White Paper: Xpansion micro-autografting kit

Background

Split-thickness skin grafting (STSG) is a standard reconstructive technique frequently used for acute wounds following surgery or trauma, severe burns, and chronic wounds that fail to heal with nonsurgical management. In this process, the patient's own healthy skin is harvested and subsequently transferred to the burnt site after resection of the dead tissue. Although efficient, it is associated with substantial problems, such as poor-quality skin, infections and scarring. In a very large burn that is accompanied by a limited donor site for STSG harvest, the skin graft is meshed and expanded up to sixfold (possibly ninefold), but the donor sites may still not suffice and the increased expansion ratios result in a fishnet appearance of the healed 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. In addition, skin grafting has been limited by access to a trained surgeon and an operating room, as well as the need for special instruments and general anesthesia. Multiple techniques (such as cultured epithelial autografts and non-cultured cell sprays) have been developed in the past to overcome these limitations but have been unable to achieve clinical relevance [1].

Minced skin technique

Minced skin technology addresses the existing limitations of skin grafting and cultured cells. Meek (1958) was the first to describe this technique for mincing a split-thickness skin graft into small pieces, allowing 10-fold expansion. However, Meek's method never gained widespread clinical application, in part because the skin graft pieces needed to be placed with the dermal side down to ensure survival. Moreover, the device for mincing the skin grafts was expensive and the method was labor intensive [2].

Xpansion micro-autografting

We have developed a simple technique for creating skin micrografts from an autologous STSG using a handheld mincing device. Pre-clinical studies of this method have demonstrated that an intraoperative expansion of 100 times is possible with complete healing of full-thickness wounds in pigs in 14-18 days [3]. Therefore, theoretically using the Xpansion micro-autografting technique the entire body surface (1.75 m^2 body surface area) can be grafted with a piece of skin only 14cm x 14cm. We have also shown that in a moist environment the micrografts will propagate from the wound bed to the wound surface and epidermal proliferation will occur from the borders, appendages, and basal layer [4]. Importantly, the orientation of the micrografts do not matter making this method easily adaptable and less labor-intensive procedure.

The Xpansion micro-autografting kit offers a simple and straightforward method of creating split-thickness skin micrografts. Micrografts are evenly-sized minced skin particles, 0.8 mm x 0.8 mm in size. All the required instruments are single-use disposable and are packaged in a convenient sterile kit. Furthermore, the method does not require an operating room or general anesthesia to complete the procedure (Figure 1) [5].

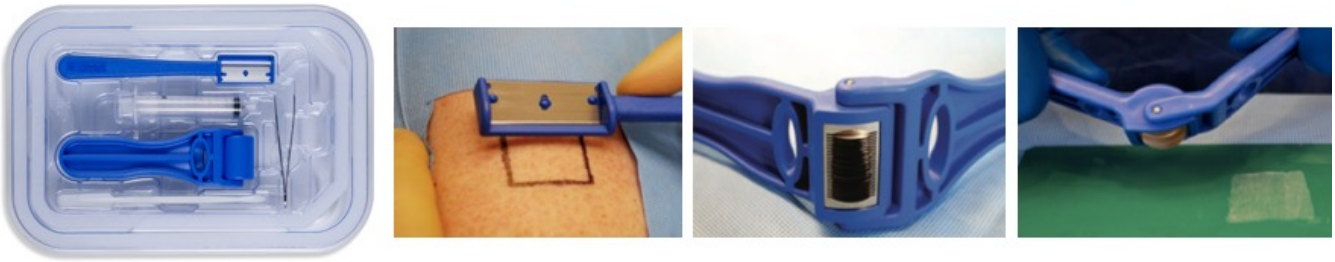

Figure 1. The Xpansion micro-autografting kit allows the health care provider to harvest, mince, and apply split-thickness skin grafts (STSG's) to wounds. The instruments provide a simple and straightforward method of creating split-thickness skin micrografts. Micrografts are evenly-sized minced skin particles, 0.8 mm x 0.8 mm in length. All the required instruments are single-use disposable and are packaged in a convenient sterile kit [5].

Multiple preclinical and clinical studies have demonstrated that this method is efficient and comparable to conventional split-thickness skin graft harvesting in the treatment of wounds and burns. Below we have described some preclinical studies and clinical cases utilizing the Xpansion micro-autografting technology.

