Challenging the Conventional Therapy: Emerging Skin Graft Techniques for Wound Healing

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Background: Split-thickness skin grafting is the current gold standard for treatment of major traumatic skin loss. However, split-thickness skin grafting is limited by donor-skin availability, especially in large burns. In addition, the donor-site wound is associated with pain and scarring. Multiple techniques have been developed in the past to overcome these limitations but have been unable to achieve clinical relevance. In this study, the authors examine the novel emerging skin grafting techniques, aiming to improve the utility of split-thickness skin grafting.
Methods: An extensive literature review was conducted on PubMed, MEDLINE, and Google Scholar to look for new skin grafting techniques. Special focus was given to techniques with potential for large expansion ratio and decreased donor-site pain.
Results: The new modalities of modified skin grafting technique, discussed in this article, include (1) Xpansion Micrografting System, (2) fractional skin harvesting, (3) epidermal suction blister grafting, and (4) ReCell technology. These techniques are able to achieve significantly increased expansion ratios compared with conventional split-thickness skin grafting and also have decreased donor-site morbidity.
Conclusions: These techniques can be used separately or in conjunction with split-thickness skin grafting to overcome the associated pitfalls. Further studies and clinical trials are needed to define the utility of these procedures and where they fit into routine clinical practice. (*Plast. Reconstr. Surg.* 136: 524e, 2015.)

Split-thickness skin grafting is the current gold standard for treatment of major traumatic loss of skin, especially from burn injuries.[1,2] Use of split-thickness skin grafting provides regeneration of epidermis and diminishes wound contraction and extracellular matrix deposition compared with nontransplanted full-thickness wounds.[3,4] However, in case of large burn injuries, treatment with split-thickness skin grafting might be limited by the availability of donor skin. To compensate for limited donor-site availability, split-thickness skin grafts are generally meshed to an expansion ratio ranging from 1:1.5 to 1:9.[5,6] However, it comes at the cost of "fishnet" appearance in the grafted skin. Also, in case of a large burn wound, the donor sites are generally used multiple times, increasing the risk of infection and donor-site scar.[7–9] Use of exogenous graft materials such as allografts, xenografts, and artificial skin substitutes provides only temporary wound coverage and eventually necessitates autologous skin grafting.[10,11] Furthermore, donor sites are associated with significant pain because the harvesting

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of split-thickness skin grafts stimulates dermal pain receptors.[12,13] Another major morbidity associated with split-thickness skin grafting is scarring at the donor site. With an exposed donor site or a meshed recipient site, there are large voids in tissue, which heal by secondary intention. This results in painful and inelastic scarring, which adversely affects the aesthetic and functional outcome of the wound healing.[14,15]

There have been multiple attempts to overcome the limitations of split-thickness skin grafting. Meek's technology was developed in 1958, and involved mechanical division of the skin graft into small pieces, allowing up to 10-fold skin expansion.[5] This technique requires the skin graft pieces to be placed with the dermal side down for survival and proliferation.[16] This resulted in a labor-intensive and time-consuming methodology, which limited widespread adoption of this technique. Modifications of the original Meek technology such as modified postage stamp graft technique, also known as the flypaper technique, have been used in burn patients in Asia.[17–19] However, these techniques continued to be labor intensive and did not provide increased expansion when compared with the original Meek technique.[16–19] Cultured epithelial autografts have also been studied as an alternative to split-thickness skin grafts. Despite the fact that cultured epithelial autografts could ultimately provide an expansion ratio up to 1:1000, several major pitfalls have prevented the more common use of this technique.[20–23] The cultured epithelial autografts are fragile with poor graft take, lack a dermal component, and are extremely susceptible to mechanical shear.[24–28] Also, this extremely expensive technique requires good manufacturing practice level laboratory facilities, which further limits its use.

Lately, there has been a push toward developing different modifications of skin grafts to address the pitfalls of split-thickness skin grafting. The new modalities of modified skin graft technique, discussed in our article, include the following: dermal-epidermal grafts, which include the Xpansion Micrografting System (Applied Tissue Technologies, Newton, Mass.) and fractional skin harvesting, and epidermal grafts, which include epidermal suction blister grafting and ReCell technology (Avita Medical, Royston, United Kingdom).

