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Feasibility study of an active wound dressing based on hollow fiber membranes in a porcine wound model

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ABSTRACT

Investigation: A novel active wound dressing (AWD) concept based on a microporous hollow fiber membrane network was investigated in an animal model. It provides a local solution-perfused environment for regenerative cell nutrition, wound irrigation, debris removal, electrolyte balancing, pH regulation, and topical antibiosis. The device is capable of supplying soluble factors, as tested experimentally for the recombinant human growth and differentiation factor-5 (rhGDF-5).

Methods: Following *in vitro* studies for rhGDF-5 using primary human keratinocytes and dermal fibroblasts, we employed a porcine partial thickness wound model with five distinct wounds on each back of $n = 8$ pigs. Four wound groups were perfused differently over 9 days and compared with a negative control wound without perfusion: (1) 1% trehalose solution, pH 5.5; (2) rhGDF-5 (150 ng/ml) in 1% trehalose solution, pH 5.5; (3) nutrition solution; and (4) rhGDF-5 (150 ng/ml) in nutrition solution with 1% trehalose, pH 5.5.

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Abbreviations: AWD, active wound dressing; BMP, bone morphogenetic protein(s); FCS, fetal calf serum; HDF, human dermal fibroblast(s); HFM, hollow fiber membrane(s); HK, human keratinocyte(s); NC, negative control; NUT, NUTRIFLEX solution setup; NUT+G, rhGDF-5 (150 ng/ml) in NUTRIFLEX nutrition solution with trehalose 1% solution setup; PC, positive control (healthy pig skin); rhGDF-5, recombinant human growth and differentiation factor-5; TRE+G, rhGDF-5 (150 ng/ml) in trehalose 1% solution setup; VAS, visual analog scale.

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Results: Promoted wound healing was observed within group 1 and more pronounced within group 2. Groups 3 and 4, with nutrition solution, showed significant adverse effects on wound healing ($p < 0.05$).

Conclusions: The investigated AWD concept appears to be an interesting therapeutic tool to study further wound healing support. Additionally, topical application of rhGDF-5 could be promising.

1. Introduction

Burn patients and patients suffering from chronic wounds have significantly lowered chances to effectively recapitulate lost skin function through natural healing by re-epithelialization. Burn victims start to lose natural vasculature at the time of injury. The microvascular system for delivery and removal of molecular and cellular wound healing building blocks is already impaired in partial thickness wounds (second-degree burn). A loss of capillaries in damaged skin results in accumulation of fluids and a shift of signal molecules, such as growth factors, where they are needed most.

As a consequence, cell supply is not optimal in the early phase of wound healing, electrolyte de-arrangements occur and toxins accumulate. This leads to pH fluctuations and generally to an unphysiological wound environment. To improve wound healing, we believe it could be interesting to address the damaged natural capillary system temporarily with an artificial replacement, as part of the wound dressing.

Conventional wound dressings, including gauze, polymer films, foams, and gels are incapable of providing a temporary and localized control of soluble factors within the wound bed and addressing the above issues. Silver sulfadiazine dressings were found to be consistently associated with poorer healing outcomes with biosynthetic on silicon-coated dressings, whereas hydrogel-treated burns showed improved healing outcomes over those treated with usual care [1]. Although systemic reviews of relevant literature were frequently conducted, it still appears impossible to draw firm and confident conclusions about the effectiveness of specific conventional dressings such dressings play a passive role during wound healing and predominantly in addressing the wound closure aspect. Therefore, providing a controlled wound irrigation cannot be realized. To overcome this situation, active wound dressings (AWD) were designed to provide convective mass transfer within the wound bed [2].

When designing an AWD system, it is crucial that a moist wound environment, prevention of microbial activity, and removal of exudates or toxins are considered. In this regard, a variety of wound dressings are available, however, not all meet the specific requirements of an ideal wound healing system to consider every aspect within the wound-healing cascade [3].

Wound dressings, specifically with a constant wound irrigation and liquid perfusion aspect, appear promising. Davis et al. [4] chose a simultaneous irrigation and negative pressure wound therapy (NPWT) approach in a full-thickness excisional wound inoculated with *Pseudomonas aeruginosa*. The authors found that NPWT with simultaneous irrigation further reduced the bioburden over control-treated wounds, whereby flow rate did not affect these outcomes [4].

The AWD, that we tested, is based on microporous hollow fiber membrane (HFM) capillaries and is intended to mimic an artificial capillary bed that can deliver any soluble factor to the wound site, while enabling continuous irrigation with solutions under a constant perfusion with adjustable negative pressure. By using an artificial capillary network, a decentralized mass exchange can be provided. Accordingly, a disposable artificial vascular system for temporary use should promote initial tissue engineering in the wound of the patient; and also provide a milieu in which regenerative cells sprayed into the wound would be supported as in a cell culture incubator. The device concept, with illustrations, was introduced elsewhere [5]. To temporarily replace the lack of sufficient vascularization in a wound, like chronic venous ulcers or burns, we used perfused microporous polyethersulfone hollow fiber ultrafiltration membranes (MicroPES TF10, Membrana, Wuppertal, Germany).

Thus, major aspects of healing strategies may be combined in one AWD concept; *i.e.*, controllable irrigation for keeping the wound moist, controllable perfusion for debris removal, antibiosis, nutrition, pH regulation, electrolyte balancing, detoxification, and topical factor supply.

Growth and differentiation factor activities, particularly, were described in every phase of skin wound regeneration [6–9]. During regeneration, a shift of endogenous factor concentrations was observed, often with pathophysiologically undesirable alterations, due to negative feedback mechanisms [10–15]. Therefore, compensation by topical delivery of external factors has been taken into account and various approaches were described [16–18]. However, optimal delivery systems and strategies for continuous local factor application are still being debated [19,20]. The AWD concept, involving continuous perfusion, potentially addresses the challenges of a short therapeutic window, irregular application characteristics, and undesirable shifts in doses of regenerative factors.

The investigated device has the potential of supplying factors in physiologically relevant dosages without generating application peaks. Moreover, similar to systemic kidney dialysis, the AWD may create a local solution-perfused environment for regenerative cell nutrition and it enables wound irrigation for milieu regulation and topical antibiosis.

In the present study, feasibility and safety of this concept were investigated *in vivo* using a porcine model. Using a HFM patch prototype (Fig. 1) and different irrigation solutions based on combinations of trehalose and NUTRIFLEX[1] nutrition

[1] Words in capital letters indicate trademarks throughout the text.