# ORIGINAL ARTICLE

# Use of epidermal skin grafts in chronic wounds: a case series

Peter AM Everts, Marco Warbout, Diana de Veth, Merel Cirkel, Nicole E Spruijt & Jaap Buth

Da Vinci Clinic, Geldrop, The Netherlands

#### Key words

Chronic wounds; Epidermal grafting; Wound care

#### Correspondence to

PAM Everts, PhD Da Vinci Clinic. Expert Centre for Wound Healing and Hyperbaric Medicine. Nieuwendijk 49.2 5664 HB Geldrop The Netherlands E-mail: everts@me.com; p.everts@davincikliniek.com Everts PAM, Warbout M, de Veth D, Cirkel M, Spruijt NE, Buth J. Use of epidermal skin grafts in chronic wounds: a case series. Int Wound J 2017; doi: 10.1111/iwj.12787

# Abstract

In stalled, chronic wounds, more aggressive and proactive wound closure efforts are needed. We describe adjunctive use of epidermal grafting in patients with chronic wounds. Wound bed preparation consisted of surgical necrotectomy or sharp debridement, hyperbaric oxygen therapy, negative pressure wound therapy, compression therapy, platelet-rich plasma therapy and/or heparan sulphate agents. Epidermal grafts were harvested from the patient's thigh and applied to the wound. Wound and donor site healing was monitored. A total of 78 patients (average age =  $64 \cdot 1 \pm 15 \cdot 6$  years) were included in the study. Common comorbidities included hypertension (47.4%), venous insufficiency (37.2%) and obesity (28.2%). Average wound duration was 13.2 months (range: 0.3-180 months). The most common wound types were dehiscence (29.5%), radiation ulcer (24.4%) and venous ulcer (17.9%). Total time from epidermal grafting to wound closure was  $10.0 \pm 7.3$  weeks. Of the 78 wounds, 66 (84.6%) reached full wound closure (49 < 3 months, 16 > 3 months, 1 without time data). Of 78 wounds, 10 (12.8%) underwent partial wound healing, while 2 wounds (2/78; 2.6%) remained unhealed. These results suggest that wound surface reduction can be achieved by proactive early application of biological therapies and epidermal skin grafts, which may help decrease time to wound healing.

# Introduction

Chronic wounds are a burden to patients and the health care system. In 2009, it was estimated that approximately 1-1.5% of the population in the industrialised world have a wound and that 2-4% of the total health care expenditure in Europe is spent on wound management (1). As the population and costs of health care have increased worldwide, chronic wound prevalence and money spent on wound care has undoubtedly increased as well. In response to the growing need for wound care products, many advanced wound care options have been developed, which include hyperbaric oxygen therapy (2,3), negative pressure wound therapy (NPWT) (4–6), platelet-rich plasma therapy (7) and heparan sulphate agents (8).

However, despite the variety of advanced therapies, the healing of chronic and complex wounds can stall or the wounds become unresponsive to treatment. Here, health care providers should become more proactive in wound surface reduction and consider the application of advanced wound therapies at an early stage. When wounds fail to respond to treatment, it is recommended that the wound be re-assessed and a new treatment initiated (9-11). Here, we describe

the adjunctive use of epidermal grafting in 78 patients with stalled wounds.

# **Key Messages**

- despite the variety of advanced therapies, the healing of chronic and complex wounds can stall or the wounds become unresponsive to treatment
- we describe the adjunctive use of epidermal grafting following wound bed preparation using surgical necrotectomy or sharp debridement, hyperbaric oxygen therapy, negative pressure wound therapy, compression therapy, platelet-rich plasma therapy and/or heparan sulphate agents in a case series of 78 patients with stalled wounds
- of the 78 wounds, 66 (84.6%) reached full wound closure, 10 (12.8%) underwent partial wound healing, and 2 wounds (2.6%) remained unhealed
- based on our results, health care providers should become more proactive in expediting wound surface reduction, initiate biological therapies early for optimal wound bed preparation and consider the application of epidermal grafting at an early stage

#### **Materials and methods**

#### Patient and wound evaluations

Patients were referred by general hospitals, University medical centres or general practitioners for treatment. During the first consultation, patient medical history and medication was reviewed by a physician and the wound assessed by a tissue viability nurse and a surgeon. After the multidisciplinary meeting reviewing aetiology, duration of wound, comorbidities, wound cultures and imaging results convened, a medical treatment plan was initiated.