DERMAL-EPIDERMAL GRAFTS

Xpansion Micrografting System

The split-thickness skin micrografts aim to provide a significantly increased expansion ratio and similar or improved quality of wound healing compared with conventional split-thickness skin grafting. The skin micrografts are created using a mincing device, which consists of 24 parallel rotating cutting disks and are 0.8 mm apart. [**See Figure, Supplemental Content 1,** which shows the Xpansion Micrografting System. (*Above, left*) Xpansion mincer device used for creation of skin micrografts from split-thickness skin grafts. (*Above, right*) Morphology and application of the skin graft to the wound bed. (*Below, left*) Principle for increased expansion ratio using skin micrografts. (*Below, right*) Complete reepithelialization using skin micrograft technique in a patient with greater than 50 percent burn injury suffered during Operation Iraqi Freedom, ***http://links.lww.com/PRS/B384***.] Using this device, the split-thickness skin graft is cut twice in perpendicular directions, resulting in split-thickness micrografts that are 0.8 × 0.8 mm in size.[29] The advantage is that by making the individual grafts smaller, the border length increases, thus increasing the regenerative capacity of the grafts. Our laboratory has demonstrated, in a previous study, that the orientation of the skin grafts (dermal side up or down) is irrelevant in a wet or moist environment.[30] Because the micrografts could be implanted without paying attention to the orientation, it simplifies the procedure.

Multiple studies have been performed in a swine model to study micrografts' potential as a treatment modality in wound healing. In a study by Hackl et al., micrografts were transplanted and spread evenly over a full-thickness wound bed with an expansion ratio of 1:100.[31] Different parameters of wound healing were compared between micrograft-transplanted wounds and nontransplanted control wounds in excisional biopsy specimens of the wound specimen. The epithelial regeneration and the number of blood vessels in the subepidermal plexus were significantly higher in the micrograft-transplanted wounds compared with the nontransplanted wounds on days 10 and 14 after the wound creation. The wound contraction was higher in the nontransplanted wounds.[30] Another study compared the healing parameters in swine full-thickness wounds transplanted with skin micrografts, split-thickness skin grafts, or cultured keratinocytes.[32] Micrografts were transplanted in a similar fashion as described above. Both the split-thickness skin grafting group and the micrograft group had significantly lower wound contraction and a better Vancouver Scar Scale score than the nontransplanted wound group. However, there was no statistical difference between split-thickness skin grafting and

micrograft groups for the above-mentioned parameters. The number of rete ridges per linear millimeter (an indicator of the strength of the dermal-epidermal junction) and the granulation tissue thickness was significantly increased in the transplanted groups compared with the nontransplanted wounds, with no significant difference between the split-thickness skin grafts and micrografts. Thus, this study showed that micrografts facilitate wound healing in a manner comparable to treatment with split-thickness skin grafting.[32] To realize the advantages of dermis in the intermediate thickness split-thickness skin graft microautograft obtained by the Xpansion device, it is essential that the dermis persists over the 10-day period until the graft is totally incorporated into the grafted wound. Singh et al. reported with histologic findings that approximately 90 percent of micrografts persist and actually contribute to the formation of neodermis in healed full-thickness wounds.[29] Thus, the advantages of having both epidermis and dermis in the minced microautografts have been corroborated. To translate the micrografting technique into a clinically applicable setting, Hackl et al. used a common moist dressing (hydrogel and foam) instead of a wound chamber, which is a polyurethane bellowed dressing that can be injected with keratinocyte media to induce a wet environment. The reepithelialization rate of the wounds treated with micrografts and moist dressing was significantly higher than the control moist dressing wounds, which further validated the readiness of micrografts to be used in human subjects.[33] Possible explanation of the orientation-independent survival of the micrografts in a wet environment would be survival by diffusion of the wound fluid instead of relying solely on neovascularization.

The micrografting technique was easily adapted in a clinical setting in a 25-year-old Iraqi civilian victim with 54 percent total body surface area full-thickness burn secondary to a propane tank explosion during Operation Iraqi Freedom. Because of the lack of donor tissue, micrografting was used to cover more than 1000 cm^2 of burned surface area, including the chest and the right ankle. The micrografts were spread evenly on the wound bed without paying attention to the dermal orientation. The grafts were covered in a layered fashion with silver product in the inner layer. The outer layer of the dressing was changed every 3 days initially and then daily with antibiotic ointment after 80 percent reepithelialization. The patient had an uneventful postoperative course and the wound closed completely in approximately 30 days. The patient was subsequently discharged from the hospital after complete recovery.[34]