Pre-clinical studies

Svensjö et al (2002) treated porcine full-thickness wounds with micrografts and found that in a moist or wet environment orientation of the micrografts (dermis up or down) is unimportant. This is central because Meek (1958) was placing the micrografts only dermis down making the technique time consuming and impractical (Figure 2). In the same study, they compared the efficacy of micrografting to STSG, cultured and non-cultured keratinocytes. The results showed that all treatments accelerated wound re-epithelialization and additionally micrografts and STSG delayed wound contraction in comparison to controls [4].

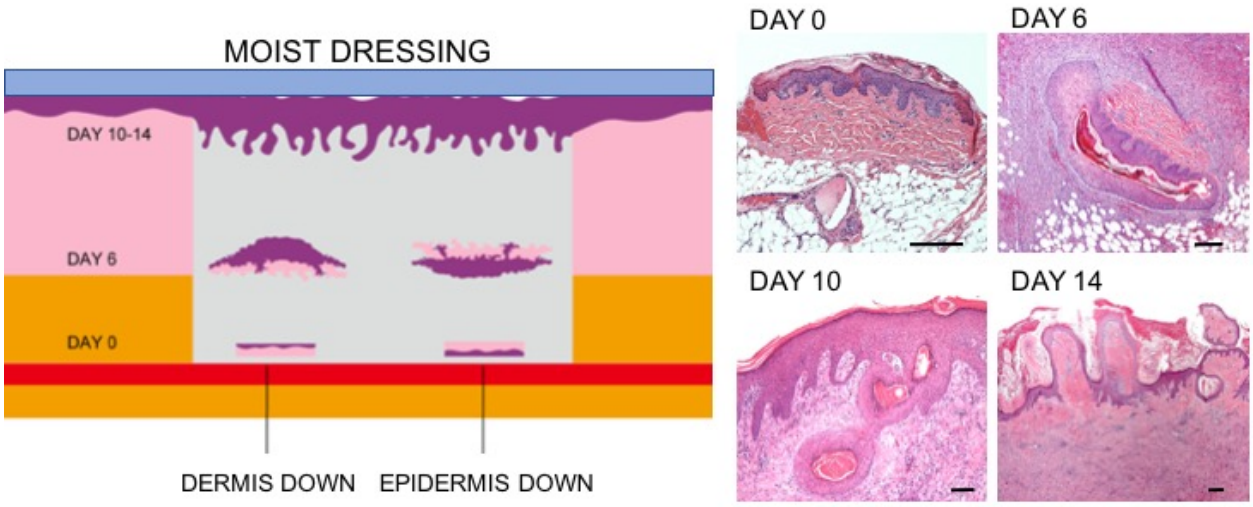

Figure 2. *On the left*: In a moist environment, the micrografts will propagate from the wound bed to the wound surface and epidermal proliferation will occur from the borders, appendages, and basal layer. Importantly, the orientation of the micrografts do not matter making this method easily adaptable and less labor-intensive procedure [4]. *On the right:* H&E stained sections showing micrograft 1 hour, 6, 10 and 14 days after transplantation. Day 6 picture shows micrograft with proliferating keratinocytes. Day 10 picture shows stratum corneum of four different micrografts surrounded by keratinocytes in different stages of migration. Day 14 after transplantation shows dermis and stratum corneum of transplanted micrografts in various stages of transepidermal elimination [3].

Kiwanuka et al (2011) also compared micrografting to STSG. Microgafts (0.8 mm x 0.8 mm) were evenly applied in 1:10 ratio to the wound bed and wound healing was studied over time. Qualitative and quantitative measurements collected from full-thickness porcine wounds demonstrated that transplantation of micrografts improved wound healing and was comparable to treatment with STSGs [6].

Hackl et al (2011) studied capacity of the micrografts to expand and showed that transplantation of micrografts in a 1:100 expansion ratio resulted in complete epithelialization of both healthy and diabetic porcine full-thickness wounds within 14 days. In comparison, nontransplanted wounds showed 62 percent reepithelialization in healthy pigs and 49 percent in diabetic pigs at the corresponding time point. The study concluded that minced skin micrografts are very effective in wound repair and can provide 100-fold expansion of a skin graft [3].