#### Surgical necrotectomy and debridement

Every wound underwent a surgical necrotectomy performed by a vascular surgeon in the wound care treatment centre.

Sharp debridements were performed by the tissue viability nurse or a physician, with the use of local anaesthesia if indicated. All wounds required multiple debridement procedures twice weekly (range: 9–47 procedures).

### Wound bed preparation

Each patient received multiple and/or different types of wound bed preparations based on individualised treatment plans. The wound bed preparation procedures are described below.

# Hyperbaric oxygen therapy

A multi-place hyperbaric chamber (IHC Hytech, Raamsdonkveer, The Netherlands) was used, in which 12 patients can be treated simultaneously. Patients were treated once daily at an absolute pressure of 2.5 atmospheres. At this pressure, 100% of oxygen was breathed through a mask during four periods for a total of 85 minutes.

#### **Compression therapy**

Compression therapy consisted of single-layer, double-layer or compression stockings. Patients could receive one or more compression treatments.

#### Negative pressure wound therapy

Wounds with exposed bone or tendon were covered with a non-adherent wound contact layer (ADAPTIC TOUCH<sup>TM</sup> Non-Adhering Silicone Dressing, Systagenix, an ACELITY Company, Gargrave, UK). NPWT dressings were cut to fit the wound size. Peri-wound skin was covered with drape for protection. NPWT [V.A.C. VIA<sup>TM</sup> Therapy (KCI, an ACELITY Company, San Antonio, TX), NANOVA<sup>TM</sup> Therapy System (KCI, an ACELITY Company), PICO<sup>TM</sup> System (Smith & Nephew Inc., Hull, UK)] or another NPWT system was initiated following the manufacturer's instructions.

#### Platelet-rich plasma (PRP) therapy

Wounds that did not show a tendency to heal after debridement, compression and/or NPWT (i.e. >10% of wound size reduction in 2 weeks) were selected for PRP therapy. At point of care, 55 ml of whole blood was pre-donated and prepared for neutrophil-poor PRP production (Protocol A), using a platelet concentrating system with dedicated sterile disposables and a 544E centrifuge (PurePRP®; EmCyte Corporation, Ft. Myers, FL). From the sequestered blood components, autologous thrombine was produced to activate the PurePRP<sup>®</sup> to form a wound topical clot to cover the wound area after a sharp debridement to stimulate and microfracture the wound bed. The platelet clot lysed, secreting platelet-derived growth factors, cytokines and other proteins in the wound bed to induce cell signalling to regenerate tissue healing (12,13). Initially, two PRP treatments were performed weekly. Thereafter, the procedures were switched to bi-weekly. After a PurePRP® procedure, the primary dressing was covered with a naturally derived porcine intestinal submucosa matrix (OASIS® wound matrix; Cook Biotech, Inc, West Lafayette, IN) followed a hydrocolloid secondary dressing (DuoDERM<sup>®</sup> extra thin dressing; ConvaTec, Greensboro, NC).

#### Heparan sulphate agent

Following sharp debridement, a heparin sulphate agent (Cacipliq<sup>®</sup>, OTR3<sup>®</sup>; Paris, France) was added to a sterile gauze dressing and applied to the wounds, remaining in contact with the wound bed for at least 5 minutes. The gauze dressing was removed and the wound dressed with a hydrofibre dressing (AQUACEL<sup>®</sup>; ConvaTec, Greensboro, NC).