The advantages of skin micrografting lie in the fact that this technique enables expansion ratios of 1:100 to be achieved, with wound healing quality comparable to split-thickness skin grafting. Because there is no concern for dermal orientation with the micrografts, it is an easily adaptable and less labor-intensive procedure. In a study published by Kamolz et al., it was demonstrated that although the achieved expansion rate with skin meshers was lower than the claimed expansion rates, micrografting technique provided more reliable and valid expansion ratios.[35] This technique has also been successfully used in the treatment of multiple chronic ulcers, which were nonresponsive to conventional therapies.[36,37] The benefit of this technique in such small wounds is that it can be used in an outpatient setting with local anesthetic agents.

Fractional Skin Harvesting

Fractional skin harvesting involves harvesting a large number of full-thickness microscopic skin tissue columns. This technique was modeled on the fractional photothermolysis technique, which was developed by the same group.[38] Fractional photothermolysis involves creation of full-thickness "microthermal zones" using laser microbeams and is less than 300 μm in diameter. The epidermis of such microthermal zones would close within 24 hours. This is followed by repair of dermal injury in 2 weeks and tissue remodeling with minimal scarring.

The effect of fractional skin harvesting technique in wound healing was studied by harvesting full-thickness microscopic skin tissue columns (approximately 700-μm diameter) using customized hypodermic needles with two cutting edges in a swine model. The extracted column of tissue from the hypodermic needle is removed by negative pressure using a fluidic device and transported through a tube of flowing air and normal saline into a collection basket. The microscopic skin tissue columns were placed randomly in the wound without maintaining the dermal side–down orientation. The healing of the donor and the graft sites were compared to control wounds that healed by secondary intention or with split-thickness skin grafting.[39] The greatest advantage of this technique involved faster reepithelialization of the harvested donor skin columns and rapid healing with minimal scarring. This was in contrast to a split-thickness skin grafting donor

site, which required at least 2 weeks for reepithelialization and had scar-like characteristics. [**See Figure, Supplemental Content 2,** which shows fractional skin harvesting. Gross appearance of donor sites for microscopic skin tissue columns (*above, left*) and split-thickness skin grafting (*above, right*) immediately after tissue harvesting. At 7 weeks, whereas the donor site for the microscopic skin tissue columns was indistinguishable from surrounding skin (*below, left*), the split-thickness skin grafting donor site remained raised, stiff, and discolored compared with the surrounding skin (*below, right*). (Reprinted with permission from Tam J, Wang Y, Farinelli WA, et al. *Plast Reconstr Surg Glob Open* 2014;1:e47), ***http://links.lww.com/PRS/B385***.]

Wounds treated with split-thickness skin grafting had a fishnet–like appearance compared with microscopic skin tissue column–treated wounds, which healed with a smooth skin texture. However, there was no significant difference in the rate of reepithelialization or histologic features between the two groups.[39] The major advantages of this technique include minimal morbidity and faster reepithelialization of the donor site without scarring and lack of the expanded mesh graft pattern in the grafted site, which is commonly seen with split-thickness skin grafting. Even though this study provides very promising results, fractional skin harvesting is a new technique, and more studies will be needed to further validate its advantage over conventional split-thickness skin grafting.

EPIDERMAL GRAFTS

Epidermal Suction Blister Skin Grafting

Epidermal blister grafting has been historically used for treatment of vitiligo over the past decades.[40–42] Recently, it has been evaluated for use as possible treatment modality in wound healing. The technique involves creation of an epidermal blister using suction, which is then manually harvested from the donor site and transferred to the recipient site. The time required for the formation of suction blisters is inversely related to the skin temperature. Traditionally, this method is time consuming and labor-intensive and limited by the need for multiple procedures to cover even small wounds. To overcome these obstacles, a novel device called CelluTome (Kinetic Concepts, Inc., San Antonio, Texas) has been introduced. It was developed by MoMelan Technologies and acquired by Kinetic Concepts in November of 2012. This harvesting tool is designed for creation of suction epidermal blisters using a constant negative pressure of 400 to 500 mmHg at approximately 37° to 41°C for approximately 45 minutes. The suction blisters are developed inside the disposable harvester, which consists of two thin stainless steel plates with an array of 1.75-mm holes and a cutter blade. More than 128 blisters can be created over an area of 25 cm^2 of donor skin, which is then peeled away with a transparent wound dressing, such as Tegaderm (3M, St. Paul, Minn.) and applied over the recipient site.[43] [**See Figure, Supplemental Content 3,** which shows epidermal suction blister grafting. (*Above, left*) CelluTome developed by Kinetic Concepts, Inc., showing the harvester and the negative-pressure system (for reprint permission, please contact KCI Licensing, Inc.). (*Above, right*) Creation of epidermal suction blister using the CelluTome. (*Below, left*) Gross appearance of donor site immediately after harvesting. (*Below, right*) Complete reepithelialization of the donor site within 2 weeks, ***http://links.lww.com/PRS/B386***.]