Further Hackl et al (2013) combined micrografts and commercially available moist dressings (Tegaderm^{TM} Hydrogel or Tegaderm^{TM} Foam, 3 M Health Care, St. Paul, MN) to treat porcine full-thickness wounds. Large 5 cm x 5 cm or 10 cm x 10 cm full-thickness wounds were created on the backs of pigs and micrografts were transplanted in a 1:100 and the commercial wound dressing was subsequently applied on the top of the wound to create a moist wound environment. The results showed that 5 cm x 5 cm transplanted wounds covered with moist dressings were 91% and 10 cm x 10 cm wounds were 66 % reepithelialized by day 18. Thus, the results concluded that micrografting technique can be effectively combined with clinically available moist dressings to regenerate the epidermis of full-thickness wounds (Figure 3) [7].

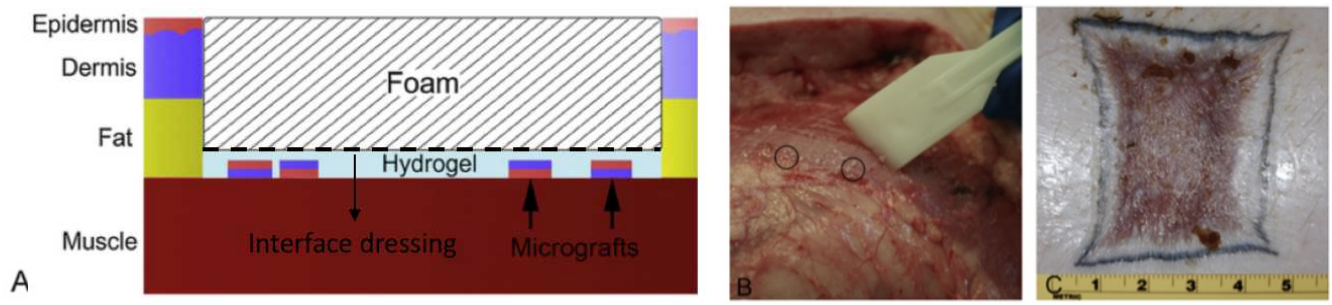

Figure 3. Transplantation of micrografts to porcine full-thickness wounds. (A) Illustration of wound with micrografts transplanted independent of orientation, covered with a moist dressing (hydrogel and Tegaderm^{TM}). (B) 5 cm T 5 cm wound immediately after wound creation. A sterile spatula is used to evenly spread the micrografts (circles). (C) Macroscopic picture of a fully epithelialized wound 18 days post transplantation [7].

Singh et al (2015) hypothesized that even smaller micrografts would increase the regenerative potential of the graft by creating many more pieces of the same original skin graft. Therefore, the grafts were minced to 0.3 mm x 0.3 mm pixelgrafts, transplanted to porcine full-thickness wounds and healing was compared to 0.8 mm x 0.8 mm micrografts. The results indicated that the pixelgrafts remained viable and contributed to skin regeneration. The pixelgraft–transplanted wounds demonstrated a faster reepithelialization rate, decreased wound contraction, and increased mechanical stability compared with non-transplanted wounds. In addition, the reepithelialization rates of the wounds were signicantly increased with pixelgrafting at day 6 after wounding compared with micrografting [8].

Nuutila et al (2017) studied the potential of using dermal micrografts for full-thickness wound healing. Four sequentially deeper 0.35-mm-thick skin grafts were harvested from the same donor site going down

to 1.4 mm in depth. The layers were minced to 0.8 × 0.8 × 0.35-mm micrografts and transplanted (1:2) onto full-thickness porcine wounds. Multiple wound healing parameters were used to assess the quality of healing over time. The results showed that wounds transplanted with dermal micrografts harvested from the upper layers of dermis demonstrated reepithelialization rates comparable to split-thickness skin micrografts at day 10 and by day 28 dermal micrografts showed quality of healing comparable to that of split-thickness skin grafts in terms of wound contraction and scar elevation index. This study indicated that it is possible to use the same donor site by harvesting multiple layers of skin grafts. Furthermore, these grafts can be minced to micrografts (0.8 × 0.8 × 0.35 mm) and expanded extensively [9].

