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Burn injury: Challenges and advances in burn wound healing, infection, pain and scarring

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ABSTRACT

Severe burn injuries are the most traumatic and physically debilitating injuries affecting nearly every organ system and leading to significant morbidity and mortality. Early burn wound excision and skin grafting are common clinical practices that have significantly improved the outcomes for severe burn injured patients by reducing mortality rate and days of hospital stay. However, slow wound healing, infection, pain, and hypertrophic scarring continue to remain a major challenge in burn research and management. In the present article, we review and discuss issues in the current treatment of burn injuries; the advances and novel strategies developed in the past decade that have improved burn management; and also, pioneer ideas and studies in burn research which aims to enhance burn wound care with a focus on burn wound infection, pain management, treatments for scarring and skin tissue engineering.

1. Introduction

Severe burn injuries are the most traumatic and physically debilitating injuries affecting nearly every organ system and leading to significant morbidity and mortality. In Australia, over 10,000 people are hospitalised each year because of severe burn or scald injuries. According to the World Health Organisation (WHO), 180,000 deaths annually are related to burn injury and in 2004, nearly 11 million people worldwide were severely burned and required medical treatment [1]. Both small burn and large severe burn injuries initiate the wound healing process which consists of several highly integrated and overlapping phases: inflammation, cell recruitment, matrix deposition, epithelialization and tissue remodelling. In additional to local wound repair, severe large burns also stimulate a persistent pathophysiological stress response and a systemic hypermetabolic-catabolic condition. These pathophysiological changes have great effects on the pharmacokinetics and pharmacodynamics of drug use in the treatment of severe burn injuries. Early burn wound excision and skin grafting are common clinical practices that have significantly improved the outcomes for severe burn patients by reducing mortality rate and days of hospital stay [2]. However, slow wound healing, infection, pain, and hypertrophic scarring continue to remain as major challenges in burn management and research. In the present article, we discuss the challenges, advances and novel strategies in burn management and research with a focus on burn wound infection, pain management, treatments of scarring and skin tissue engineering.

Abbreviations: WHO, World Health Organisation; TBSA, Total body surface area; NIKS, Near-diploid Immortalised Keratinocyte S; NPWT, Negative pressure wound therapy; NPWTi, Negative pressure wound therapy instillation; NPWTci, Negative pressure wound therapy continuous instillation; MDR, Multi-drug resistant; MRSA, Methacillin resistant staphylococcus aureus; VRE, Vancomycin resistant enterococci; ESBL, Extended-spectrum beta-lactamases; VISA, Vancomycin intermediate susceptible staphylococcus aureus; EPE, Enhanced permeability and retention effect; PK, Pharmacokinetics; PD, Pharmacodynamics; IV, Intravenous; IV-PCA, Intravenous patient-controlled analgesia; TRP, Transient receptor potential; TRPV1, Transient receptor potential vanilloid-1; KO, knockout; Na_v, Voltage gated sodium channels; MSCs, Mesenchymal stem cells; ADSCs, Adipose derived stem cells; TLRs, Toll-like receptors; TGFβ1, Transforming growth factor-beta1; MMPs, Matrix metalloproteinases; VEGF, Vascular endothelial growth factor; IL-6, Interleukin-6; ECM, Extracellular matrix; PDL, Pulsed dye lasers; Nd:YAG, Neodymium-doped yttrium-aluminium-garnet; NAFL, Non-ablative fractional lasers; AFL, Ablative fractional lasers; PCL, Poly (ε-caprolactone); PU, Polyurethane; PGA, Poly (glycolic acid); PLLA, Poly (L-lactide); 3D, 3-Dimensional; CAD, Computer-aided design; PLA, Poly (lactic acid); PLGA, Poly (lactide-*co*-glycolide).

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2. Clinical practice in the treatment of burn injury

2.1. Skin grafting

When burns or scald injuries are deep partial-thickness in the dermis or completely destroy all skin layers, wounds cannot be closed by

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the primary healing process or by suturing [3], rather additional surgical procedures are required. The gold-standard treatment for partial- and full-thickness burn injuries is early excision of necrotic tissue followed by autologous skin grafting (Fig. 1). Skin grafting involves the transplantation of healthy skin from an undamaged donor site of the patient to the wound site. Autologous skin grafts can be full thickness, consisting of epidermis and dermis, or split-thickness, consisting of the epidermis and upper part of the dermis. Unfortunately, in practice, donor skin is extremely limited for patients with severe burn injury >50% total body surface area (TBSA) [4,5]. This problem can be overcome by repeated harvesting of the donor sites over a period of time. However, healing of donor sites can be slow with additional scarring and possible pigmentation disorder [6,7]. While autografts can be meshed to increase the available surface area of the graft up to four times, the meshing process compromises the quality of the original graft and the recipient area heals with an irregular meshed pattern [8] and can result in severe scarring [9].

