is the best chance a patient has for full healing. An excised wound bed, an artificial dermal template, and a granulation tissue induced by cellulose sponge are all methods to prepare the wound for a split-thickness skin graft. All three wound bed covers are easy to apply and can be placed on bones and deep wounds, often without pain. Achieving reduced scar formation begins with a well-primed wound bed that can significantly improve the outcome of skin replacement.

Superficial burns are minor skin injuries that affect the epidermis. The epidermis is the outermost area of the skin that contains keratinocytes. Superficial burns in this layer are also known as first-degree burns. They recover within two weeks, with minor scarring or damage to the skin (*1).* Partial-thickness burns also, known as second-degree burns, affect a deeper layer of skin, the dermis, not causing no damage to the muscles or bones. The dermis is the fibrous layer below the epidermis. It is composed of collagen, glycosaminoglycans, and elastin *(2).* Restoration of these partial-thickness burns is ensured by keratinocyte migration from dermal appendages that occurs within a few hours. Healing begins around the edges, due to the body's necessity for rapid wound closure *(3).* One of the important goals of skin grafting is to ensure that the early excision and wound covers reduce the presence of necrotic and infected tissue. Successful skin grafting can help patients gain mobility and speed up their healing process.

Skin grafts

Skin grafting is the process of transferring cutaneous tissue from one portion of the body to another. It is used to cover large burn wounds. The full-thickness skin graft is the procedure most surgeons prefer for the best cosmetic and functional results, but it is of limited availability. Many surgeons use split-thickness skin grafts instead *(4).* Split-thickness skin grafts can be grafted on many different wounds. Split-thickness skin grafts contain the epidermis and a portion of the dermis. Full-thickness skin grafts contain the epidermis and entire dermis. Split-thickness skin graft donor sites retain portions of the dermis, including dermal appendages. The donor site can regrow new skin in two to three weeks *(5).* Donor sites can be used again after healing has occurred. Split-thickness skin grafts are useful when donor sites are limited, as with burns and large wounds. Careful planning is required before selecting wound covers. Overuse of a specific wound cover or carelessness can result in damage greater than the original injury *(6).*

Split-thickness skin grafts can be used on three different treated wound types. They can be applied on an excised wound bed directly after excision. An artificial dermal template, which provides stability, durability, flexible wound closure, and scaffolding for tissue repair, can be used as a permanent wound cover since it can replace either the dermis, epidermis, or both. The dermal substitutes offer biodegradable support to assist engraftment. This procedure is used as a temporary wound cover since it assists in protecting the wound and helps to induce granulation tissue formation before grafting. Granulation tissue can also be induced by a cellulose sponge, which can accelerate host-graft interaction.

Split-thickness skin graft on excised wound bed

A split thickness skin graft can be used to cover an unprimed excised wound bed. In this case, there is nothing on the wound bed itself besides the split-thickness skin graft. The aim is to provide coverage and repair with no defect or minimal deformity *(7).* No prime is placed before the split-thickness skin graft. It can be safer for patients who are allergic to multiple agents. Since the excised wound bed does not contain a wound bed cover, the cost is reduced, and the hospital stay is likely to be reduced. Patients who do not have chronic burn wounds and do not need a wound bed cover are more likely to heal faster.

In the first phase of healing, known as inhibition, the wound bed will become white after the inclusion of oxygen. The skin graft absorbs oxygen and nutrients from the wound bed, so it does not need another oxygen source *(2).* In the next phase, a vascular network is established via inosculation between the cut vessels on the underside of the skin graft and the capillary beds in the wound bed. The wound becomes pink. During the revascularization phase, endothelial cells proliferate and move from the donor site by following pre-existing vascular basal lamina. Endothelial cells eventually degrade. Once the graft has integrated into the wound bed, it undergoes a maturation process that takes a year or more to complete the healing process. For fast wound healing and adequate tissue coverage, a clean wound base is needed for the split-thickness skin graft to undergo normal phases of healing *(8).*

Results of excised wound bed covered with a split-thickness skin graft

An excised wound bed with split-thickness skin graft is the recommended

[1]Senior Student, Department of Biological Sciences, Indian River State College, Fort Pierce, Florida

procedure to cover large areas with less donor skin. Donor sites can be used again after they are healed completely. The average time frame for donor sites to be harvested again is about fifteen days. According to a recent study by Khan *(7)*, multiple factors can affect the ability of the skin graft to undergo the process of graft adherence. Some potential interfering factors are poor blood supply to the grafted area, systemic factors, poor nutrition, health of the patient, and age *(7)*. Patients who have obtained fast healing are more likely to minimize long-term wound care and experience reduced pain (*5*).

