Adjunctive treatments for wound healing in the diabetic foot

Mike Edmonds

ARTICLE POINTS

1 Adjunctive treatments may be needed to stimulate wound healing in hard-to-heal diabetic foot ulcers.

2 Such treatments include vacuum-assisted closure, growth factors, skin substitutes, extracellular matrix proteins, protease inhibitors and hyperbaric oxygen.

3 Clinical evidence to support the efficacy of these new treatments is now accumulating.

4 Decisions about when to introduce these agents may be based on healing rates from clinical studies.

5 Adjunctive treatments are expensive and should be used to supplement standard treatments, not to replace them.

KEY WORDS
- Chronic wounds
- Adjunctive treatment
- Wound healing
- New technology

Mike Edmonds is a Consultant Physician, King's College Hospital, London.

Introduction

Treatment of diabetic foot ulcers aims to achieve wound closure as quickly as possible – the longer a diabetic foot ulcer remains unhealed, the greater the risk of infection, hospitalisation and limb amputation. The large numbers of people with diabetic foot ulcers that end in lower limb amputations have led to the development of new treatment modalities. Clinical evidence suggests that, when used in conjunction with standard regimens, the new treatments heal more ulcers and significantly reduce the time to healing compared with standard care alone. This article reviews some of these adjunctive therapies and the evidence supporting their use.

The diabetic foot needs multidisciplinary management to control mechanical, wound, microbiological, vascular, metabolic and educational aspects of care. Foot ulcers require pressure relief (mechanical control), sharp debridement and dressings (wound control); neuro-ischaemic ulcers may need vascular intervention (vascular control). Achieving good metabolic control of blood glucose, serum lipids and blood pressure is also important, as is education to teach proper foot care (Edmonds, 2006).

When diabetic foot ulcers fail to heal in response to standard management, adjunctive treatments to stimulate wound healing may have to be used. These include vacuum-assisted closure, growth factors, skin substitutes, extracellular matrix proteins, protease inhibitors and hyperbaric oxygen.

Vacuum-assisted closure

The vacuum-assisted closure (VAC) therapy unit (KCI Medical, Kidlington) has become an established method to achieve closure of wounds, including diabetic foot wounds. The VAC therapy unit applies gentle negative pressure to the wound through a tube and foam sponge. These are applied to the wound over a dressing and sealed in place with a plastic film to create a vacuum. The sponge is replaced every 2–3 days. Exudate from the wound is sucked along the tube to a disposable collecting chamber. It is important to use the therapy unit only on wounds that have been thoroughly debrided (KCI Medical Ltd, 2005; Antony and Terrazas, 2004; Webb, 2002). The negative pressure improves the dermal blood supply and stimulates granulation (Banwell and Téot, 2003; Jones et al, 2005), which can form even over bone and tendon. It reduces bacterial colonisation and diminishes oedema and interstitial fluid (McCallon et al, 2000). Recently, instillation tubes have been added to the therapy unit to facilitate the application of topical antibiotics.

In the diabetic foot, the application of a continuous negative pressure of 125 mmHg to the wound has been found useful in promoting healing (KCI Medical Ltd, 2005). The VAC therapy unit is used to treat postoperative wounds after minor amputations or surgical debridement in the diabetic ischaemic foot, especially when revascularisation is not possible (Armstrong and Lavery, 2005). Increasingly, it is also being used

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1 In a pivotal study, vacuum-assisted closure (VAC) therapy led to a higher proportion of healed wounds and faster healing rates than standard moist wound care alone.

2 Guidelines on the use of VAC therapy in the treatment of diabetic foot wounds drawn up in 2004 at the Tucson Expert Consensus Conference were updated in 2006 at a Miami Consensus Conference.

3 Platelet-derived growth factor BB (Regranex) stimulates fibroblasts and other connective tissue cells in the skin, enhancing cell growth and repair.

4 Regranex Gel (100µg/g) healed significantly more chronic diabetic ulcers than placebo gel (50% versus 35%) in a pivotal study.

5 Tissue-engineered skin substitutes are another potential new therapy for chronic non-healing diabetic foot ulcers; examples include Apligraf, Dermagraft, and OrCel.

to treat postoperative wounds in people with diabetic feet who are in end-stage renal failure and on dialysis treatment, and also to treat heel ulcers.

Initial studies to assess the outcome of VAC therapy in diabetic foot ulcers were promising. Armstrong and colleagues (2002) investigated the outcomes of VAC therapy in 31 people who had surgical debridement for indolent diabetic foot wounds (mean pre-therapy wound duration of 25.4 weeks). A VAC device was applied for 4.7 ± 4.2 weeks: 90.3% (n=28) of wounds healed at the level of debridement in a mean of 8.1 weeks and only 9.7% (n=3) went on to higher level amputation.

A pivotal, adequately powered key study has recently been completed (Armstrong and Lavery, 2005). In this US-based study, 162 people with postoperative wounds following partial diabetic foot amputation were enrolled in a 16-week, 18-centre, randomised clinical trial. Participants were randomly assigned to receive either negative pressure wound therapy delivered via a VAC therapy unit (*n*=77), with dressing changes every 48 hours, or standard moist wound care (control group; *n*=85). More participants were healed in the VAC group than in the control group (43 [56%] versus 33 [39%], *P*=0.040). The rate of wound healing, based on the time to complete closure, was faster in the VAC group than in the control group (*P*=0.005).

