

Gamma-irradiated human skin allograft: a potential treatment modality for lower extremity ulcers

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ABSTRACT

Gamma-irradiated human skin allograft consists of epidermis and dermis. Unlike bioengineered tissues which require cold storage and timely use once received from the manufacturer, gamma-irradiated human skin allograft can be stored for as long as 24 months at room temperature. This modality is applied in a fashion similar to that of bioengineered skin grafts. In this article, we present case studies with concise reviews of the available evidence to discuss the potential use of gamma-irradiated human skin allograft on wounds in the lower extremity.

Key words: Diabetes • Wound • Graft • Skin • Ulcer

INTRODUCTION

The evolution of skin grafts dates back thousands of years, with its history beginning in ancient India where Sanskrit texts document transplants performed by Hindi proto-surgeons in 3000–2500 BC. Ceramists of the Koomas cast performed reconstructive surgery on noses that were mutilated as disciplinary actions for crimes, such as theft and adultery (1).

Within the last 50 years, the use of skin grafts has become a popular method in

facilitating wound closure, especially in burn units. The most frequently utilised skin grafts include allografts, autografts and xenografts. An allograft is a graft from the same species, an autograft is obtained from oneself, and a xenograft is from a different species.

The 1800s saw the first reported utilisation of the allograft for wound care. This was demonstrated in sheep in 1803. In 1871, Pollock (2) notes the donation of a piece of his own skin for the treatment of one of his patients. These kinds of grafts became more routine when Brown (3) had successful results at their facility in St. Louis. This led to the use of skin grafts at Brooks Army Hospital for burn patients. Zaroff *et al.* (4) in 1966 reported a 10-year experience at this site listing wounds of multiple patients who benefited from allografts.

About the same time, Morris *et al.* (5) documented their outcomes. They found that chronic ulcerations that contained a high superficial bacterial burden could be reduced with the repeated use of an allograft. To test their hypothesis, they inoculated Guinea-pig

Key Points

- skin grafting dates back thousands of years
- it is only in the last 50 years however that skin grafting has become popular for wound closure
- allografts were popular in the early 1960s

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Key Points

- allografts and xenografts were popular as temporary dressings prior to autograft
- indeed they proved valuable in the preparation of the wound bed for autografting
- in spite of the availability of allografts many caregivers prefer to use fresh skin. This however has the draw back of potential virus transmission (e.g. HIV)
- gamma-irradiated skin grafts appear to reduce this risk

ulcers with *Staphylococcus aureus* and wiped the wound surface with saline. One group was treated with saline/vaseline gauze and the other was provided with an allograft with non adherent dressing. Surprisingly, they found that viable split-thickness skin allografts, when frequently changed, inhibited the rate of bacterial growth when compared with conventional dressings. Readiness for autografting became evident when the allograft was adherent to the wound bed. Another interesting phenomenon noted was the spontaneous epithelialisation from the wound margins.

Burleson *et al.* (6) studied the antibacterial effects of partial thickness wound dressings by measuring the superficial bacterial burden of inoculated rat ulcers. Four groups were assessed: no wound coverage, split-thickness autograft coverage, full-thickness porcine skin coverage and commercial porcine skin coverage. Bacterial colonies were measured prior to coverage, then every 2 days. Tissue bacterial colony counts were performed prior to coverage and on the 4th and 8th day when dressings were changed. They concluded that bacterial counts dropped 98% and ulcer sites were sterile in 50–78% of the experiments. Additionally, they measured wound temperature, pH and PO₂ with and without biological dressings. Results showed that wounds treated with biological dressings have a decrease in wound temperature and a slight increase in acidity. They felt that these minor changes in the surface biology of the wound bed aid in allowing the host's own immune system to sterilise the wound bed.

