World Wide Wounds

Next generation products for wound management

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Key Points

1. Novel technologies are being developed to improve healing in difficult to treat wounds.
2. Emerging dressing types include bioactive dressings and tissue-engineered skin substitutes.
3. Randomised controlled clinical trials to examine safety and efficacy of many of the new materials are lacking and clinical uptake has been slow.
4. When choosing the optimum treatment for patients, it is important to take into account ease of use, patient satisfaction and cost-effectiveness.

Abstract

This review attempts to clarify the developments of novel types of 'bioactive' dressings as well as tissue-engineered 'skin substitutes'. This is an evolving field, where emerging products try to find their own particular clinical or commercial niche. The importance of controlled clinical studies to test the effectiveness of these products is stressed. Considerations to be taken into account, both for novel dressing types and for skin substitutes include ease of use, patient satisfaction and cost-effectiveness.

Introduction

Normal wound healing requires both restoration of cover by re-epithelialisation, and restoration of support by ingress of collagen. The first occurs by migration and proliferation of keratinocytes from the wound edges and by differentiation of stem cells from remaining hair follicle bulbs. The second occurs by influx of growth factors secreted by macrophages, platelets and fibroblasts, by fibroblast proliferation and subsequent synthesis and remodelling of collagenous dermal matrix. However, in the case of full-thickness acute burn injuries and chronic wounds (pressure ulcers, venous ulcers and diabetic foot ulcers), these processes are defective and new technologies are being developed to improve the healing in these conditions.

The uptake and use of these technologies, however, has often been slower than expected. For example, despite improvements in cell culture techniques and developments in dermal matrices, tissue-engineered skin substitutes have yet to achieve widespread use by clinicians. There are a number of reasons for this, not least the difficulty in setting up controlled studies to test the treatments; in addition, the poor take rate of keratinocyte grafts has been a major problem. Compared to 90% cover routinely achieved by traditional split-thickness grafting, the typical take rate of 40-60% achieved with cultured sheets is generally regarded as unacceptable [1]. The suitability of dressings for use with such grafts has only recently been investigated. As there is low mechanical stability of the graft at early time-points, the optimum dressing type may be paramount if the best take rates are to be obtained and good histological results of the regenerated skin achieved.

The importance of formal testing of new dressings against traditional methods, prior to their use in clinical practice, was recently emphasised [1]. In a prospective, randomised, controlled porcine wound study, four different dressings were assessed with reference to the amount of epidermal cover gained and the histological quality of the regenerated skin at three weeks post-grafting. Superior histology was observed with polyurethane foam (Allevyn) although this had a similar take rate to paraffin gauze, and substantially inferior results were observed with polythene sheet (Opsite) and silicone sheet [1]. This study demonstrates the complex interaction of primary and secondary layer wound care products and how they impact on trial results.

The following discussion focuses on novel types of 'bioactive' dressings, the tissue-engineered 'skin substitutes', and the trials used to test their effectiveness. Growth factor treatments and their potential use in healing chronic wounds have recently been described [2] and will not be discussed further.

Bioactive dressings

Antimicrobials

An important consideration in the design of new dressings is their ability to combat microbial infection. Many dressings now exploit 'bioactive' properties to promote

healing and control infection. These include the now well-known sustained release iodine and silver dressings (e.g. Iodosorb, Actisorb Silver 220). Actisorb Plus is an activated charcoal cloth impregnated with silver. It is reported to absorb bacteria, which are then inactivated by the silver [3]. Now marketed as Actisorb Silver 220, it is intended for use over partial or full thickness wounds such as pressure ulcers, venous ulcers, diabetic ulcers and acute and chronic wounds, and is claimed to be the only dressing currently available in the USA that 'combines broad-spectrum antimicrobial action, bacterial toxin management and odour control' (J+J news, March 2003).