# **Epidermal harvesting**

The donor sites (inner thigh, contra lateral to the wound sites) were prepared for graft harvesting by hair removal and cleansing with 70% ethanol. The epidermal harvesting system (CELLUTOME<sup>™</sup> Epidermal Harvesting System; KCI, an ACELITY Company, San Antonio, TX) was attached to the donor site. Epidermal microdomes were created using heat and negative pressure (30–45 minutes, depending on skin thickness). The epidermal micrografts were transferred to the wound using a non-adherent contact layer (ADAPTIC TOUCH<sup>™</sup> dressing). The epidermal grafts were bolstered with NPWT. The donor sites were covered with a hydrocolloid dressing (DuoDERM<sup>®</sup> extra thin dressing) and left in place for at least 7 days. Wound and donor site healing were monitored at each dressing change.

#### **Results**

#### **Patient demographics**

A total of 78 patients with an average age of  $64 \cdot 1 \pm 15 \cdot 6$  years and average body mass index (BMI) of  $28 \cdot 0 \pm 5 \cdot 2 \text{ kg/m}^2$  were included in the study (Table 1). Common patient comorbidities included hypertension (47.4%), venous insufficiency (37.2%), obesity (28.2%) and diabetes (20.5%). Wound duration was 13.2 months (range: 0.3-180 months) with an average wound surface area of  $14.9 \pm 20.6$  mm<sup>2</sup> (Table 2). The most common wound types were wound dehiscence (29.5%), radiation ulcer (24.4%) and venous ulcer (17.9%).

#### Table 1 Patient demographics

Characteristic	n=78
Age (years ± sd)	64·1 ± 15·6
Gender	
Female	56 (71.8%)
Male	22 (28.2%)
BMI (kg/m <sup>2</sup> $\pm$ sd)	$28.0 \pm 5.2$
Comorbidities	
Hypertension	37 (47.4%)
Venous insufficiency	29 (37.2%)
Obesity (BMI > $30 \text{ kg/m}^2$ )	22 (28·2%)
Diabetes mellitus	16 (20.5%)
Peripheral arterial disease	14 (17.9%)
Stroke	10 (12.8%)
AMI	9 (11.5%)
COPD	7 (9.0%)
CHD	4 (5.1%)

AMI, acute myocardial infarction; BMI, body mass index; CHD, congestive heart disease; COPD, chronic obstructive pulmonary disease; sd, standard deviation.

Table 2 Wound characteristics

Wound characteristic	n=78
Wound duration (months ± sd)	13·2 ± 25·2
Wound area (mm <sup>2</sup> $\pm$ sd, $n = 76$ )	14·9±20·6
Wound type	
Dehiscence	23 (29.5%)
Radiation ulcer	20 (25.7%)
Venous ulcer	14 (17.9%)
Diabetic ulcer	7 (9.0%)
Arterial ulcer	4 (5.1%)
Crush injury	3 (3.8%)
Osteomyelitis	2 (2.6%)
Compromised flap	2 (2.6%)
Martorell ulcer	2 (2.6%)
Immunosuppressive medication	1 (1.3%)

Sd, standard deviation.

#### Wound bed preparation

Prior to epidermal grafting, the wounds underwent various means of wound bed preparation, including hyperbaric oxygen therapy (39.7%), NWPT (85.7%), compression therapy (55.7%) and PRP (29.2%) (Table 3).

#### Wound-healing outcomes

Total duration of wound healing from the first debridement to final wound closure was 26 weeks. Average time after epidermal grafting to wound closure was  $10.0 \pm 7.3$  weeks, with 66 wounds (84.6%) reaching full wound closure (Table 4). Of the healed wounds, 49 healed within 3 months, 16 healed after 3 months, and the remaining healed wound was missing time to heal data. Ten wounds (12.8%) underwent partial wound healing, showing an average wound reduction of  $44.5\% \pm 20.1\%$ . Two wounds showed no wound surface area reduction after 3 months follow up.

Table 3	8 W	/ound	bed	preparation
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Wound bed preparation	N (%)	
Hyperbaric oxygen therapy $(n=70)$	31 (44.3)	
Negative pressure wound therapy $(n=70)$	60 (85.7)	
Compression therapy $(n=70)^*$	39 (55.7)	
Single-layer compression	7 (17.9)	
Double-layer compression	35 (89.7)	
Compression stocking	11 (28.2)	
Oedema therapy	1 (2.6)	
Platelet-rich plasma ( $n = 72$ )	21 (29-2)	
Heparan sulphate agent ( $n = 77$ )	23 (29.9)	

\*Patients could have one or more compression therapy treatment.