The advantages of allografts and xenografts as temporary and permanent dressings for wound defects have been addressed many times in the literature. Hackett *et al.* (7) in 1974 conducted a study of various ulcerations of the lower extremity and compared treatment between the two types of grafts until wound closure. They found that patients treated with allografts had shorter hospital stays and their wounds were better prepared for autografts. In 1984, Pruitt *et al.* (8) found that by covering the wound with allograft protected it from desiccation by decreasing amount of fluid loss. This protection of the wound by a biological dressing also prevented further contamination and injury of the newly developing capillary budding.

Their theory was that angiogenesis was promoted by allowing vascular in-growth to incorporate the dermal layer of the graft.

As with all healing wounds, there is the possibility of keloid scarring which has long been a complication in postsurgical and traumatic injuries, especially in dark skinned individuals. Keloid scars result when healing skin produces an excess amount of tissue that extends beyond the confines of the original wound. An increase in skin tension, particularly in young individuals where the rate of collagen synthesis is greater, may predispose certain wounds to develop keloid formation (9). While the exact cause is not known, it has been postulated that aberration of the metabolism of the melanocyte-stimulating hormone may be responsible for this prolific change. By utilising an allograft to facilitate wound closure, this process has been known to decrease keloid proliferation.

GAMMA-IRRADIATED SKIN GRAFTS

In spite of the multitude of allografts available today, which present well-documented benefits, many surgeons continue to remain skeptical. Purde *et al.* (10) conducted a survey to estimate the current use and levels of enthusiasm for allograft skin in the United States. They found that 69% of the burn-care centres preferred to use fresh skin; however, this was only available 47% of the time. Thus, by default, preserved allograft was utilised to compensate for the lack of fresh skin. The greatest concerns with the use of allograft in the past have been cost, rejection and disease transmission. There have been documented cases of viral hepatitis transmission and one case of human immunodeficiency virus (HIV) transmission; however, HIV was transmitted only because the donor had not undergone the full screening evaluation before the graft was applied. Since this isolated incident, there have been no other documented cases of such transmission (11). Other limitations of fresh allograft skin include the need for freezer storage conditions at 4°C and the limited effective shelf life of approximately 7–10 days.

Gamma-irradiated skin grafts appear to eliminate these factors making it a convenient, economically accessible product for the treatment of superficial lower extremity wounds. In the past, cadaveric skin was very hard to

obtain. Many of the donors could not be used because of the nature of their diseases resulting in the expiration of their bodies' tissues. The type of storage facilities required also presented an obstacle. Based on the plethora of past studies involving allograft, most authors recommend its use and find it an adjuvant to 'jump start' the wound bed granulation and epithelialisation (3,12,13). Xenografts from multiple species have been used clinically; however, the sterility is questionable. One of the most commonly utilised is the porcine cutaneous skin graft, but these have been found to be less effective in decreasing the bacterial load on the surface of the underlying wound bed.

The first irradiated cadaveric human skin allograft storable at room temperature is now available in limited quantities (GammaGraft, Promethean Health Sciences, Pittsburgh, PA, USA). It is stored in aluminium foil packaging and preserved in a penicillin/gentamycin solution, which contributes to the antimicrobial effect. This storage condition aids in preventing epidermal separation, which is common in cryopreserved allograft. Maintaining the epidermis in skin grafts allows for preservation of the underlying dermis. Without the epidermis intact, the underlying dermis will desiccate, rendering the graft less effective (14).

The process of radiating the skin has multiple advantages, serving as a preservative as well as a sterilising adjuvant. Gamma-irradiation coupled with extensive serological testing performed by skin banks insures safety (15–18). This, coupled with its simplistic application, handling and accessibility, yields a product that we have found very useful in the healing of lower extremity wounds. Gamma-irradiated human skin allograft is primarily used as a temporary dressing but can be left on until epithelialisation. It seems to decrease pain at the site of application and acts as a protective dressing due to its self-adhering qualities. Furthermore, as with other types of grafts, it decreases the amount of fluid and protein loss and decreases the bacterial burden that inhibits wound healing. The epidermal and dermal layers arguably make this superior to synthetic dressings and skin dressings that lack keratinocytes.