A recent study evaluated the use of CelluTome in a nonhealing ulcer secondary to pyoderma gangrenosum, which was nonresponsive to conservative treatment. The patient received a single harvest of epidermal blister using the above-mentioned technique. There was a 63 percent wound area reduction and complete healing of the donor site at 1-week follow-up. The wound completely reepithelialized in 7 weeks. There was either complete healing or substantial reduction in the wound areas in four other patients with this technique.[44]

The epidermal graft harvesting can be performed in an outpatient setting without anesthesia. Because the blisters are cleaved through the lamina lucida of the dermal-epidermal junction, it invokes little inflammatory response. This might explain complete healing of the donor site within 2 weeks with minimal pain. Epidermal grafts provide autologous keratinocytes, which accelerate the process of reepithelialization. In the above-mentioned study, the epidermal blister grafts did not incorporate into the underlying granulation tissue and the reepithelialization occurred from the wound edges rather than the bulk of the graft. Based on this observation, it can be argued that the epidermal blister grafts act like a bioengineered skin, and promote wound healing through release of autologous keratinocytes and growth factors.

ReCell Technology

Autologous noncultured cell therapy is another emerging technique for treatment of various skin wounds, especially burns. The principle

behind this approach involves isolation of cells from the donor tissue and immediate autologous replantation to the patient's wound.[45] This technique circumvents the 2- to 3-week delay associated with cultured epithelial autograft.

The most recognized commercial product using this technique is ReCell, where noncultured autologous cells are applied by spraying. The whole procedure can be performed in approximately 1 hour and enables treatment of large wounds without needing a scaffold. With this technology, intercellular detachment of the donor split-thickness skin graft is initiated by incubation in trypsin solution at 37°C for 20 minutes. After digestion, the sample is mechanically agitated to separate the cells. Finally, the cells are suspended in a lactate solution and sprayed over the wound.[46] [**See Figure, Supplemental Content 4,** which shows ReCell technology. (*Above, left*) Enzymatic digestion (30 to 60 minutes). (*Above, right*) Mechanical separation of epidermis from dermis. (*Below, left*) Cell suspension in lactate solution. (*Below, right*) Application over the burn wound. (Reprinted with permission from Gravante G, Di Fede MC, Araco A, et al. A randomized trial comparing ReCell system of epidermal cells delivery versus classic skin grafts for the treatment of deep partial thickness burns. *Burns* 2007;33:966–972), ***http://links.lww.com/PRS/B387***.] Wood et al. showed that, using this system, the average yield of viable cells per cubic centimeter of donor split-thickness skin graft was 1.7 million (prespray) and 1.4 million (postspray).[47] In the same study, it was shown that 86 percent of the original cells were viable after 24 hours' storage at 4°C. In a cell type identification experiment with fluorescence-activated cell sorting, it was shown that the suspension contains primarily keratinocytes (65 percent) and fibroblasts (30 percent), with a small population of melanocytes (3.5 percent).[47]

In a preclinical study, ReCell was combined with the dermal substitute Integra (Integra LifeSciences Corp., Plainsboro, N.J.) to treat porcine full-thickness wounds. Wounds were initially treated with Integra followed by spraying of cells, isolated with the ReCell system, on the underside of the dermal template. The study indicated that cells stay viable, migrate through Integra, and self-organize into a differentiated epidermis. These results suggest that combining the ReCell system with a dermal component would offer a potential therapy for skin reconstruction of a full-thickness wound.[48]