Patients will a higher concentration of melanin can obtain hyperpigmentation, as well as discoloration of the grafts *(5)*. Choosing a functionally similar donor site can help to produce better aesthetic results. The majority of unprimed split-thickness skin graft patients have experienced no hyperpigmentation. Minor scarring is noted, along with a good color match and texturization of skin *(9)*. However, some patients have experienced a reduction also known as a contracture of the skin graft over time.

Artificial dermal template cover

Patients who require fuller and more substantial coverage can be treated with an artificial dermal template. It will provide a better result than split-thickness skin grafting directly on the excised wound bed *(10)*. When this procedure is combined with the excised wound bed, it can provide patients with temporary coverage in the multistage reconstruction of extreme burns. This procedure involves a permanent artificial dermal template that is primed onto the excision area *(7)*. The placement of the artificial dermal template cover occurs directly after excision. The template is placed onto the wound bed before the split-thickness skin graft. It is used as a permanent wound cover since it replaces the dermis and/or epidermis.

Dermal templates are becoming more commonly used in post-burn excision and general reconstruction *(6)*. Different types of dermal templates have been used, including biodegradable templates and biocompatible products such as AlloDerm™. Lagus *(6)* showed that the biodegradable two-layer matrix of the dermal template provided patients protection against invasion of microbes. A biodegradable scaffold is introduced for cell attachment and to facilitate handling. It leaves behind a non-immunogenic framework of skin replacement *(11)*. The procedure aims to allow the ingrowth of fibroblasts and other cells, as well as vascular tissues. It has been shown that promoting dermis regeneration in this manner can enhance tissue regeneration *(12)*.

Dermal templates are a useful new tool for post-burn reconstruction. They allow surgeons to excise larger affected areas. Coverage of the wound with a dermal template forms a neodermis *(13)*. The neodermis provides a suitable bed for the application of split-thickness skin grafts. Neodermis creates a skin cover that has better qualities than just the split-thickness skin graft alone. This procedure allows for less post-operative contracture *(14)*.

An artificial dermal template is one of the most common wound bed covers introduced to burn wound patients simply because it is easy to apply and can be placed all over the body *(15)*. In areas that are more difficult to reach, a negative pressure wound vacuum with a bolster is used for this procedure. Braza *(2)* recently used a type of cotton dressing as a bolster with a negative pressure wound vacuum. The negative wound vacuum has been used to reduce the extent of the injury in patients with open fractures and acute or chronic burn wounds. The vacuum can create a controlled and closed environment and reduce exudation, thereby enabling local circulation and tissue granulation *(16)*. During the skin graft procedure, the vacuum can be applied as a bridge that secures the graft in place. It can also be used as a dressing for the graft at the donor site.

Several additional benefits are associated with artificial dermal templates. Van *(17)* states that the growth of new blood vessels into the matrix is related to pore diameter. Porosity has been shown to facilitate the migration of inflammatory cells, endothelial cells, and fibroblasts. The same study showed that an acellular dermal matrix is produced by decellularizing allogenic or xenogeneic dermal tissue. During this process, triggers of rejection were removed. Many patients from the study noted favorable scar quality at the site of the split-thickness skin graft induced by the dermal template as well as favorable functional motor results.

Granulation tissue induced by cellulose sponge cover

Granulation tissue is defined as a new connective tissue and blood vessels that form on the surface of a wound during the healing process. It is important in cases where the dermis has been compromised, and it can also be useful in situations where areas of poor vascularization cannot be grafted upon, such as on the retina and cornea *(9)*. Granulation tissue induced by cellulose sponge matrix supported by cotton fibers is also used on patients with acute or chronic burn wounds. This wound bed cover is considered a temporary cover since it will induce the formation of new granulation tissue as the basis of the new dermis, and it will also protect the wound itself.

However, the cellulose sponge is seen as a degradable material because it is unstable for a long period *(18)*. Among the favorable gel types and sponges used specifically in wound care are cellulose-based hydrogels. Hydrogels are an arrangement of crosslinked polymer chains that are hydrophilic *(11)*. Cellulose has a very high-water holding ability, which provides a moist wound environment that aids healing (19). Cellulose sponge has been used in experimental surgeries for many years due to effective granulation tissue formation. After cleaning the wound bed, the cellulose is used to induce granulation tissue formation. The cellulose sponge smooths and prepares the wound bed for the split-thickness skin graft transplantation *(19)*.