Application of gamma-irradiated human skin allograft is similar to that of bioengin-

ered tissues with the preparatory phase being rather less extensive. Fenestration of the graft allows for drainage and we have obtained better results in doing so. When applying the graft, it is best to grasp it at the edges with forceps. The graft is applied with the shiny dermis side down towards the wound and the dull epidermis side up. Care must be taken to not separate the epidermal layer, which may be detrimental to the underlying dermis and may result in graft failure. Once the graft has been applied, it must lay flat. To prevent mechanical removal of the graft when the dressing is changed, a non adherent dressing as well as a gauze dressing serves to protect the graft. Once again, care must be taken to reduce the amount of movement of the dressing so that the graft will not be sheared off.

After 24–48 hours with gamma-irradiated human skin allograft in place, the wound should be inspected to ensure adherence. If this has not occurred, or if there is fluid retention, then the graft should be removed with the dressing and the wound evaluated for possible infection or non viable debris. The wound should be thoroughly cleansed and debrided to a healthy granular wound bed. Once this is complete, a new piece of gamma-irradiated human skin allograft can be applied. While the graft may be stapled or sutured in place, we have generally not found this necessary. There have been documented cases of patients taking showers with the graft intact; however, we do not recommend this due to the nature of most lower extremity wounds.

CASE REPORTS

Case 1

A 66-year-old male with a chronic diabetic foot ulcer had stopped making progress while using conventional treatment modalities to the point of a 2 cm in diameter wound that was located on the medial aspect of the arch of the foot (Figure 1). Gamma-irradiated skin graft with Acticoat (Smith+Nephew, Largo, FL, USA), Allevyn (Smith+Nephew) and a dry sterile dressing consisting of gauze and coban was applied to the wound (Figure 2a). At week 1, the dressing was removed and it was observed that the graft was still intact. At week 2, the dressing was removed but the

Key Points

- the first irradiated cadaveric human skin allograft is now available in the USA
- the process of irradiating the skin has multiple advantages serving as both a preservative and a sterilising adjuvant
- application of gamma-irradiated human skin allograft is similar to that of bioengineered tissues with the preparatory phase being less extensive

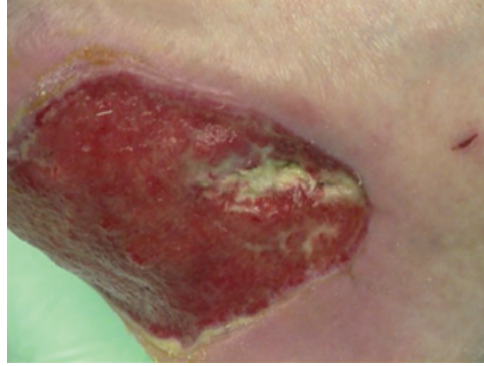


Figure 1. Initial ulceration.

Key Points

- case 1 is a chronic non healing diabetic foot ulcer with 2 pieces of gamma-irradiated skin being applied at 3 week intervals
- case 2 is a venous stasis ulcer with case 3 and 4 being chronic wounds on diabetic individuals
- all wounds were treated with gamma-irradiated skin in addition to dressings for bacterial and moisture balance. Adjunct therapies were applied as necessary dependent on underlying aetiology (e.g. compression or off-loading)

graft had sloughed. Despite the sloughing, the ulcer site decreased in size by half. A new piece of gamma-irradiated skin was applied and wound closure achieved within 3 weeks (Figure 2b).

