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Innovations in wound medicine

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ABSTRACT

The prevalence of chronic wounds is closely correlated to civilisational diseases and the ageing population. They are causing morbidity and mortality of millions of patients worldwide. Besides the individual distress, chronic wounds induce enormous and rapidly growing costs for our health care systems and society in general.

Therefore medically effective and cost efficient treatment methods are desperately needed.

"Regenerative Medicine" might offer innovative scientific solutions, including the application of stem cells, growth factors and new bioactive materials. These appliances are experimentally well described, however, clinically poorly performed. Main reasons are both legislative and economic.

This review specifies current research projects, up to date technique, innovative preclinical and clinical approaches in wound care, and activities to translate these cutting-edge techniques into clinical routine.

1. Introduction

Skin is the largest organ of the human body; for a long time it was merely seen as a simple coat just covering the body. In the meantime we know more about the diversity of physiological organic functions it has to fulfil. These functions include mechanistic, metabolic, regenerative, energetic, and immunologic aspects. Skin tissue was the first tissue which has been, at least in parts, successfully tissue engineered in vitro and has been as well successfully translated back into clinical application. Based on the fact that skin is one of the most active and continuously regenerating organs, it is a prime objective for regenerative therapies, as well as a fascinating model to learn more about the human body's intrinsic regenerative mechanisms.

Modern wound medicine starts to integrate and support the body's own regenerative capacities more systematically. Techniques of "Regenerative Medicine" are in the scientific focus, including the use of stem cells, growth factors and new bioactive materials, and combinations of these methods. Autologous stem cells of different origins (bone marrow, adipose tissue) are currently under active observation, mainly in pre-clinical research projects and increasingly in early phase clinical trials. Due to the (European) Legislative situation for "Advanced Medicinal Products" and for "Tissue/Cell Transplantation", production processes often need GMP/GLP facilities and major financial support, particularly in the establishment of the infrastructure of the GMP-facilities and the conduct of clinical trials.

2. Skin wound therapies

There does not exist *the* wound therapy, because there does not exist *the* skin wound.

Fortunately the majority of all skin wounds heal spontaneously. This is due to the fact that the human body adapted its regenerative capacity during evolution.

As a result special care is only needed, if the wound gets more complex, or if it affects deeper structures or the organism all together is in a suppressed condition.

2.1. Loss of epidermis (superficial)

The isolated loss of the epidermis, leaving the dermis intact, heals completely and without scar formation within 4–8 days. In a situation like this no specialized therapy is needed. Nevertheless a variety of therapeutically options exist, most available products just have a cooling, some additionally a local analgetic effect, and others just help to keep the wound moist.

2.2. Loss of superficial dermis (superficial dermal)

Superficial dermal injuries display blister formation. If the blister ground is exposed to air it is extremely painful.

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The up to date state-of-the-art treatment option is the occlusive therapy; it includes removing of the blisters and occlusive wound dressings.

There exist several products (silver nitrate, Marfenid, Vinegar, iodine, silver sulfadiazine, etc.) which enable microbiological control, but some of them lack sufficient moisturing capacity for the wound surface. A Rampand product – Flammacine® (silver sulfadiazine), which is simple to handle and has a favourable cost-effectiveness ratio. Disadvantages are painful daily dressing changes and the drying out of the wound area.

In the occlusive treatment the closure of the wound surface is realized with synthetic membranes under strictly sterile conditions (for example Biobrane™ or Suprathel). Advantages are that these products stay in place until complete wound healing, therefore painful dressing changes are no longer needed; nevertheless, frequent wound controls are necessary.

2.3. Loss of deep dermis (deep dermal)

After a deep dermal injury has occurred the necrotic superficial layers of the skin have to be removed either biologically or surgically until vital layers are exposed.

After bleeding control, split skin grafts are transplanted if deeper layers of dermis are involved, keratinocytes (as solution or as sheets) can be use if enough dermal tissue is preserved and the regenerative capacity of the patients is postulated to be sufficient.

If after extensive thermal trauma the remaining non-damaged body surface does not allow for sufficient amounts of split skin grafts to be taken, temporary skin substitutes, such as heterologic or xeno split-skin grafts, or amnion can be used for a short period of time to prevent both infection and also hypertrophic granulation and later scar tissue formation.