Multiple clinical studies have further validated the utility of ReCell. It has been used in varied arenas of wound healing, ranging from deep dermal partial-thickness burns to chronic nonhealing ulcers.[46,49] In a randomized trial, Gravante et al. compared the ReCell and the conventional split-thickness skin grafting for epidermal replacement in 82 patients with deep dermal partial-thickness burn wounds.[46] An adequate epidermal replacement was achieved with both techniques; also, aesthetic and functional outcomes were similar between the two procedures. However, the reepithelialization rate was faster with split-thickness skin grafting compared with ReCell. In contrast, postoperative pain was significantly reduced with ReCell. This study showed that ReCell is a feasible, simple, and safe technique that gives results similar to split-thickness skin grafting in the treatment of partial-thickness burns. It is possible to achieve a 1:80 expansion ratio with this technique, which would be especially helpful for large wounds with limited donor skin availability.[44] In another clinical study, the effectiveness of the ReCell system was examined in the treatment of chronic ulcers. Twenty patients with chronic ulcers, nonresponsive to conventional therapies, were treated with the ReCell system. Ninety-five percent of these patients had 80 percent reepithelialization by 2 months. The function and aesthetics of the patients were good, with minimal associated pain. The study concluded that the ReCell system provides the regenerative tissue stimulation necessary for the closure of chronic ulcers.[49]

The ReCell system offers a feasible alternative for burn and wound surgery. Benefits of this technique include quick application and the possibility of treating large areas without need for a scaffold. The drawbacks are poor attachment and loss of cells caused by mechanical pressure while spraying. In addition, high costs limit the more routine use of this technique.

Comparison of Dermal-Epidermal versus Epidermal-Only Grafts

Although the first two techniques include dermis in the grafts, the last two techniques use only epidermis for wound healing. There are several distinct advantages of including dermis in the grafts. By containing both epidermis and dermis in the Xpansion minced micrografts and microscopic skin tissue columns, wound contraction is minimized.[50] This is especially important in the vicinity of joints and on the face, where wound contraction can result in a limiting contracture. Another advantage of having dermis in the micrografts is that the fibroblasts in the mesenchymal mesodermal tissue produce high levels

Table 1. Expansion Ratio and Donor-Site Characteristics of Novel Skin Grafting Techniques Compared with Conventional Split-Thickness Skin Grafting

Technique	Thickness of Skin Graft (Dermis-to-Epidermis Ratio)	Expansion Ratio	Donor-Site Size	Donor-Site Healing	Donor-Site Pain
STSG	Partial (3:1)	1:2–1:9	Very large	Heals with scar	Significant
Full-thickness skin graft	Full (8:1)	1:2–1:5	Very large	Heals with linear scar	Decreased (primarily closed)
Xpansion Micrografting System	Partial (3:1)	Up to 1:100	Small	Same as STSG	Similar but over a significantly small area
MSTCs	Full (8:1)	Same as STSG	Small	Heals with minimal scarring	Not specified
CelluTome epidermal suction blister grafting	Epidermal only (0)	Same as STSG	Small	Heals with minimal scarring	Minimal
ReCell technology	Epidermal only (0)	Up to 1:80	Small	Same as STSG	Same as STSG

STSG, split-thickness skin grafting; MSTCs, microscopic skin tissue columns.

of growth factors that facilitate the proliferative phase of wound healing.[51,52] A third advantage of containing dermis in a minced microautograft is to provide tensile strength to the repaired wound. Epithelial grafts containing only epidermis are not stable and provide very limited strength. The tensile strength (ultimate load divided by cross-sectional area) ranges from 5 to 30 N/mm^2.[53–56] This is maximum at 21 N/mm^2 at age 8 years and decreases to 17 N/mm^2 at age 95 years. In contrast, epidermal-only grafts do not stimulate dermal pain receptors and can be easily performed in an outpatient setting.

CONCLUSIONS

These emerging alternatives to conventional split-thickness skin graft harvesting provide a highly increased expansion ratio, which is especially beneficial in the treatment of large burn wounds. A comparison of each of these techniques vis-à-vis split-thickness skin grafting is outlined in Table 1. The decreased wound contraction and scarring helps in overcoming the complications of split-thickness skin grafting. Furthermore, procedures such as epidermal suction blister grafting or Xpansion micrografting can be performed in an outpatient setting with minimal donor-site–associated pain. Donor-site healing is also significantly improved with some of these techniques. These techniques can be used separately or in conjunction with split-thickness skin grafting. Further clinical trials are required before they can be integrated into routine clinical practice.

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