2.2. Skin substitutes

Skin substitutes could protect large burn wounds when donor skin is limited, to enhance wound healing, increase the dermal component of healed wound, reduce inflammatory responses and subsequent scarring [10–13]. Since 2000, over 30 new skin substitutes have been tested or used in the treatment of burn injuries (Table 1). Skin substitutes can be categorized into biological substitutes, synthetic substitutes or a combination of both. Biological substitutes can be further categorized into 1) natural scaffolds such as Alloderm, an intact, de-cellurised and dermal human matrix, 2) constructed scaffolds such as Integra, composed of lyophilized collagen, supplemented and cross-linked, or 3) cultured scaffolds, such as cultured epithelial graft, autologous cultured fibroblasts and keratinocytes. Biological skin substitutes have components that resemble natural skin, yet these skin substitutes are relatively simple compared to the complexities of human skin. The majority of skin substitutes available for clinical practice contain allogenic biological products, and the risk of disease transmission poses as a limitation particularly for natural biological skin substitutes. Despite extensive and strict sterilization procedures, current methods are insufficient to certify biological skin substitutes to be free of any unknown diseases or prion diseases from animal material, such as Creutzefled-Jakob disease [14]. Furthermore, there is evidence to suggest that allogeneic skin is highly immunogenic and that cellular remnants in the extracellular matrices (ECM) may be responsible for reduced skin graft take or even rejection [9]. Human derived allogenic skin is further limited by its supply. Autologous biomaterials have the advantage of culturing cells for a large surface area from a small skin biopsy, however culturing cells is time consuming and may comprise wound healing [15,16].

In contrast to biological substitutes, synthetic substitutes are free from any risk of disease transmission. However, only a few synthetic skin substitutes are on the market today. Although synthetic materials have greater structural integrity compared to natural products, its poor bioactivity remains a major concern [17]. In addition, poor host response may lead to negative effects on scar quality. Despite limitations in materials and cost, the development of bio-engineered skin is increasing due to innovative possibilities with new techniques and biomaterials, providing a glimpse into a promising future. These steps have promoted a shift in focus from traditional surgical interventions to skin tissue-engineered regeneration.

2.3. Wound dressings

Wound dressings are developed for wound coverage to aid re-epithelialization, prevent wound infection, skin desiccation, and further skin damage. Wound dressings can be categorized into four groups: biological dressings; conventional dressings; biosynthetic dressings and antimicrobial dressings. Biological dressings include cadaver allograft skin (transplantation between individuals of the same species), xenograft (transplantation between individuals of different species) and human amnion, which have been adopted to temporarily cover wounds for reepithelization. Although biological dressings are effective in terms of improving the quality of wounds for further skin grafting, they cannot be used as a permanent skin replacement due to immunological disparities [8]. Furthermore, many issues are associated with biological dressings, such as inconsistent quality, limited supply, and the risk of pathogen transfer [44]. Conventional dressings which do not contain antibiotics or medications, e.g. Vaseline gauze or silicone sheets are also widely used to temporarily cover wounds during reepithelialisation. However, these dressing tend to adhere to the

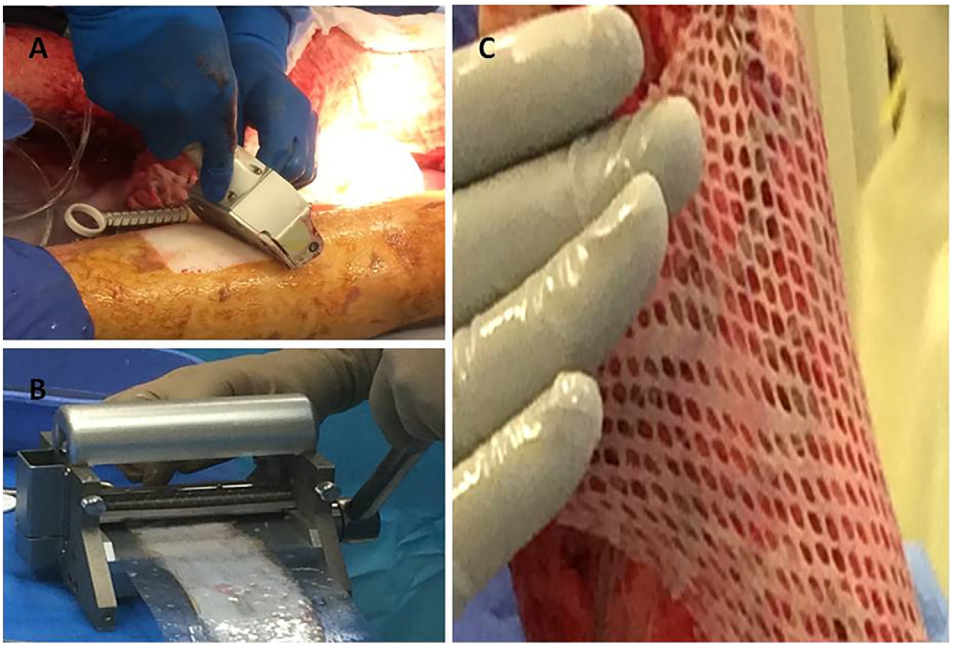

Fig. 1. Autologous skin grafting: (A) partial-thickness skin graft taken from the healthy donor site. (B) Skin graft is meshed to increase the surface area (C) Application of skin graft on the wound bed.

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