Guidelines on the use of VAC therapy in the treatment of diabetic foot wounds were drawn up by a multidisciplinary expert panel convened at the Tucson Expert Consensus Conference on VAC Therapy in 2004 (Armstrong et al, 2004). These were updated in February 2006 by a second multidisciplinary expert panel at a consensus conference on VAC therapy, held in Miami (Andros et al, 2006).

Growth factors

Growth factors play an important role in wound repair by stimulating chemotaxis, cellular proliferation, extracellular matrix formation and angiogenesis (Harding et al, 2002); deficiency in these factors might lead to impaired wound healing (Harding et al, 2002). Platelet-derived growth factor BB (PDGF-BB) stimulates fibroblasts and other connective tissue cells located in the skin and is beneficial in enhancing wound-healing processes (Senet, 2004).

Four placebo-controlled trials of PDGF-BB have been carried out. These included a pivotal study of 382 people, which showed that Regranex Gel (100 µg/g [Janssen-Cilag, High Wycombe]) healed 50% of chronic diabetic ulcers – significantly more than the 35% healed with a placebo gel (Wieman et al, 1998).

Skin substitutes

Tissue-engineered skin substitutes have emerged as a potential new therapy for chronic non-healing wounds, including diabetic foot ulcers. Skin substitutes can be divided into cell-containing matrices and cell-free matrices.

Cell-containing matrices

Allogeneic products that use living cells with matrix include Apligraf (Novartis, Camberley), Dermagraft (Smith and Nephew, Hull), and OrCel (OrTec International, New York, US).

Apligraf

Apligraf is a bilayered skin substitute. The epidermal layer is formed by human keratinocytes and the dermal layer contains human fibroblasts in a bovine collagen lattice (Veves et al, 2001). It is manufactured under aseptic conditions from human neonatal foreskin tissue.

In a randomised 12-week trial in 208 people with non-infected, neuropathic diabetic foot ulcers, 56% of those treated with the bilayered construct, Apligraf, achieved complete wound closure, compared with 38% in controls (saline moistened guaze; *P*=0.0042). In addition, Apligraf reduced the time to complete closure (median 65 days versus 90 days, *P*=0.0026). Studies have demonstrated that Apligraf works through the delivery of growth factors and cytokines to the chronic wound

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1 Diabetic neuropathic foot ulcers treated with OrCel, a bilayered cellular matrix, healed faster than those treated with standard care alone.

2 Cell-free matrices interact with the wound bed, releasing growth factors that stimulate wound healing and angiogenesis.

3 In a small, randomised controlled study, wound closure was achieved in 49% of diabetic ulcers treated with OASIS Wound Matrix, compared with only 28% in those treated with Regranex Gel.

4 GraftJacket, an allogeneic acellular matrix graft, healed 82.4% of diabetic wounds, which initially measured a mean of 4.6±3.2 cm^2, over the 20-week evaluation period, following a single application with weekly dressing changes.

environment (Dinh and Veves, 2006).

Dermagraft

Dermagraft is an artificial human dermis. Human fibroblast cells obtained from neonatal foreskin are cultivated on a three-dimensional polyglactin scaffold.

In a randomised, controlled, multicentre study of 281 people with neuropathic foot ulcers, significantly more participants in the Dermagraft group than the control group (who were treated with saline moistened guaze) experienced complete wound closure within 12 weeks (50.8% versus 31.7%, $P<0.05$; Naughton et al, 1997).

In another randomised study of 12 weeks duration, 340 people with chronic diabetic foot ulcers were treated with living foreskin fibroblasts in a polyglactin-910 surgical mesh. The incidence of complete wound closure of neuropathic foot ulcers by study end was 30% in the active group and 18% in the control group ($P=0.023$; Marston et al, 2003).

OrCel

OrCel, a bilayered cellular matrix (BCM), is a porous collagen sponge containing cocultured allogeneic keratinocytes and fibroblasts harvested from human neonatal foreskin.

Forty people with chronic, diabetic, neuropathic foot ulcers were randomised to receive either standard care (moist saline gauze cover) for up to 12 weeks ($n=20$) or active treatment ($n=20$). Active treatment comprised standard care plus an application of BCM at each weekly visit for up to a total of six applications, followed by standard care alone for an additional 6 weeks or until complete healing. By 12 weeks, seven of the 20 wounds (35%) treated with BCM showed complete healing compared with four of the 20 wounds (20%) treated with standard care alone. Diabetic neuropathic foot ulcers treated with BCM showed a faster rate of wound healing than those treated with standard care alone. Mean wound closure rates over the course of the trial were faster for BCM-treated wounds than for wounds treated with standard care alone (1.8% per day versus 1.1% per day, $P=0.0087$; Lipkin et al, 2003).

Cell-free matrices

Cell-free matrices interact with the wound bed, releasing growth factors that stimulate wound healing and angiogenesis (Martin et al, 2005).