Case 2

A 46-year-old male with a venous stasis ulcer on the lateral side of his leg had healed to the point of his wound measuring 5.2×2.9 cm after several months of wound vacuum-assisted closure therapy. Gamma-irradiated



Figure 2. (a) Reapplication of graft. (b) Ulcer at the end of 3 weeks with remnants of graft intact.

skin graft with Acticoat (Smith + Nephew) and a compression dressing consisting of an Unna boot and coban (3M, St Paul, MN, USA) was applied to the wound (Figure 3). Dressings were changed three times per week with the graft remaining in place for 2 weeks. At this time, it was noted that the size of the wound had decreased by one-half of its original size. Again, a new piece of gamma-irradiated skin was applied and evaluated on a biweekly basis. Unfortunately, this patient was lost to follow-up before complete healing of his wound.

Case 3

A 48-year-old male with a history of diabetes and chronic foot ulcerations on bilateral lower extremities was participating in a research study for a non healing venous stasis ulceration on his right leg. During his treatment, he developed two circular ulcerations on the medial aspect of his left leg. Once the wounds were freed of non viable tissue and thoroughly cleansed, gamma-irradiated human skin allograft skin graft was applied to both sites. The wounds were evaluated on a weekly basis. On the 4th week, the graft had sloughed and the wounds on the left lower extremity had completely healed.

Case 4

A 72-year-old male with a history of chronic renal failure and diabetes presented with non healing wounds after a limb salvage procedure was performed on his right foot (Figure 4a). The patient subsequently developed an ulceration on the medial aspect of the right first metatarsal head measuring 4.5×2.5 cm. Additional wounds on the right foot included a plantar wound under the second metatarsal



Figure 3. Application of gamma-irradiated skin graft to venous stasis ulceration.



Figure 4. (a) After therapeutic larvae application, prior to gamma-irradiated skin application. (b) Application of gamma-irradiated skin graft. (c) Complete epithelialisation after multiple applications of gamma-irradiated skin grafts.

head measuring 3.4×1.5 cm and a medial instep wound measuring 5.4×2.4 cm. Gamma-irradiated skin was applied at weekly intervals for 4 weeks. At the end of the 4-week period, the plantar second metatarsal wound and the medial arch wound had healed. Because of the structural deformity of the first ray, the patient underwent a corrective procedure, which eliminated the high pressure in this area and the ulceration subsequently closed (Figure 4b,c).

Case 5

An 82-year-old male with a history of multiple venous stasis ulcerations on the medial aspect of the right lower extremity presented with two ulcerations. The proximal ulceration was treated with gamma-irradiated skin graft for 4 weeks, at which time, the graft had sloughed and the ulceration had completely healed. The distal ulceration site remained open and was being treated with Unna boot applications. Finally, a gamma-irradiated skin graft was applied to the distal ulceration. Six weeks later, the ulceration had reduced to <0.2 mm in diameter. Compressive therapy was continued for the next month and closure of the wound was achieved.

DISCUSSION

At our institution, we have seen the most significant results in smaller wounds on the dorsal aspect of the foot and lower leg. This corresponds to common sense, as plantar foot wounds add an additional challenge due

to the possibility that the graft will shear off the wound during ambulation. Most patients will require multiple applications of this allograft over the course of several weeks. We have found that it is best to trim excess graft from the wound edges and keep the area covered with a silicone dressing (Mepitel, Molnycke, Sweden) or some other non-adherent gauze, such as Acticoat (Smith + Nephew). Within approximately 2 weeks, the wound margins begin to decrease in size and eventually the entire graft falls off, at which time, the wound should be approaching epithelialisation or can be precursor for an autograft. The graft may stay in place for as long as 6 weeks. If the wound is full-thickness, it may only stay in place for 1–2 weeks depending upon the amount of graft adherence. It is imperative that the wound bed be thoroughly cleansed and infection under control before the graft is applied. Wounds that are covered in necrotic tissue or fibrous film should be debrided to a healthy granular wound bed.