Surgeons use cellulose as a wound bed cover because it mimics the extracellular matrix structure It provides enhanced cell proliferation from epithelial origins, promoting regeneration *(3)*. The rate of cell invasion, as well as the formation of new tissue, are rapid in cellulose sponge. Such sponge has been used to stimulate granulation tissue formation in the wound bed after deep excision of burn wounds and after traumatic injuries *(9)*. Cellulose sponge is known for its elasticity as well

as its ability to be compressed and expanded repeatedly. With these capabilities, the sponge can minimize damage to the body's internal structure and provide passage for cells to enter through the inner parts of the cellulose sponge *(6)*. Cellulose sponges can be manufactured by adding supportive strengthening fibers and sodium sulfate crystals. The crystals act as pore-forming material in a cellulose viscose solution *(19)*. Granulation tissue induced by cellulose sponge can serve as a platform for fibroblast growth, making it suitable as a wound dressing *(20)*.

Granulation tissue induced by cellulose sponge can produce beneficial results with few disadvantages. When surgeons used induced granulation tissue procedures, they found no allergic reactions, no macrophages, and no giant cells *(21)*. No major significant body reaction was seen when the wound bed was induced by the cellulose sponge cover *(18)*. Pre-treatment of wound bed and induction of granulation tissue formation can accelerate host-graft interaction by stimulating graft vasculature and inducing cell proliferation. Priming granulation tissue with cellulose sponges induces granulation tissue formation and allows a significantly stronger vascular response compared to the excised wound bed and artificial dermal template-primed cover *(22)*. New bone in growth is developed during the implantation procedure. When the wound bed cover is imbedded onto bones, it allows cellulose to gain strength by the cotton fibers helping to develop new bone ingrowth *(19)*. This further suggests that pre-treatment with non-permanent cellulose sponge plays a role in the early formation of highly vascularized granulation tissue in both the split-thickness skin graft as well as the wound bed itself.

Skin flap advantages

A skin flap combines healthy skin and a layer of skin called the hypodermis, or subcutis, which is directly below the dermis and epidermis *(23)*. The flap tissue is taken from an area that is close enough to the wound that needs to be covered. A flap can be introduced onto the skin fascia or, in specific circumstances, onto muscles or on areas that contain a lot of collagen, such as the nose, around the eyes, and the ears. Generally, a flap cover is used when the bulk is needed. The flap remains partly connected to its original site through its blood supply *(18)*. A flap reconstruction allows the surgeon to reconstruct deeper wounds that cannot be covered using skin grafts *(14)*.

Assessment of the wound will determine the design of the flap and whether a flap is needed *(24)*. Several surgeons have shown that there are disadvantages to the use of flaps since they are relatively expensive, difficult to use, and prone to infections. Alternatively, artificial dermal template and granulation tissue templates give coverage without a flap *(25)*. However, since these tissue covers do not use flaps, it is hard for the wound covers to use their patients' blood supplies. Surgeons must rely on a well-vascularized wound bed for graft ingrowth *(2)*.

Healing phases, macrophages, and microbes

Wound healing is made up of four phases, known as hemostasis, inflammation, proliferation, and maturation phases *(26)*. Hemostasis is the process of wound closure due to clotting. The inflammatory phase begins when the injured blood vessels begin to leak, causing swelling *(27)*. The proliferative phase is when new tissues are forming. Finally, the maturation phase will occur when collagen is remodeled, and the wound fully closes. During these four phases, a microbial issue, such as an infection, may occur. Careful screening of prospective donor material aims to reduce the risk of transmission of infective agents, but this risk may not be eliminated *(27)*.

Macrophages play a key role in infection. Two types of macrophage phenotypes are present during wound healing. M1 or classically activated macrophages are, induced by microbial agents *(28)*. M2 macrophages, which are branded as an anti-inflammatory, can elicit a type 2 hypersensitivity response. The M2 macrophages can be further classified into subdivisions according to stimuli of activation and achieved transcriptional changes (*26)*. The activated M1 macrophages show proinflammatory activities, instead of activating tissue remodeling or being profibrotic. M2 macrophages participate in angiogenesis, connective tissue remodeling, and resolution of inflammation.

