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A preliminary investigation of the reinnervation and return of sensory function in burn patients treated with INTEGRA®

James R. Anderson [a,b], Mark W. Fear [a,c,*], Jacqueline K. Phillips [d], Linda F. Dawson [e], Hilary Wallace [f], Fiona M. Wood [a,f,g,h], Suzanne M. Rea [f,g,h,1]

[a] The McComb Foundation, Royal Perth Hospital, Perth, WA, Australia
[b] Faculty of Medicine, Dentistry and Health Sciences, University of Western Australia, Australia
[c] School of Medicine, University of Notre Dame Australia, Fremantle, WA, Australia
[d] The Australian School of Advanced Medicine, Faculty of Human Science, Macquarie University, NSW, Australia
[e] Faculty of Health Science, Murdoch University, Perth, WA, Australia
[f] Burn Injury Research Unit, School of Surgery, University of Western Australia, Australia
[g] Royal Perth Hospital, Perth, WA, Australia
[h] Princess Margaret Hospital, Perth, WA, Australia

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ABSTRACT

Background: Loss of sensory function in scar after burn is common, although the basis for this loss is not clear. Additionally, little is known about the effects of different treatment modalities on sensory function and neuroanatomical outcomes in burn patients. Here, we investigated the effects of the use of the INTEGRA® dermal scaffold on neuroanatomy and sensory function in acute burn patients.

Hypothesis and objectives: We hypothesized that the use of artificial dermal templates would inhibit or reduce reinnervation after excision, since regrowth of nerves requires complex molecular interactions. Therefore the primary objective of this study was to identify whether there is regrowth of nerve fibres in the INTEGRA® dermal scaffold. The secondary objective was to identify whether the INTEGRA® dermal scaffold reduced nerve regrowth or limited sensory function outcomes in acute burn patients.

Methods: Five patients treated with INTEGRA®, cultured epithelial autograft spray (prepared using ReCell® (CEA)) and split skin graft (SSG) were assessed for sensory function in scar and uninjured contralateral control skin. Neuroanatomy of scar and control sites was assessed using immunohistochemistry for PGP9.5, CGRP and substance P neuronal markers. Nerve density and sensory function was also assessed in a comparative group ($n = 8$) treated with CEA and SSG only.

Results: Neuroanatomy was not significantly different in the INTEGRA® patients when compared to the CEA/SSG group only. The patients treated with INTEGRA® had worse sensory function than those with CEA/SSG only.

Conclusions: Peripheral nerves do reinnervate the INTEGRA® dermal scaffold. There is no statistically significant reduction in reinnervation observed when compared to a control group. It is possible that the use of artificial dermal constructs, while permissive for nerve

* *Corresponding author at*: The McComb Foundation, Telstra Burns Outcome Centre, Royal Perth Hospital, Wellington Street, Perth, WA 6000, Australia. Tel.: +61 411 355 944.
E-mail address: mark@mccomb.org.au (M.W. Fear).
[1] Address: Burn Injury Research Unit, M318, University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia. Tel.: +61 8 6488 8133.
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regrowth, limit functionality when compared to nerves that regrow through dermal tissue. Further research to understand the causes of this, and into enhancing reinnervation in dermal scaffolds may improve sensory outcome in the most severely burned patients.

1. Introduction

Cutaneous innervation is critical for sensory function and to provide the ability to respond to environmental stimuli. Burn results in direct damage to the cutaneous nerves, which require regrowth during the healing process to regain sensory function. The initial loss of nerve fibres appears to be followed by an increase above normal fibre density in the healing wound, but ultimately leads to a long-term reduction in nerve fibres in the resulting healed tissue compared to skin from non-injured individuals [1–8]. In some cases, it has also been reported that this reduction is specific to the healed site [3–5], while other reports suggest the reduction in innervation is systemic [6,7]. Sensory function in scar tissue has been reported to be reduced when compared with matched control sites in multiple studies looking at touch threshold, sharp touch sensitivity and responses to other stimuli [3–8]. In some cases, this appears to be associated with a decrease in nerve fibre density in the scar tissue [3–5] whereas other studies suggest the relationship between nerve density and sensory function is not so straightforward [6–8].

INTEGRA® (Integra Life Sciences, Plainsboro, NJ, USA) is a dermal regeneration scaffold consisting of bovine collagen and chondriotin-6-sulfate which has been used following large burns where the availability of autologous skin grafts is limited. The dermal template has been shown to provide a scaffold for the proliferation and spread of fibroblasts and endothelial cells [9]. A more recent study has identified vascularisation as well as sensory abnormalities such as itch in reconstructive cases [10]. In addition, no adnexal structures, elastic fibres or nerve endings in INTEGRA® treated patients were identified after 18 months post-reconstructive surgery in this study of 25 patients and 30 anatomical sites [10]. Given the possible implications of a complete lack of reinnervation in patients treated with INTEGRA®, and the paucity of data in the literature, particularly with respect to burn treatment, we investigated neuroanatomy and sensory function in acute burn injury patients treated with INTEGRA®, SSG and CEA. We compared the results to a similar group treated with CEA and SSG only. Nerve density in both scar and uninjured control tissue was assessed using immunohistochemistry and antibodies for Protein gene product 9.5 (PGP9.5, pan-neuronal marker) [11] as well as calcitonin gene related peptide (CGRP) and Substance P immunohistochemistry to detect unmyelinated C fibres associated with neuroinflammation and nociception [12,13]. Sensory function was determined using 2-point discrimination, light touch and sharp touch sensory tests, as previously described [6].

2. Materials and methods

This study was carried out in accordance with the NHMRC regulations regarding human research and was approved by the Royal Perth Hospital Ethics Committee.

2.1. Recruitment

Five adult patients were recruited who had sustained an upper or lower limb thermal burn which was successfully surgically treated with INTEGRA® dermal scaffold, CEA and SSG at least 24 months prior to recruitment (range: 30–115 months). The size of injury ranged from 20 to 85% total body surface area (%TBSA). For comparison, 8 additional patients that were treated with CEA and SSG only were also recruited. All subjects were required to have had a full-thickness burn, and also an area of uninjured 'control' skin that was site-matched to the injured site to be studied. Patients with failed graft'take', a chemical burn injury, documented neurological condition or whose injuries were the result of self harm were excluded.

2.2. Treatment of burns

2.2.1. CEA + SSG only

CEA + SSG only was used on full-thickness acute burns when sufficient donor sites were available. The CEA and meshed SSG were applied simultaneously to fascia, as previously described [14].

2.2.2. INTEGRA + CEA + SSG

Briefly, INTEGRA was used in all cases for primary grafting after acute burn injury. INTEGRA was placed on fascia after full thickness excision. Meshed SSG + CEA was applied simultaneously to these wounds in a second procedure, with the use of CEA to facilitate epidermal closure. These procedures have been previously described [14].

The use of CEA + SSG only or INTEGRA + CEA + SSG was determined by TBSA. All burns were of the same depth.

2.3. Examination sites

For the INTEGRA® treated patients, scar test sites were selected which had available uninjured control sites on a contralateral side (1 patient). If this was not possible an uninjured site adjacent to the burn was chosen for the control (4 patients). For the CEA + SSG treated group (control), uninjured contralateral control sites were used for 5 patients, with uninjured adjacent sites used for 3 patients. The scar site selected was typical of the overall scarring of that area as assessed using the Vancouver scar rating scale (VSS [16]). The