Clinical case reports

Danks & Lairet (2010) used Xpansion to treat a large burn injury at a U.S. military hospital during Operation Iraqi Freedom. A 25-year-old host nation civilian with a total body surfaced area (TBSA) of 2.04 m^2 suffered a flash burn to approximately 54% of his body (all of which full-thickness) after a propane tank explosion. The Xpansion device was used to cover a total of 6% TBSA during two of the planned operative periods. The chest (1037 cm^2) and right ankle (130 cm^2) were covered using the mincing technique. The mincing technique was used when there was limited donor skin and in body regions that could be closely observed. The micrografts were manually placed on the wound bed with forceps approximately 5 mm apart. The grid lines were removed, and the grafts were covered in a layered fashion with one layer consisting of a silver product. The outer dressings were changed every 3 days until approximately 80% was re-epithelialized. The burns were then daily dressed with antibiotic ointment and sterile dressings. Frequent re-evaluation of the micrografted tissue showed healing wounds that were reminiscent of healed donor sites. No significant graft loss was noted, and total time to complete closure was approximately 30 days. The authors' concluded that Xpansion was simple to use and readily adaptable in almost any environment [10].

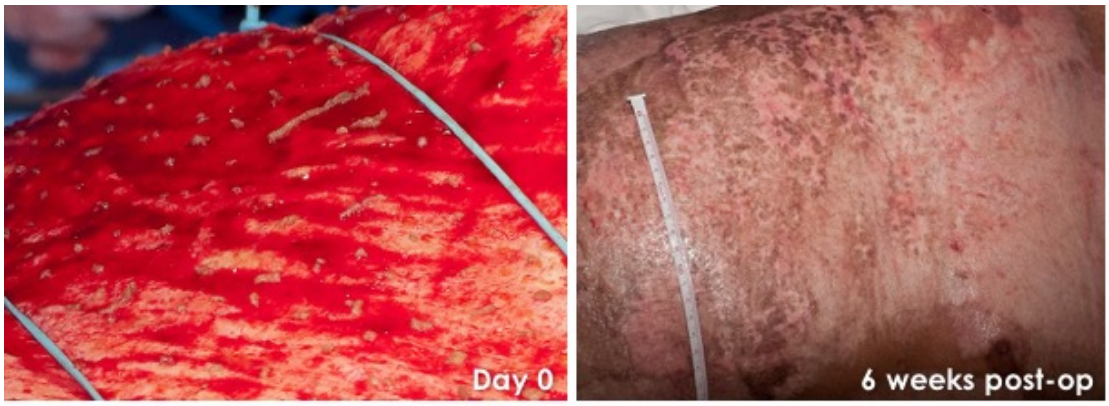

Figure 4. Patient's chest grafted using micrografting technique showing completely healed burn wound 6 weeks post-operatively [10].

Hamnerius et al (2016) tested Xpansion micro-autografting kit for outpatient transplant procedures. An 85-year-old woman had a wound measuring 6 × 8 cm (width × height) on her right anterior-lateral lower leg displaying exposed muscle, subcutaneous fat, and dermal tissue. The wound was cleansed, subcutaneous tissues were adapted with sutures to cover the muscle, and the wound was grafted with skin harvested and processed with Xpansion. The expansion rate was 1:12 (donor site 2 × 2 cm), and the procedure lasted approximately 15 minutes including local anesthesia and bandaging. The patient was admitted to the hospital for 12 days to allow for daily inspections, leg elevation, and the planning for home

care. Eight days post-transplantation, graft take was evident and wound healed completely at day 25. A follow-up at 6 weeks showed a wound that remained healed and that exhibited a spotty pattern of incorporated micrografts. The donor site also healed displaying redness but no hypertrophic scarring, typically what is seen in split-thickness skin donor sites at this time point (Figure 5) [11].