CONCLUSION

The use of preserved skin grafts to facilitate wound closure is not a new concept. In the last 50 years, cryogenically stored allografts have been used to prepare wounds before autografting or when the patient is not prepared to undergo harvesting of the autograph as has been documented in burn patients. We have found gamma-irradiated allograft readily accessible and efficacious for use on difficult

Key Points

- case 5 was an additional patient with venous stasis ulceration
- the most significant results were observed in smaller wounds on the dorsal aspect of the foot and lower leg
- plantar wounds are more difficult as grafts can shear off during ambulation
- we have found gamma-irradiated allograft readily accessible and efficacious for use on difficult wounds

Key Points

- the cost of gamma-irradiated human skin allograft may be lower when compared to traditionally cryogenically preserved skin grafts
- we feel this modality adds yet another tool in the clinician's armamentarium

wounds. This seems to decrease patient's hospital stay by providing wound closure, as well as, a decrease in pain and rate of recurrent infections. The cost of gamma-irradiated human skin allograft may be lower when compared to traditional cryogenically preserved skin grafts. According to Purde *et al.* (10), the gold standard for temporary coverage of excised burn wounds against which other temporary coverings are judged is fresh or cryopreserved human cadaveric allograft. While there is no evidence yet to support a gold standard for lower extremity wounds, we feel that this modality adds yet another tool in the clinician's armamentarium.

REFERENCES

- 1 Herman AR. The history of skin grafts. *J Drug Dermatol* 2002;3:298-301.
- 2 Pollock GD. Cases of skin grafting and skin transplantation. *Trans Clin Soc Lond* 1871;4:37.
- 3 Spence RJ, Wong L. The enhancement of wound healing with human skin allograft. *Wound Healing* 1997;77(3):731-45.
- 4 Zaroff LI *et al.* Multiple uses viable cutaneous homografts burned patient. *Surgery* 1966;59:368.
- 5 Morris JP, Bondoc C, Burke JF. The use of frequently changed skin allografts to promote healing in the nonhealing infected ulcer. *Surgery* 1966;60(1):13-9.
- 6 Burleson R, Eiseman B. Mechanism of antibacterial effect of biological dressing. *Ann Surg* 1973;177:181.
- 7 Hackett M, Bowen J. Preliminary report on the conservative use of lyophilized homograft and xenograft in the closure of raw areas. *Br J Surg* 1974;61(6):427-9.
- 8 Pruitt BA, Levin NS. Characteristics and uses of biological dressings and skin substitute. *Arch Surg* 1984;119:312.
- 9 Rockwell WB, Cohen IK, Ehrlich HP. Keloids and hypertrophic scars: a comprehensive review. *Plast Reconstr Surg* 1989;84:827.
- 10 Purde GF *et al.* A multiple center clinical trial of biosynthetic skin replacement, dermagraft, compared with cryopreserved human cadaveric skin for temperature coverage of excised burn wounds. *J Burn Care Rehabil* 1997;18(1):52-7.
- 11 Clarke JA. HIV transmission and skin grafts. *Lancet* 1987;1:983.
- 12 Falanga V *et al.* Rapid healing of venous ulcers and lack of clinical rejection with an allogenic cultured human skin equivalent. *Arch Dermatol* 1998;134:293-300.
- 13 Snyder RJ, Simonson DA. Cadaveric allograft as adjunctive therapy for nonhealing ulcers. *J Foot Ankle Surg* 1999;38(2):93-101.
- 14 Promethean Life Sciences, INC.
- 15 American Red Cross Tissue Bank, Accredited by the American Association of Tissue Banks.
- 16 Eade GG. Relationship between granulation tissue bacterium and skin grafts in burned patients. *Plast Reconstr Surg* 1958;22:42.
- 17 Wood WB Jr. Phagocytosis with particular reference to encapsulated bacteria. *Bacteriol Rev* 1960;24:41-9.
- 18 Hussmann J *et al.* The use of glycerolized human allograft as temporary and permanent covers in adults and children. *Burns* 1994;20(1):s61-6.