# Table 4 Wound closure outcomes

Wound closure			
Closure within 3 months $(n = 72)$	49 (68.1%)		
Closed after 3 months ( $n = 72$ )	16 (22.2%)		
Total wound healing time (weeks $\pm$ sd, $n = 72$ )	10 ± 7·3		
Full wound closure ( $n = 78$ )	66 (84·6%)		
Partial wound closure ( $n = 78$ )	10 (12.8%)		
Percent of wound closure (mean $\pm$ sd; $n = 10$ )	44·5% ± 20·1%		
Non-healing ( $n = 78$ )	2 (2.6%)		

sd, standard deviation.

#### Cases

Two cases representative of wound care in this patient population are presented below.

# Case 1

A 63-year-old male presented with chronically recurring wounds on his right foot with underlying osteomyelitis following Haglundse exostose removal over 20 years earlier (Figure 1A). The current wounds had been present for 33 weeks. Oral antibiotics (amoxicillin/clindamycine acid) were initiated. The patient underwent sharp debridement twice a week for 3 months followed by 6 weeks of compression therapy (Figure 1B). The patient also underwent 39 sessions of HBOT and three PRP applications. The wound was closed 3 weeks following epidermal grafting (Figure 1C). The epidermal harvesting system was attached to the patient's prepared thigh (Figure 2A). The donor site showed signs of healing 1 week post-epidermal harvesting (Figure 2B) and was fully healed without complications 2 weeks post-epidermal harvesting (Figure 2C).

#### Case 2

A 51-year-old female presented with a 4-week-old wound following a breast reconstruction post-radiation wound (Figure 3A). Oral antibiotics (amoxicillin and clavulanic acid) were initiated. The wound underwent sharp debridement twice per week for 16 weeks followed by treatment with a heparin sulphate agent to stimulate extracellular matrix repair. The patient also underwent 40 sessions of HBOT and NPWT for 2 weeks. The wound showed improvement 2 weeks post-epidermal grafting (Figure 3B) and was fully healed 6



Figure 1 Chronic recurring skin infection on right foot with osteomyelitis. (A) Wound at presentation. (B) Wound after multiple debridements. (C) Wound fully healed 3 weeks post-grafting.



Figure 2 Case 1 donor site post-graft harvesting. (A) Donor site immediately after graft harvesting. (B) Donor site 1 week post-graft harvesting. (C) Donor site fully healed 2 weeks post-graft harvesting.

weeks post-grafting (Figure 3C). Epidermal grafts were harvested from the patient's prepared thigh (Figure 3D). The donor site showed signs of healing 1 week post-epidermal harvesting (Figure 3E) and was fully healed without complications 2 weeks post-epidermal harvesting (Figure 3F).

# Discussion

During wound healing, epithelialisation in the shortest possible time is critical to avoid potential infections and improve the patient's quality of life. As such, we recommend that health care providers should become more aggressive and proactive in wound bed preparation and consider using therapies aimed at complete wound closure at an early stage. We report that adjunctive use of epidermal grafting, along with adequate wound bed preparation, bolster dressings and NPWT, in 78 patients with chronic wounds resulted in complete closure of 68% of wounds within 3 months.

Early published experiences using epidermal grafts harvested with a commercially available harvesting system to manage wounds have been promising. Richmond *et al.* first used epidermal grafts in patients with pyoderma gangrenosum, a disorder characterised by recurrent skin ulcers (14). In these patients, wound closure was observed within 3 months in three out of five patients, and wound improvement was seen in the remaining two patients. Gabriel *et al.* described their initial experiences using epidermal grafts in four patients with various wound types and comorbidities, including diabetes, obesity and cancer. They reported complete wound healing in three out of four wounds and a 50% reduction in the fourth wound (15).

Similarly, Serena *et al.* utilised epidermal grafting in patients with chronic wounds in a resource-poor country. Six out of seven wounds either improved or completely healed within 4 weeks of grafting (16).