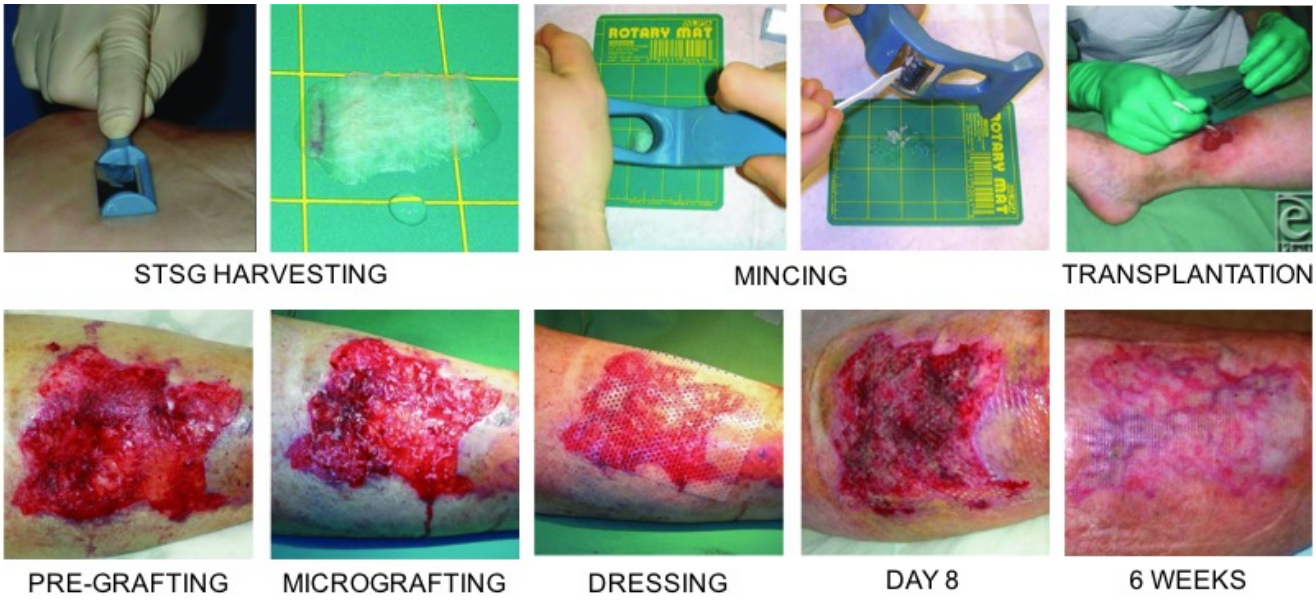

Figure 5. *Top panel*: Transplantation procedure: The handheld dermatome is run back and forth with mild pressure over the skin that has been moisturized with saline. An approximately 4-cm STSG graft has been harvested and laid onto the cutting mat, which was wetted with a few droplets of saline. Subsequently, the handheld mincer is run first once over the STSG and then once more in a 90° angle in relation to the first time. Any skin fragments that stick to the mincer are removed with a spatula and transferred to the other fragments on the cutting mat. The skin fragments are kept together and spread out onto the wound bed. *Lower panel*: An acute wound measuring approximately 6 × 8 cm (width × length) with exposed muscle fascia, subcutaneous fat, and dermal tissue. After suturing and transplantation silicone dressing is placed on the top of grafts. Picture 8 days post-transplantation showed evidence of graft take, seen as lighter colored epithelial islands. Follow-up 6 weeks post-grafting showed a spotty pattern of the skin grafts separated by red scar tissue without any hypotrophy.

In another outpatient case by Hamnerius et al (2016) an otherwise healthy 54-year-old woman had a pretibial ulcer on the right leg for 18 months. Despite conservative therapy with compression bandages for 3 months, the ulcer failed to heal. Transplantation of micrografts was performed with an expansion rate of 1:1.25 (donor site 2 × 6 cm, wound 3 × 5 cm) and the procedure lasted approximately 20 minutes including local anesthesia and bandaging. Routine visit 3 days postoperatively showed grafts in place. Ten days postoperatively, there were signs of partial graft take, but the wound also exhibited some pus and scattered signs of folliculitis was seen in the surrounding skin. Treatment was initiated with isoxazolyl penicillin 500 mg 3 times daily for 10 days. On days 17 and 24, the wound showed healing and free of infection. On day 31, the surrounding skin once again presented with folliculitis as well as eczema. The wound, however, continued to heal as demonstrated by expanding epithelial islands and diminishing open wound area. Treatment with isoxazolyl penicillin and topical corticosteroids was started. On day 45 postoperatively, the wound was healed completely. At 5 months follow-up, the wound had remained healed and the donor site was hardly visible. The study concluded that the Xpansion device was successfully used to treat and close a traumatic lower limb wound and a persistent chronic venous leg ulcer. The donor site itself healed by secondary intent with minimal cosmetic impairment [11].