2.4. Loss of full skin (deep)

If an acute full-thickness skin defect has occurred the wound has to be debrided surgically. In a condition like this the underlying tissue is subjected to infection and trauma, since the protecting barriers, dermis and epidermis are lost. Therefore complete wound closure is the most important aim. This can be achieved with split skin graft transplantation, if needed, after pre-treatment with a dermis substitute (Integra®) and neo-dermis formation, keratinocytesheet transplantation may be sufficient.

A different therapeutic strategy is needed if a chronic full thickness skin defect exists. In chronic wounds an ''anti-healing environment'' exists and a combination of inhibitory factors prevents healing. On top, chronic wounds are usually as a minimum colonized with a multitude of microorganisms, sometimes even (locally) infected. These microorganisms have to be removed before a wound closure attempt can be successful. Using classical surgical debridement techniques the wound-environment has to be changed from anti-proliferate into pro-proliferate.

In this situation granulation tissue formation can take over or a neo-dermis can be grown using a dermis substitute. Later split skin grafts can be transplanted on the prepared new wound bed. If a pro-proliferative environment cannot be created, for example, due to advanced loss of vital and vascularized tissue, plastic surgical techniques have to be employed by using local or free tissue transfers to substitute the previous tissue loss in an adequate manner.

3. Innovative approaches and clinical trials

We will focus on very promising pre-clinical studies and on clinical phase II and III trials.

4. Regenerative approaches

Chronic wounds are the cause for suffering of millions of patient's world-wide and cause billions of dollars of costs to the health care systems [1].

Unfortunately the number of clinical trials offering high evidence levels is very rare in this area of research.

One reason for this unfavourable situation might be the difficulty in obtaining standardized and comparable wound conditions in patients, which are needed for proper scientific work.

The only reproducable wound in clinical practice is the surgically induced split-skin graft donor site. Therefore this wound type is commonly used as a study target in a many studies to compare different therapeutical strategies.

Would it be possible to activate and deactivate all necessary factors needed for wound healing and regeneration, just as needed in the distinct situation, we would have a merely universal tool for acceleration of normal regeneration and wound healing in our hands. However, it has to be taken into consideration that many, especially chronic wounds, are biologically seen far away from a normal wound healing situation. Therefore, in these instances, pathological healing processes have to be reduced in favour of biological normalization of the wound milieu.

5. Pro-regenerative agents

There are a multitude of publications investigating the effects of pro-regenerative agents on skin regeneration, but only very few of them report about the use in humans.

One pro-regenerative agent which gained increasing attention within the last years is erythropoietin (EPO). Several pro-regenerative effects, like anti-inflammatory and -apoptotic effects, stem cell activation and angiogenesis, could be shown for systemic EPO application in acute and chronic, ischeamic and diabetic environments [2–4], as well as for local application in diabetic environments [5]. In a full-thickness-defect mouse model treated with EPO, the healing process clearly improved in a dose dependent manner [6].

In a standardized murine scalding injury model the authors could demonstrate statistically significant faster wound healing and re-epithelialization after topical EPO application. Additionally the extracellular matrix proliferation was much faster and an increased gangiogenesis could be shown, with increased CD31, VEGF and eNOS levels [7].

In the same murine scalding injury model we could demonstrate the combined existence of the EPOR and the EPO-β1-hetero-receptor in the injured and the non-injured mouse skin. In the non-injured skin the receptors were downregulated after EPO treatment, but in the injured skin the receptor expression was stable under EPO treatment. Additionally a faster skin regeneration, which was of higher quality could be shown [8]. In patients even sclerodermic ulcers improved statistically significant under EPO therapy [9]. Keast and Fraser reported about four paraplegic patients, whose decubital ulcers improved significantly under systemic EPO treatment [10].

At present, the first large, prospective, randomized, double-blind, multi-centre trial, founded by the German federal ministry of education and research, is being carried out to investigate the wound healing effects of EPO in severely burned patients (EudraCT Number: 2006-002886-38, Protocol Number: 0506, ISRCT Number: ISRCTN95777824).

A promising approach, which is already used in a wider extent in clinical routine, is the treatment with platelet-rich-plasma (PRP) [11–14]. PRP is a bio mimetic, highly potential mixture of platelets and multiple growth-factors with chemo tactic and pro-mitotic qualities [15–17]. PRP suppresses pro-inflammatory cytokines and