Resident's Page

Skin substitutes in dermatology

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INTRODUCTION

Skin substitutes are a heterogeneous group of biological and/or synthetic elements that facilitate wound closure and replace the functions of skin, either temporarily or permanently.[1] The history of skin substitutes dates back to as early as 1500 BC when xenografts were used for wound coverage.[2] Xenografts gave way to homografts such as cadaveric skin, amnion, and autografts. Newer technologies paved the way for bioengineered skin substitutes.[1,2]

No perfect or ideal skin substitute exists. An ideal skin substitute is non-toxic, immunologically compatible, has low antigenicity, and does not transmit disease. The skin substitutes function to minimize the loss of water, electrolytes, and protein, reduce bacterial load provide coverage of tendons, nerves, and vessels thus preventing desiccation, decrease pain, restore function, and facilitate early movement.[3]

Skin substitutes can be classified into three types [Table 1] according to:

A. Skin layer to be replaced: Subdivided into epidermal, dermal, dermal–epidermal composites
B. Durability: Temporary and permanent
C. Origin of grafting material: Biologic – those generated from biologic materials such as animal or human tissue (allogenic, autogenic, or xenogenic); synthetic – produced in the laboratory; biosynthetic – combination of synthetic and biologic elements.[4,5]

Several skin substitutes are currently available for a variety of applications. Naturally occurring or biological materials like amnion, cadaveric skin allograft and porcine skin xenografts are used worldwide as temporary skin substitutes.[2] Alloderm, TransCyte, Kollagen, and NeuSkin are some of the commercially available products in India. The choice of a suitable substitute for each clinical application depends upon their advantages and disadvantages.

A. CLINICAL APPLICATIONS

Burns

Skin substitutes can play a major role in the treatment of burns as they aid in restoration of cutaneous continuity.[1] Various types of skin substitutes have been studied and proven to be useful in the management of partial and full thickness burns.[6,7] They are effective, improve wound healing, and decrease the duration of hospitalization.[6,8-12]

Ulcers resistant to conventional healing

The healing success of any chronic wound depends essentially on its wound bed.[13] Skin substitutes not only provide a covering for the ulcer, but also actively participate in the healing process by stimulating angiogenesis and reepithelialisation.[14] Numerous randomized controlled studies have assessed the efficacy of various skin substitutes and have been proven to improve wound healing in venous ulcers, diabetic foot ulcers and pressure ulcers.[15-20]

In a large multicentre randomized study, a composite graft (Apligraf) was found to be significantly better in healing large venous ulcers of more than one year duration than compression therapy alone.[15] Marston *et al*. in a large multicenter randomized controlled prospective study found that wounds treated with a dermal allogenic graft (Dermagraft)

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Table 1: Skin substitute categories, select examples of commercially available products and their characteristics[1,4,5]

Type of skin substitute	Suggested mode of action	Examples (commercial names)	Composition	Advantages	Disadvantages
Epidermal, Allogenic	Grafted keratinocytes from donor skin stimulate host growth factors and promote wound healing	Celaderm	Keratinocyte sheets from foreskin	Readily available, no biopsy needed	Temporary, superficial coverage, poor aesthetic result
Epidermal, autologous	Cultured keratinocytes from patient's own skin transplanted onto the wound bed multiply and re-epithelialise	Epicel	Cultured keratinocytes on petrolatum gauze	High rate of graft take, little or no rejection, wide and permanent coverage	Fragile, poor cosmesis, time consuming, high production cost
		Laser skin	Cultured keratinocytes on a matrix of hyaluronic acid ester		
Dermal, xenogenic	The matrix provides structural support for growth of new tissue and vasculature. Proteins promote wound healing	Biobrane	Porcine collagen on silicone/ nylon mesh	Ready availability, minimal exudate formation, less wound pain	Possible bovine allergy, may need multiple applications, higher infection rates
		Integra	Bovine tendon collagen and shark chondroitin on silicone membrane		
		Oasis	Porcine intestinal collagen and extracellular matrix		
		Permacol	Porcine dermis		
Dermal, allogenic	Act as scaffold for cellular and vascular growth into the wound bed and allow secondary tissue regeneration. Proteins of the extracellular matrix stimulate wound healing	Alloderm	Human cadaveric decellularised dermis	Immunologically inert, immediately available, easy to remove, low pain	Risk of transmission of human pathogens, need multiple applications
		TransCyte	Neonatal fibroblasts grown on nylon mesh		
		Dermagraft	Neonatal fibroblasts grown on bioabsorbable polygalactin mesh		
		FlexHD	Human cadaveric dermis		
Composite	Combination of bovine and human elements provides near normal skin architecture and improves wound healing	Apligraf	Bovine collagen, allogenic human keratinocytes and fibroblasts	Readily available, favorable cosmetic results	Risk of rejection, low infection risk
		Gammagraft	Human skin allograft		
		Mediskin	Porcine xenograft		
		Orcel	Allogenic human fibroblasts and keratinocytes on bovine collagen matrix		