In Kristianstad (Sweden) Svensjö et al (2017, unpublished) treated a melanoma patient by excising the metastasis on the abdomen. However, the metastasis recurred 6 months later. Therefore, another larger (20 cm x 20 cm) excision was performed and the wound was grafted with STSG and treated with negative pressure. One week after transplantation of the STSG the wound started bleeding that caused the STSG to fail. Subsequently the wound was grafted with micrografts using Xpansion kit to avoid another graft failure. The micrografts took well and the wound started healing and was completely closed 5 weeks postoperatively (Figure 6) [12].

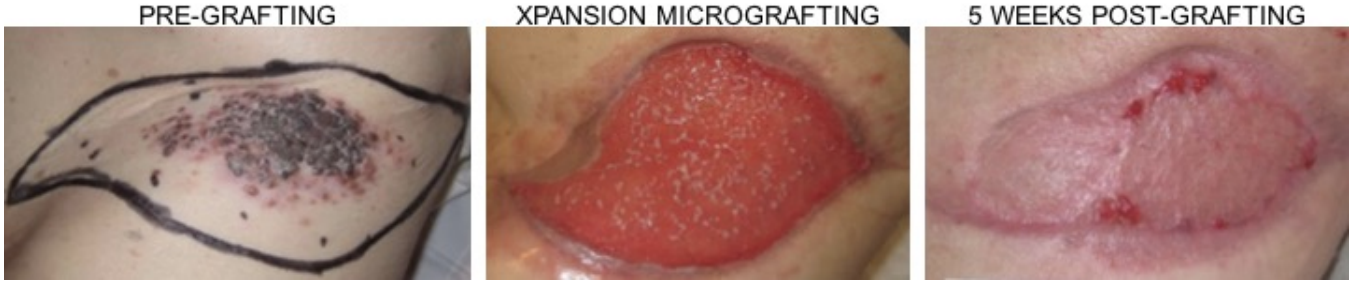

Figure 6. 20 cm x 20 cm excision was performed and the wound was grafted with micrografts using Xpansion kit. The micrografts took well and the wound started healing and was completely closed 5 weeks postoperatively.

Xpansion kit was used in the burns centre in Royal Brisbane and Women's hospital in Australia to treat a patient with a 90% TBSA who continued to have graft break downs and had a very little usable donor site skin areas (2017, unpublished). The Xpansion was used to harvest random small viable donor sites which were subsequently minced to micrografts and applied. Areas of patient's chest, right knee and leg were grafted with micrografts. The results demonstrated that areas grafted with micrografts healed better than areas grafted with 4:1 meshed STSGs (Figure 7). The micrografts took well and three weeks postoperatively they were not visible anymore. The surgeons found the Xpansion kit easy to use [13].

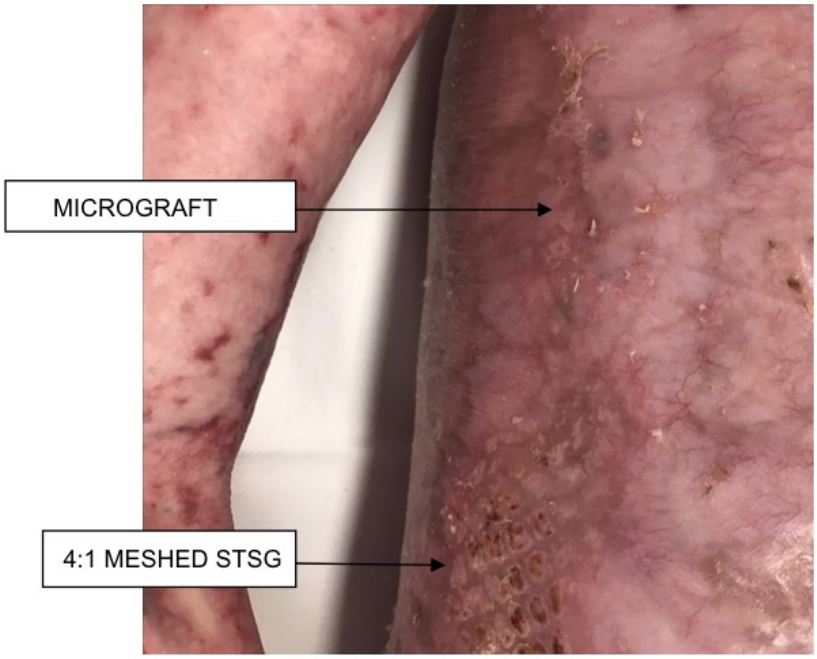

Figure 7. Areas of patient's chest were grafted with micrografts and meshed STSG. The results demonstrated that areas grafted with micrografts healed better and with a better aesthetic outcome than areas grafted with 4:1 meshed STSGs.

