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Artificial dermal templates: A comparative study of NovoSorb™ Biodegradable Temporising Matrix (BTM) and Integra® Dermal Regeneration Template (DRT)

Perdita A. Cheshire [a,b,*], *Marisa R. Herson* [a,b], *Heather Cleland* [a,b], *Shiva Akbarzadeh* [a,b]

[a] *Skin Culture Laboratory, Victorian Adult Burns Service, The Alfred, Commercial Road, Melbourne, Victoria, Australia*
[b] *Department of Surgery, Monash University, Commercial Road, Melbourne, Victoria, Australia*

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ABSTRACT

Background: Artificial dermal templates play an important role in physiologic wound closure after injury. In addition to contributing to stable, durable and flexible wound closure, they provide a scaffold for tissue repair. Several dermal templates are commercially available, with animal-derived Integra® dermal regeneration template perhaps the most widely used. NovoSorb™ Biodegradable Temporising Matrix (BTM) is a fully synthetic alternative that eliminates any risk of cross-species residual antigenicity. In this study, we aimed to compare early response after application of NovoSorb™ BTM with Integra® in terms of temporary wound closure, host cell infiltration, neovascularisation and collagen deposition in a mouse model.

Methods: Twenty athymic nude mice received full-thickness skin excision followed by grafting of the dermal template ($n = 10$ NovoSorb™ BTM, $n = 10$ Integra®), with the grafts excised and assessed after two weeks.

Results: All twenty mice achieved temporary wound closure with no evidence of wound contracture. Microscopically, all twenty grafts became infiltrated with host cells along the entire length of the template, with NovoSorb™ BTM demonstrating a particular abundance of host inflammatory cells. Evidence of new collagen deposition and neovascularisation was observed in both templates, with NovoSorb™ BTM demonstrating a more extensive vascular network at this time point. However, a greater inflammatory response was also observed in the NovoSorb™ BTM grafts at this time point.

Conclusions: In this study, NovoSorb™ BTM demonstrates favourable properties as a dermal template, but further investigation is required to assess the significance of the differing inflammatory and vascular response to its implantation compared with Integra®.

* *Corresponding author at*: Skin Culture Laboratory, Victorian Adult Burns Service, The Alfred, Commercial Road, Melbourne, Victoria, Australia.
E-mail addresses: perdita.cheshire@monash.edu (P.A. Cheshire), Shiva.Akbarzadeh@monash.edu (S. Akbarzadeh).
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1. Introduction

Dermal templates are widely used for wound reconstruction, particularly after deep burns when split thickness skin grafts alone are insufficient for effective tissue reconstruction. Dermal substitutes allow for reconstruction of the dermis by providing a scaffold that promotes new tissue in growth, and when combined with a temporary impermeable seal, enable immediate (albeit temporary) wound closure, slow fluid loss and create a physical barrier to external pathogens [1]. In the long term, dermal templates may be associated with improved functional and cosmetic outcomes, including reduced scar formation [1,2]. Dermal templates can be broadly categorised as decellularised dermis derived from human or animal sources, or artificially constructed scaffolds comprised of highly purified biomaterial or entirely synthetic polymers.

Integra® (Life Sciences Corp., New Jersey, US) is perhaps the best-established artificial dermal template and is approved for use in full-thickness or deep partial thickness burns as well as reconstruction of scar contractures. Integra® consists of a matrix of purified collagen from bovine tendon crosslinked with glycosaminoglycan obtained from shark cartilage, and may be supplied with a removable silicone layer that functions as a temporary epidermis. There is considerable evidence to support its use clinically [3–10] and evidence from multiple animal models has demonstrated its ability to facilitate host cell infiltration, neovascularisation and deposition of endogenous collagen [11–15]. Ultimately, these processes lead to the biodegradation of the Integra® matrix and the formation of neodermis in its place. Definitive wound healing is achieved by re-epithelisation and vascularisation of this neodermis.