Another new generation product, Acticoat, utilises novel silver-coating technologies in a dressing designed to prevent wound adhesion, control bacterial growth and facilitate burn wound care. It consists of a rayon/polyester non-woven core, laminated between layers of silver-coated high-density polyethylene mesh. It is claimed by the manufacturers to provide an effective antimicrobial barrier for up to 3-5 days against 150 pathogens, including both Methicillin Resistant Staphylococcus aureus (MRSA) and Vancomycin-resistant Enterococci (VRE) (see www.acticoat.com/faq.html, Acticoat 7 data sheet).

There have been a number of controlled clinical studies to evaluate the safety and efficacy of Acticoat. In a matched-pair, randomised, prospective clinical study for the treatment of burns, Acticoat was assessed for ease of use, patient comfort and antimicrobial effectiveness compared to standard care in the same institution [4]. Results were in general promising with patients reporting less pain on removal with Acticoat, and nurses reporting no significant difference in ease of application. Frequency of burn wound sepsis and occurrence of secondary bacteraemia were both reduced [4]. A comprehensive laboratory study of the antimicrobial activity of Acticoat has also been reported [5]. In a number of tests, Acticoat demonstrated improved antimicrobial performance over existing silver-based products [5]. As well as killing bacteria more rapidly, it had the lowest minimum inhibitory concentration and minimum bactericidal concentration. The importance of examining multiple test criteria was highlighted.

In a controlled study on donor site wounds [6], Allevyn showed significantly better results than Acticoat with respect to time to healing and extent of re-epithelialisation. No significant differences were seen in the incidence of bacterial cultures, and while scarring appeared initially worse with Acticoat, this resolved by three months. Overall, the findings did not support the use of Acticoat for this application, although they did support its continued use for burn sites.

Interactive dressings

Exploitation of the bioactive properties of dressings is not confined to antimicrobials, but is becoming more commonplace with the increase in use of alginates, hydrocolloids, and materials containing collagen or other extracellular matrix components (in particular hyaluronic acid). As well as maintaining a moist wound environment, these dressings are believed to interact with cells or matrix proteins in the wound bed to promote healing.

Alginates are highly absorbable biodegradable dressings derived from seaweed (e.g. Kaltostat, Tegagen, SorbSan, SeaSorb, Algisite M, Algosteril) (see Alginate Dressings: Frequently Asked Questions). They contain building blocks of mannuronic acid (M) and guluronic acid (G) building blocks: the high-M alginates are soft and gel-like, while the high G alginates are more stable and are ribbon or rope-like [7]. Large quantities of alginates are used each year to treat exudating wounds such as leg ulcers, pressure sores and infected surgical wounds. As well as controlling exudate by ion exchange, alginates are believed to exert a bioactive effect by activating macrophages within the chronic wound bed to generate pro-inflammatory signals (such as tumour necrosis factor (TNF)-alpha, interleukin (IL)-1, -6 and -12) [8]. This may then initiate a resolving inflammatory response characteristic of healing wounds. It is now well known that chronic wounds are characterised by a macrophage rich inflammation[9] and any putative macrophage defect probably relates to the functional status of the macrophages present at the wound site [10]. *In vitro* studies have demonstrated that some dressings containing alginates can activate macrophages, as evidenced by their increased production of TNF-alpha[7]. Research is currently under way to modulate alginate dressings to enhance these effects, and to incorporate antimicrobial silver into alginate preparations [11](e.g. Acticoat Absorbent). In addition, new preparations (e.g. AGA-100) are being developed which have a reduced cytotoxicity to cells such as fibroblasts compared to both Kaltostat and Sorbsan[12], [13].

Promogran is a sterile, freeze-dried matrix made up of collagen and oxidised regenerated cellulose (ORC). This treatment is available as a 3mm thick hexagonal sheet in two different sizes (28 cm^2 and 123 cm^2) and is recommended for use on all types of chronic wounds that are free of necrotic tissue and show no clinical signs of infection. Once in place it must be covered with a low-adherent secondary dressing to maintain a moist wound-healing environment. It can be used in conjunction with standard compression therapy and need only be changed as clinically required.