healed significantly faster than conventionally treated wounds.[17] In a study on 23 patients, Brem *et al*. found that 13 of the 21 pressure ulcers treated with a composite graft (Apligraf) healed in a mean time of 29 days.[20]

Cutaneous repair following surgery for skin cancer

Many studies report the usefulness of skin substitutes in repair of wounds following excision of cutaneous malignancies.[21,22]

Dermatologic conditions

Pyoderma gangrenosum

The etiology of the condition is still unclear. Conventional treatment includes corticosteroids and immunosuppressants. Treatment with cultured human skin equivalent (Graftskin) in a 26-year-old female showed 30–40% wound closure rate in the first 2 weeks, with complete reepithelialisation at the end of 6 weeks.[23] There have also been case reports with other skin substitutes, showing favorable responses in pyoderma gangrenosum.[24-28] However, controlled studies are required to confirm these observations.

Vitiligo

Vitiligo is a common depigmenting disorder with limited therapeutic possibilities. Therapeutic use of cultured epidermis and melanocytes has been promising in the treatment of vitiligo.[29] Andreassi *et al*. grafted autologous keratinocyte cultures in 11 vitiligo patients and demonstrated progressive improvement in the condition at 3, 6, 12, and 18 months achieving 90–100% repigmentation in 6 of them.[30] Other researchers have used melanocyte cultures with satisfactory results.[31,32]

Other skin disorders

Skin substitutes have also been applied successfully in healing of wounds in cases of epidermolysis bullosa,[33] aplasia cutis,[34] harlequin ichthyosis,[35]

ulcerative sarcoidosis,[36] necrobiosis lipoidica,[37] and bullous morphea.[38]

B. LABORATORY APPLICATIONS

Tissue engineered skin has been found useful in research studies involving various skin diseases. Reconstructed skin models have augmented research analysis involving the cellular and immunological elements of psoriasis, the study of skin pigmentation, skin melanoma, wound healing and allergens with greater flexibility, increased convenience, good reproducibility, and reduced costs.[39-42] Genetic modification of cultured skin grafts can act as vehicles for cutaneous gene therapy in conditions such as epidermolysis bullosa[43] and Netherton syndrome.[44]

CHALLENGES

Despite the favorable results, skin substitutes cannot replace all the native functions of skin as the currently available ones contain at most only two skin components, thus influencing engraftment, aesthetic, and functional outcome. Wound bed preparation is a major challenge in case of skin substitutes requiring revascularization. Inadequate angiogenesis can lead to rejection of the skin substitute. It is also most vulnerable to infection at this stage. Hypopigmentation or uneven distribution of pigmentation may occur, either due to the absence of melanocytes or melanocyte retention. Compared with normal skin tissue, scars that develop at the margins of skin substitutes are less resistant to mechanical tension and have poorer function and aesthetic qualities. Transmission of infection is a major concern involving skin substitutes though meticulous precautions are taken during all stages of their preparation.[13,45]

CONCLUSION

The development of a multitude of skin substitutes has expanded the options for dermatologic surgeons when treating complex wounds. Familiarity with their components, uses, strengths, and disadvantages could facilitate the appropriate use of these products for dermatologic conditions.

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