NovoSorb™ Biodegradable Temporising Matrix (BTM; PolyNovo Ltd, Port Melbourne, Victoria, Australia) is a fully synthetic dermal template in the form of a biodegradable polyurethane foam with a temporary non-biodegradable polyurethane seal [16,17]. This novel synthetic polymer is inexpensive to produce and avoids the risk of cross-species immune rejection or disease transmission, as well as circumventing ethical and cultural objections to using animal-derived products [1]. Proof-of-concept studies have determined its safety and ability to provide permanent wound closure when combined with a split thickness skin graft in a two-stage procedure in sheep, pigs and humans [17–21].

This study was designed to assess wound closure, host cell infiltration, neovascularisation and collagen deposition in Novosorb™ BTM in full thickness wounds in an athymic mouse model. A second cohort of mice was grafted with Integra® for comparison in parallel. The aim of the study was to determine whether this fully synthetic polymer performed comparably in the early after application phase to the current widely used animal-derived alternative dermal template.

2. Methods

2.1. Surgical protocol

This project was granted ethical approval from the Alfred Medical Research and Education Precinct Animal Ethics Committee (approval E/1482/2014/A). Male athymic nude mice aged 10–12 weeks were anaesthetised with isoflurane (2 L/min) and a full-thickness surgical wound created by excising a circular section of skin 1.2 cm in diameter, approximately 1 cm below the occipital protuberance and several millimetres to the left of the midline. Mice were grafted with either polyurethane-sealed NovoSorb™ BTM ($n = 10$) or bilayered (silicone-sealed) Integra® ($n = 10$). The dermal templates were cut to size and soaked in sterile phosphate-buffered saline (PBS) for 30 min prior to application to the wound bed, ensuring the template edges aligned with the excised wound margin. A non-absorbent but porous wound dressing (SurfaSoft®) was applied over the graft to allow air exchange and fluid drainage but prevent adherence of bandaging to the graft itself, followed by sterile gauze on top to provide wound pressure and absorb any exudate from the wound. An adhesive, waterproof dressing (Tegaderm™) was applied to cover and protect the graft, and a self-adherent bandage (Coban™) was applied to hold the bandaging in place for the duration of the experiment. Mice received an intraperitoneal injection of analgesia (3 mg paracetamol) under anaesthesia followed by *ad libitum* analgesia (added to their food) for the next four days. Mice were monitored daily for signs of wound infection including the presence of excessive exudate, an aversion to handling, sustained weight loss or general inactivity.

2.2. Graft excision and histology

Two weeks after skin grafting, mice were euthanized *via* carbon dioxide inhalation. Bandages were removed and the graft site photographed, before excision of the graft and a small margin of surround tissue for histological analysis. After rinsing in PBS, the excised grafts were fixed in 4% paraformaldehyde for 20 min and then bisected, with one half cryopreserved in optimal cutting temperature compound and the other half further fixed in 10% neutral buffered formalin followed by processing and embedding in paraffin. Cryosections (20 μM) and formalin fixed, paraffin embedded (FFPE; 8 μM and 5 μM) sections underwent routine staining for histological assessment with haematoxylin and eosin and Masson's trichrome stain.

2.3. Immunohistochemistry

Neovascularisation was assessed by immunohistochemistry using CD31, a marker of endothelial cells. Briefly, cryosections were thawed before fixing in 2% formalin for 20 min. After 3 × 5 min PBS washes, sectioned were permeabilised in 80% methanol at −20 °C for 15 min followed by 3 × 5 min PBS washes. Endogenous peroxidase activity was quenched by incubating the sections with 3% hydrogen peroxide (H_2O_2) for 15 min at room temperature, followed by 3 × 5 min PBS washes. Sections were blocked in 10% normal goat serum (Applied Biological Products Management, Australia) in 10% bovine serum albumin (MP Biomedicals, USA) in PBS for 2 h at room temperature, followed by incubation in rat anti-CD31 antibody in blocking buffer (1:100; BD Biosciences, USA, cat no. 550274) overnight at 4 °C. After 3 × 5 min PBS washes the