In the presence of wound exudate, the matrix absorbs liquid and forms a 'soft, conformable, totally biodegradable gel, which rebalances the wound environment' (www.dressings.org/dressings/promogran.html). The gel binds and inactivates matrix metalloproteinases, which when present in excessive levels, have a detrimental effect on wound healing as they damage regenerating tissue [14]. The gel also binds growth factors secreted by macrophages and fibroblasts in the wound bed, protecting them from degradation by these proteases. As the gel is digested during the course of healing, the growth factors are released back into the wound bed in their active form. Laboratory studies have now reported on the possible mechanisms of action of Promogran in matrix modulation. Promogran was shown to significantly reduce the activities of neutrophil-derived elastase, plasmin and matrix metalloproteinase in chronic wound fluid when compared with wet gauze [15]. Mechanistically, this was suggested to occur by physical binding of the enzymes.

A prospective, randomised, controlled multicentre trial examined the effectiveness of Promogran in the treatment of diabetic foot ulcers [16]. Out of a total of 276 patients from 11 centres (mean age 58.3 years) half of the patients were treated with Promogran and half with moistened gauze as controls. After a maximum follow up of 12 weeks, 37.0% of the Promogran-treated patients had complete wound closure,

compared to 28.3% of control patients, although this difference was not significant (P=0.12). In the subgroup of patients with ulcer duration of less than six months, borderline significance was achieved (P=0.56). Clinically, however, both patients and investigators expressed strong preferences for Promogran and it was concluded that it might be a useful adjunct to treatment, particularly for ulcers of less than six months.

Tissue-engineered 'skin equivalents'

Surgical grafting of split-thickness autologous skin is the standard method for rapid closure of full-thickness burn wounds. However, advances in cell culture techniques have involved the development of autologous and allogeneic grafts using either sheets of fibroblasts in a biodegradable matrix [17] or cultured keratinocyte sheets [18]. It is now well established that superior results are obtained if both dermal and epidermal components are combined, for example in a bilayer skin equivalent[19]. The requirement of basement membrane proteins and the importance of dermal-epidermal interactions have previously been highlighted [20]. Design principles for cultured skin substitutes have recently been examined[21], as has the theoretical potential of their use on burns [22]. A clinical evaluation of skin substitutes has also been reported [23].

Cell-free matrices

Two approaches are currently used in the production of cell-free dermal matrices. The first is a synthetic matrix, usually comprising collagen and other extracellular matrix components, that attempts to recreate the desired physical and chemical properties of the dermis. One example now in clinical use is Integra artificial skin, developed by Burke and Yannas in the early 1980s [24]. The second approach is the use of native dermis, from which the cellular components have been removed. This may be treated to preserve the dermal architecture (e.g. Alloderm).

Integra (a dermal regeneration template) comprises a porous collagen/chondroitin-6 sulphate matrix overlaid with a thin silastic sheet, which acts as a scaffold for dermal regeneration. Its unique action essentially inhibits granulation and promotes the growth of neo-dermis through the collagen and glyosaminoglycan matrix. The silastic layer provides a temporary epithelial covering, which is removed prior to secondary grafting with a thin split-thickness autograft or cultured keratinocyte sheet.

The results of a multicentre, randomised, controlled trial on the use of Integra for major burns found the take rate of Integra to be significantly lower compared to controls (80 vs. 95%, P<0.0001, using meshed autograft wherever possible) [25]; there were no differences when compared with other allografts. Epidermal grafts were added following vascularisation (usually around 14 days) and take rates were good (median 90%). Donor site thickness for split thickness grafts over the Integra was significantly lower than for controls (0.006 vs 0.013 in.), which allowed significantly faster healing. Overall performance was considered to be at least as good as controls, except for the inconvenience of the requirement of a second operation (usually around three weeks after the first, for epidermal grafting) and the apparently poor resistance of the artificial dermis to infection [25]. A number of other reports on the use of

Integra in reconstructive surgery are available [26],[27]. Reported disadvantages also list the requirement of a second operation, as well as the risk of infection beneath the silastic layer, of the silicone becoming detached, and problems with contraction. Addressing the first of these problems may prevent occurrence of the remainder and, to this effect, the results of a one-step operative procedure in animal studies have been positive [28]. However, obvious advantages of Integra are its immediate availability in large quantities, the simplicity and reliability of its use and the functional and cosmetic properties of the resulting cover [29]. While it was originally intended for use in acute burn injuries[24], [30], it is now becoming accepted as an application in general plastic surgery, and has been used with success in a number of cases[29],[31].