Based on the wound-healing results in those early reports, larger case studies featuring complex patients and wounds have been recently published. Fearmonti utilised epidermal grafting in 22 patients with 23 lower extremity wounds and who had multiple comorbidities, including diabetes, obesity, peripheral arterial disease and coronary artery disease (17). The average percentage of reepithelialisation was 88.1% in these patients. Eleven wounds (52.4%) showed complete reepithelialisation, while 10 wounds showed partial reepithelialisation ranging from 50% to 99%. The remaining two wounds experienced complete graft loss due to patient non-compliance (17). In a slightly larger case series, Bhatia used epidermal grafting in 34 patients with multiple comorbidities and chronic wounds. Following epidermal grafting, 82.4% (28/34) showed complete healing, 1 wound showed improved healing, 4 wounds did not heal and 1 wound was lost to follow up (18). In these patients, the mean epithelialisation rate was 7 weeks. Similar results were seen in the more recently published Lincoln and colleague case series. The authors examined the use of epidermal micrografts in 82 patients with 90 complex wounds and comorbidities, such as hypertension, obesity, peripheral vascular disease and diabetes (19). Following application of epidermal micrografts, 75 wounds (83.3%) showed complete reepithelialisation, 4 wounds (4.4%) improved, and 11 (12.2%) failed to heal. The mean time to wound healing was 16.9 weeks (19).



Figure 3 Wound after breast reconstruction post-radiation therapy. (A) Wound at presentation. (B) Wound 2 weeks post-grafting. (C) Wound fully healed 6 weeks post-grafting. (D) Donor site 1 week post-graft harvesting. (E) Donor site fully healed 2 weeks post-graft harvesting.

Our use of epidermal grafting in patients with stalled wounds achieved similar results as the published studies above, with a majority of the wounds reaching full closure without complications. Our findings are also supported by two recent international studies using epidermal grafting to manage wounds. Prakash et al. treated 18 patients with epidermal grafts in India, a resource-poor country (20). Of the 18 wounds, 16 (88.9%) showed complete healing, with a mean time to wound epithelialisation of 3.7 weeks. The UK multicentre study examined epidermal grafting in 35 patients with either acute wounds (n=10) or chronic wounds (n=25) (21). Complete wound healing was achieved in 22 (62.9%) patients, two wounds showed improvement, three wounds showed no change, one wound showed improved wound bed activity, and seven wounds became infected, resulting in graft loss. Time to complete wound healing ranged from 6 to 20 weeks, and no differences in wound-healing times were observed between the acute and chronic wounds.

Minimal pain at the donor sites during harvesting was reported by our patients. This is supported by the findings of the healthy-human study by Osborne and colleagues. This study measured pain using the Wong-Baker FACES pain rating scale during epidermal graft harvesting (22,23). The healthy subjects (n = 15) reported minimal pain during and immediately after graft harvesting and were completely pain free by 7 days post-harvesting. Minimal pain during harvesting in patients was also reported by Hachach-Haram *et al.* (21) and Lincoln *et al.* (19). A majority of studies using epidermal grafting in wound management did not set out to directly measure patient-reported pain. While the published literature suggests the patients experience minimal to no pain, planned pain studies are needed. Additionally, the donor sites in our study also healed without complications 1-2 weeks post-epidermal harvesting, similar to what has been reported in the published literature (14-21).

For chronic or complex wounds, aggressive and proactive efforts are needed to reach full wound closure. A multidisciplinary panel from Kirsner and colleagues provided guidelines for the use of epidermal grafting to achieve wound closure (24). The panel recommended that all patients be assessed and the appropriate patient-specific treatment plan selected (24). Once the patient and wound have been optimised (i.e. controlled blood glucose, wound infection management), preparation of the wound bed should be undertaken followed by wound closure methods (24). In our patients, we utilised epidermal grafting following various wound bed preparation therapies, such as hyperbaric oxygen treatment, NPWT, compression therapy, heparan sulphate agents and/or PRP therapy. Based on the presented data, health care providers should become more proactive in expediting wound surface reduction, initiate biological therapies early for optimal wound bed preparation and consider the application of epidermal grafting at an early stage.

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