GraftJacket

GraftJacket (Wright Medical UK Ltd, Chester) is an allogeneic acellular matrix graft. In its development it undergoes a process that removes the epidermal and dermal cells and thus does not trigger an immune response (Martin et al, 2005).

Recently, experience has been gained with the use of this therapy in the treatment of diabetic wounds (Martin et al, 2005). Seventeen patients received surgical debridement and were placed on therapy consisting of a single application of an acellular matrix graft, with weekly dressing changes. This led to healing in 82.4% of wounds, which initially measured a mean of 4.6±3.2 cm^2, over the 20-week evaluation period (Martin et al, 2005).

OASIS Wound Matrix

OASIS Wound Matrix (Cook SIS Technology, Indiana, US) is derived from the pig small intestine submucosa. A recent study compared the healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS Wound Matrix and those treated with Regranex Gel (Niezgoda et al, 2005). After 12 weeks' treatment, complete wound closure was observed in 49% of the OASIS-treated patients ($n=18$) compared with only 28% of the Regranex-treated group ($n=10$; $P=0.055$).

Integra

Integra (Integra NeuroScience, Andover) is a bilayered matrix wound dressing which provides a scaffold for dermal regeneration and organisation, and protection for the treated wound. As healing progresses, an endogenous collagen matrix is deposited by

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1 Hyaff (esterified hyaluronic acid) produces a hydrophilic gel when in contact with wound exudate; this covers the wound, promoting granulation and healing.

2 Promogran inhibits proteases in the wound and protects endogenous growth factor.

3 Hyperbaric oxygen has been shown to reduce the number of major amputations in ischaemic diabetic feet, although studies involved small numbers of patients.

4 One important question is when should these agents be introduced in the management of diabetic foot ulcers.

5 Clinical decisions about when to use advanced or more experimental therapies may be based on healing rates.

6 Studies in venous and diabetic ulcers suggest that an initial healing rate of >0.6 mm per week enables healthcare professionals to predict healing with a sensitivity and specificity of 80%.

fibroblasts. When the dermal layer is adequately revascularised, the temporary silicone layer is removed and a thin, meshed layer of the person's own skin (epidermal autograft) is placed over the 'neodermis'.

Extracellular matrix proteins

In addition to the use of growth factors and skin substitutes, there has also been considerable interest in the application of extracellular matrix proteins to accelerate healing in diabetic foot ulcers (Edmonds et al, 2000).

Hyaluronic acid is a polysaccharide that facilitates the growth and movement of fibroblasts, but is unstable when applied to tissues (Edmonds et al, 2000). When esterified, as in hyaff, it becomes more stable and, in contact with wound exudate, produces a hydrophilic gel that covers the wound (Edmonds et al, 2000). This creates a hyaluronic acid-rich tissue interface that promotes granulation and healing.

In a controlled, randomised clinical trial, Hyaff-based autologous grafts, both dermal and epidermal, were used to treat two groups of diabetic foot ulcers – plantar ulcers (n=42) and postoperative wounds on the dorsum of the foot (n=37; Caravaggi et al, 2003). Participants were randomised to either the control group (non-adherent paraffin gauze; n=36) or the treatment group (Hyaff-based autologous graft; n=43). People in both groups had off-loading, comprising total contact casting for plantar ulcers and a rigid-sole shoe for dorsal ulcers. After 11 weeks there was no significant difference in the rates of healing of plantar ulcers between the control and treatment groups, whereas the dorsal ulcers in the treatment group showed an increased rate of healing compared with the control group (67% versus 31%; P=0.049).

Protease inhibitors

A frequent characteristic of chronic wounds is elevated protease activities.

Promogran (Johnson & Johnson Ltd, Maidenhead) is a protease inhibitor dressing consisting of oxidised regenerated cellulose and collagen. It inhibits proteases in the wound and protects endogenous growth factors (Cullen et al, 2002). In a 12-week randomised controlled study of 276 people with chronic diabetic plantar ulcers, 37% (51/138) of the Promogran-treated participants achieved complete wound closure compared with 28% (39/138) of the control group who were treated with saline moistened gauze (P=0.12; Veves et al, 2002).

Hyperbaric oxygen

Adjunctive systemic hyperbaric oxygen therapy has been shown to reduce the number of major amputations in people with ischaemic diabetic feet (Faglia et al, 1996). Studies involving relatively small groups of people have shown that hyperbaric oxygen accelerates the healing of ischaemic diabetic foot ulcers. It is thus reasonable to use hyberbaric oxygen as an adjunctive therapy in severe or life-threatening wounds (Wunderlich et al, 2000).

Concluding remarks

One important question is when to introduce these agents in the management of diabetic foot ulcers. Clinical decisions about when to use advanced or more experimental therapies may be based on healing rates. Studies in venous and diabetic ulcers suggest that an initial healing rate of >0.6 mm per week enables healthcare professionals to predict healing with a sensitivity and specificity of 80% (Falanga and Sabolinski, 2000). These adjunctive treatments are expensive, hence they should not be used to replace basic treatments but to supplement them when there is difficulty in healing. ■

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