Alloderm is essentially normal human dermis with all the cellular material removed. It is then virus-screened and preserved by freeze drying [32]. The first non-randomised control study of Alloderm use in 67 patients in 10 institutions [33] showed a variation in results relating to dressing technique. Thinner grafts overlying the Alloderm exhibited better take, which was deemed advantageous in terms of the donor site. Its use has now been described in various applications with some degree of success[34],[35],[36],[37].

Cell-containing matrices

As with cell-free matrices, cell-containing matrices include both synthetic matrices, often made of polyglycolic acid mesh (e.g. Dermagraft), as well as natural biological substrates usually comprising collagen and glycosaminoglycans (e.g. Apligraf). Alternatively, non-cellular matrices, such as the hyaluronic acid scaffolds, (e.g. Hyalograft-3D, Laserskin) are recommended for culture with autologous patient cells prior to grafting.

Dermagraft was developed by Cooper *et al* [38] using a polyglactin-910 surgical mesh seeded with human dermal fibroblasts. They subsequently demonstrated that Dermagraft allowed revascularisation and could support human meshed split thickness skin grafts [39]; the use of cultured keratinocyte sheets in combination with Dermagraft gave poorer results [40]. In a small clinical study on patients with full thickness burns, slightly poorer take rates of split skin autografts were observed on Dermagraft than on control wound beds, although these results did not allow for statistical analysis [41]. No clinical signs of immunological or other adverse reactions to the Vicryl mesh were reported, and further studies did not indicate a predisposition of the graft to bacteriological contamination compared with normal skin autograft.

Apligraf (originally called Graftskin) is recommended for use on venous ulcers and is the only bilayered living skin equivalent currently approved by the FDA. Its use in a parallel, multicentre, randomised control trial has been reported [19]. Of 275 patients, 63% (92 of 146) of the Apligraf cases compared to 49% (63 of 129) of controls (compression-therapy treated) were healed within six months. No clinical or laboratory evidence of rejection or sensitisation was apparent. For treatment of acute wounds, Graftskin (Apligraf) gave better than expected results with respect to take rates and

improved healing[42], although no major trials for this application appear to have been reported.

More recently, 208 patients with non-infected neuropathic diabetic foot ulcers in 24 centres in the US, were randomly treated with either Graftskin (Apligraf, 112 patients) or saline-moistened gauze (96 patients) [43]. Treatment was applied weekly for a maximum of four applications. At 12-week follow-up, complete healing was observed in 56% of the Graftskin patients compared to 38% of controls (P=0.0042). Median time to closure was significantly lower for Graftskin patients than for controls (65 vs. 90 days). Graftskin was positively recommended for use on difficult-to-heal diabetic foot ulcers. It has also been assessed for use on refractory atypical ulcers with good results [44].

Hyalograft 3-D and **Laserskin** (Hyaff-11) are indicated for use on diabetic foot ulcers and venous leg ulcers. Comprised entirely of a benzyl ester derivative of hyaluronic acid, they may be used as scaffolds for the cultivation of fibroblasts and keratinocytes. Results of an animal study and preliminary clinical data on Laserskin have shown durability, good take rates, and low infection rates when cultured with autologous keratinocytes and autologous/allogeneic fibroblast feeder cells [45]. Caravaggi *et al* [46] subsequently described the use of these products in the treatment of diabetic foot ulcers using a two-step technique. Following wound debridement, the fibroblast grafts were applied and covered with paraffin gauze. Keratinocyte grafts were then applied after approximately seven days and covered with gauze for a further seven days prior to inspection. Complete healing with no complication was achieved in 53 of 58 patients (91%) in an average time of 72±48.18 days. Subsequent histology showed good integration of grafts into newly formed granulation tissue. While these preliminary results are promising, the authors acknowledged that they should be followed up with a randomised, controlled clinical trial.