In St. Antonious hospital in Utrecth, Netherlands two patiens were treated with the Xpansion kit. The first patient was a 90-year-old male suffering from a lower leg pressure ulcer. Despite of conservative therapy the ulcer had failed to heal and had stayed open for 3 months. The wound was debrided, skin graft was harvested on the upper leg, minced to micrografts and applied on the wound. Subsequently, the wound was covered with a silicone gauze, Advacyn gel and foam. Dressings were changed on days 3, 6 and 9. On days 3 and 6 small signs of infection were observed but by day 9 the micrografts had taken and the wound had started re-epithelializing. By day 24 both the donor site and the pressure ulcer had completely healed. The second patient was a 92-year-old female suffering from a leg ulcer that had stayed open for 6 months. The ulcer was debrided, grafted with 0.8 mm x 0.8 mm micrografts and covered with silicone gauze, Advacyn gel and foam. Dressings were changed on days 3, 6, 9, 17 and 24. On day 17 both the donor site and the ulcer had almost re-epithelialized and by day 24 completely healed (Figure 8) [14].

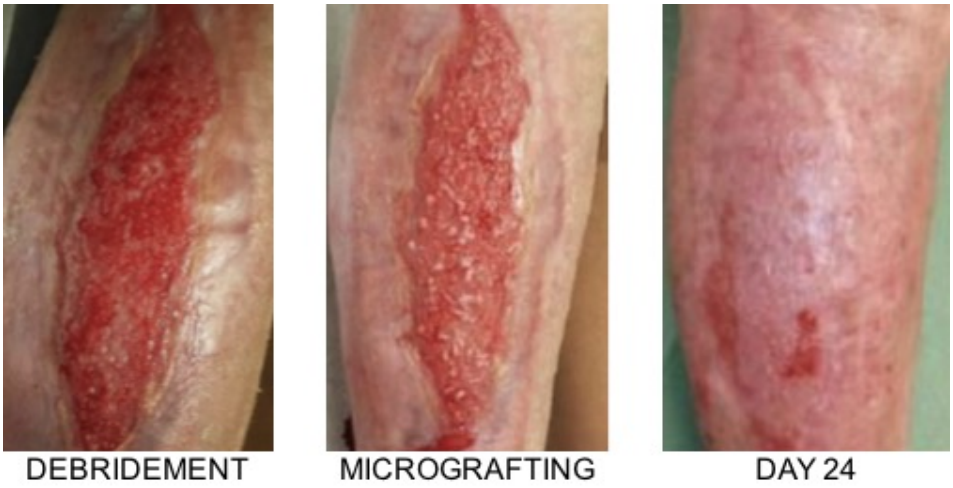

Figure 8. A 92-year-old female suffering from a leg ulcer that had stayed open for 6 months was treated with the Xpansion micro-autografting kit. The ulcer was debrided, grafted with 0.8 mm x 0.8 mm micrografts and covered with silicone gauze, Advacyn gel and foam. Dressings were changed on days 3, 6, 9, 17 and 24. On day 17 both the donor site and the ulcer had almost re-epithelialized and by day 24 completely healed.

Conclusions

The Xpansion micro-autografting kit provides a simple and straightforward method of creating split-thickness skin micrografts. Micrografts are evenly-sized minced skin particles, 0.8 mm x 0.8 mm in length that enables up to 100-fold expansion of a STSG. The kit allows the health care provider to harvest, mince, and apply micrografts to wounds and does not require an operating room or general anesthesia to complete the procedure. Multiple preclinical large animal studies as well as clinical cases have shown that split-thickness micrografts are the preferred closure method for challenging, hard-to-heal wounds, both acute and chronic.

References

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