Scientists were able to identify the presence of these macrophages by utilizing the CD163 marker to find the involvement and infiltration of the split-thickness skin graft response to the wound bed cover. The expression of the CD163 marker shows the involvement of an anti-inflammatory repair M2 macrophage phenotype *(26)*. A week after surgeons had grafted the granulation tissue induced with the cellulose sponge cover, results showed a higher increase of the CD163 marker compared to the dermal template cover or the excised wound bed cover. The persistence of M1 macrophages without M2 macrophages results in chronic inflammation and can impair healing in numerous scenarios *(28)*. This suggests that macrophages play a key role in the quality of vascular response, inflammatory response, and the progression of the wound healing proliferative phase. Macrophages can differentiate into various phenotypes with distinct functions, which make it hard to identify the macrophages and their effects. Both M1 and M2 macrophages are required for scaffold vascularization, and if the balance of macrophage phenotype is pushed far enough towards either M1 or M2, then vascularization and integration will not be achieved. Tissue engineering strategies that apply control over macrophages are desirable, as they can utilize the patient's body's healing response to naturally promote regeneration *(28)*.

Microbial issues are present with different wound covers in different severity. During that last few decades, researchers have proposed that bacteria might be involved in and contribute to the lack of healing of chronic wounds *(29)*. Since the presence of *Pseudomonas aeruginosa* was found in the wound bed, microbes have been thought to play a role in healing. A study by Hogsberg suggests that *Pseudomonas aeruginosa* resides in a biofilm deep in the tissue and is protected from antibiotics and the immune system. *Pseudomonas aeruginosa* has been present in many wounds as a biofilm *(30)*. The bacteria can colonize due to the

biofilm's ability to prevent successful antibiotic treatment. When surgeons treated wounds with cefuroxime alone or sometimes in combination with gentamicin, the infection was gone soon after the cefuroxime was placed onto the wound *(30)*.

When using granulation tissue that is induced by cellulose sponge, the wound surface was protected from microbial invasion and further injury. When surgeons applied Acticoat™ (an antimicrobial wound dressing that can be placed over the burns), it protected the wound against bacterial penetration *(11)*. Since the cellulose sponge can absorb bacteria as well as debris from the site of the wound, the sponge can attract inflammatory cells.

Chondroitin sulfate is another anti-inflammatory substance that has been used to prevent microbial invasion. Chondroitin sulfate has anti-inflammatory properties and has been shown to decrease the influx of inflammatory cells during synovial inflammation *(3)*.

Combinatorial Effects

Results show that pre-treatment of the wound bed can speed up healing when used with wound bed covers or templates. Healing can be accelerated due to wound bed to skin interaction, which stimulates blood flow from one area of the body to another by reconnecting the blood vessels *(31)*. This induces cell proliferation. Research shows that the combination of unprimed split-thickness skin grafts and artificial dermal template wound cover has improved the quality and elasticity of reconstructed tissue *(15)*. The combined procedures also produce better aesthetic results. It takes an estimated two weeks for the skin graft to heal, depending on the severity of the burn. Lagus states that after one week of priming the wound bed with granulation tissue induced by the cellulose sponge, patients had more CD31+ molecules *(30)*. Therefore, increased the development of preexisting cell to endothelial cells. The results also showed that granulation tissue induced by the cellulose sponge resulted in larger vessels compared to other wound bed covers *(32)*. However, wound bed priming for the sake of priming alone may result in a delayed grafting operation. It can result in a longer stay in the hospital with increased costs as well as a longer period of open wounds with increased risk of infection and loss of body fluids. Surgeons' results on pre-treatment demonstrated that priming the wound bed before skin grafting utilizes significant early healing before the split-thickness skin graft is presented. Pre-treatment with a cellulose sponge increased the size of vessels, as well as increased numbers of M2 macrophages and proliferation of keratinocytes, suggesting better early nourishment of skin grafts compared to the use of other materials that do not use wound primers.

Discussion

Analysis of wound covers and techniques suggests a mixture of strengths and weaknesses. Split thickness skin grafts do not give enough dermal support for an optimal host to graft interaction. Surgeons can introduce temporary wound covers to help protect the wound and induce granulation tissue formation before grafting. Although granulation tissue induced by the cellulose sponge has been used as a temporary wound cover, for patients with more severe and chronic injuries, a permanent wound bed cover can be used. The cover replaces the dermis or epidermis and can promote the migration of endothelial cells and therefore begin the growth of new vessels. Permanent wound covers can offer biodegradable support to help assist the split-thickness skin graft to the wound bed. The artificial dermal template can be used as a permanent wound cover. To avoid scar contracture, as well as an undesirable aesthetic result at the injury site, a skin flap can be introduced. Skin flaps and wound covers are prone to microbial infections. To prevent infection, and the spread of infection, cefuroxime, and Acticoat can be applied onto the wound bed. Studies have provided surgeons with a variety of ways to help burn patients via the introduction of wound covers that stimulate blood flow with minimal scarring and are easy to apply.

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