Cost versus effectiveness of new treatment regimens

What most studies fail to address, despite being a major determinant factor in treatment, is cost. The cost-effectiveness of new treatments in comparison to standard care must be considered, not only in terms of direct treatment costs, but also in terms of length of initial hospital stay, requirements for home care, additional bandaging regimens, and quality of the overall outcome.

Whilst the new treatment regimens initially may be perceived to be more expensive than traditional treatments, in many cases this additional cost is justifiable. With respect to novel dressing types, considerable clinical experience in the Wound Healing Research Unit at Cardiff has indicated that not only are some of the new treatments cost effective [47], but they have also proven to be extremely beneficial in terms of their ability to reduce pain, odour and leakage from the wounds. One of the most recent reports of this kind [48] describes the use of Promogran for the treatment of deep diabetic foot ulcers, in conjunction with good wound care practice in four European countries (France, Germany, Switzerland, UK). Promogran was found to be cost effective, perhaps even cost saving, in all countries, with slightly faster rates of healing compared with standard methods.

The cost-effectiveness of tissue-engineered skin replacements, has been borne out by evidence from a number of studies. In particular Schonfeld *et al* [49] examined the economics of Apligraf use in the treatment of venous leg ulcers. Using a tested decision analysis technique, the cumulative probabilities of ulcers healing over a 12-month period for patients treated with Apligraf (Graftskin) were significantly higher than those treated with compression therapy using Unna's boots. Apligraf treatment also resulted in an average of three months longer in the healed state per year than Unna's boot treatment. The annual estimated medical cost of patient management with Apligraf treatment equated to $20 041 compared to $27 493 for traditional therapy. Despite the initial outlay being greater, use of Apligraf led to a considerably lower overall treatment cost. Improvements in patient quality of life have also been reported [50]. Similarly, studies using Integra in reconstructive surgery, either for the release and resurfacing of tight and painful scar tissue [31], or for full-thickness cutaneous burns [26], have concluded that any additional costs could be justified by the distinct clinical benefits to patients over current treatments.

Conclusions

This review has attempted to clarify and characterise the different types of emerging agents, both novel 'bioactive' dressings and engineered skin substitutes, which are available to treat problem wounds.

For new dressing types, 'bioactivity' appears to be the way forward in maintaining a moist healing environment, offering antimicrobial properties and in cellular interactions. With respect to the silver-containing dressings, the mode of delivery appears to be an important consideration.

It is possible that tissue-engineered skin substitutes may eventually obviate the requirement for patient allografts for immediate wound coverage. However, clinical uptake of such treatments has generally been slow. Currently, the only treatment able to produce fully functional skin with all appendages (including sweat glands and hair follicles) is the full thickness autologous graft. In such a complex and competitive field, the importance of randomised controlled studies to test the effectiveness of these new products must be stressed. Where a product has been approved for a specific use, for example on venous leg ulcers, its prospective use in alternative situations still requires controlled clinical examination and meta-analysis may not be enough to justify transfer. A common limitation of studies is the small number of patients recruited, which means that results may not be conclusive. Unfortunately, it is still the case that busy clinicians and nursing professionals may prefer to continue with traditional treatments for managing patient's wounds given the logistical difficulties of setting up such studies. However, the potential benefits of the new treatments are evident. Indeed, after 20 years of research, some products (e.g. Integra) are now proving invaluable in general use.

However, with so many products coming onto the market, the difficulty is in choosing the optimum treatment for the requirements of each patient. What is required is a commitment to good quality clinical and basic research and a genuine interest in improving wound healing.

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A research paper published in October 2002 provides further data suggesting that Promogran may accelerate healing in the treatment of chronic venous leg ulcers (Vin F, Teot L, Meaume S. The healing properties of Promogran in venous leg ulcers. *J Wound Care* 11(9): 335-341).

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