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Accelerating the aesthetic benefit of wound healing by triterpene☆

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ABSTRACT

Intention of the study (EudraCT No 2009-017418-56) is a proof of aesthetic benefit of triterpene treatment in superficial wounds. In an open, prospective, controlled, randomized, blindly evaluated multicentre phase II clinical trial a triterpene ointment (OG-S10) is compared intra individually with a state-of-the-art moist wound healing dressing (Mepilex®) in split thickness skin graft donor sites. The graft wound areas at the upper leg were divided into two equal halves, one proximal and one distal site. Decided by randomization the one site was treated with triterpene and the other in comparison with moist dressing. Triterpene treatment went on for 14 days as covering the wound at every change of wound dressing with the ointment (100 mg/cm^2). The comparative treatment went on as covering the site by this dressing alone. The outcome of these different treatments was evaluated by two blindly observing distant experts on the basis of photographs of the wound healing progress. Photographs were taken day 14, 3 month and 1 year after treatment. The only criterion for evaluation of the two sites was similarity of the wound area to the surrounding skin in terms of colour and texture: which of the two sites, the proximal or the distal, was aesthetically superior in normal skin appearance after 14 days at the end of treatment, after 3 month of follow up and 1 year after treatment? The descriptive comparison is demonstrating quite a remarkable advantage of the ointment versus the moist wound dressing in promoting wound healing: even having in mind the small number of 24 patients within the protocol, the superiority of aesthetic benefit by triterpene treatment after 14 days (22 out of 24 patients), after 3 month (15 out of 19 patients) and after 1 year (8 out of 10 patients) is obvious.

1. Introduction

The goal in aesthetic surgery is aesthetic benefit for the patient. Rapid epithelisation of superficial wounds is an important element in achieving that aesthetic benefit. Clinical research to actively promote the healing process using locally applied drugs is part of the quality standards in aesthetic medicine (Metelmann et al., 2011). Triterpene is among the most promising compounds being investigated in this area.

Triterpenes show the potential to enhance epidermal permeability barrier recovery (Lee et al., 2006) and to stimulate wound healing (Harish, 2008) via the induction of basal cell proliferation (Jäger et al., 2008). Woelfle et al. (2010) have demonstrated the influence of highly purified triterpenes from birch cork to promote keratinocyte differentiation as the main process, including the terminal differentiation to corneocytes. The clinical effect of locally applied triterpene in the treatment of surgical lesions, e.g. CO_2-laser skin ablations, appears to be accelerated reepithelialisation, reducing the risk of infections of acute wounds, the risk of chronification of wounds and as a result the risk of unaesthetic scars (Metelmann et al., 2010).

An ointment of 10% triterpene dry extract from birch cork (TE) as active ingredient with refined sunflower oil (90%) was provided by Birken AG, Niefern-Öschelbronn, Germany. This ointment is a semisolid oleogel (OG-S10) directly useable for clinical purposes. The active ingredient consists of >80% (w/w) betulin and together 10% (w/w) of the triterpenes betulinic acid, lupeol, erythrodiol, and oleanolic acid. n-Heptane (95%; v/v) is used as an extraction solvent.

OG-S10 is intended for cutaneous use. The treatment area should be covered by a 1 mm layer in thickness (about 100 mg/cm^2).

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Concerning safety aspects TE has met the full safety program. OG-S10 has been tested before in two GCP clinical trials, including 138 patients suffering from actinic keratosis (28 + 110). In addition betulin emulsions (Birkencreme A and G and Imlan Crème Pur) were investigated in two pilot trials and two GCP clinical trials including 135 patients. The patient population included neurodermitis (33), psoriasis (24), actinic keratosis (28), and laser wound (50) patients. Safety data from these studies support the very good local tolerability of OG-S10 in healthy and damaged skin. No adverse events have been reported so far.

2. Material and methods

The aim of the study (EudraCT No 2009-017418-56) was to evaluate the aesthetic benefit of triterpene treatment in superficial wounds. In an open, prospective, controlled, randomized, blindly evaluated multicentre phase II clinical trial OG-S10 was compared intra individually with a state-of-the-art moist wound healing dressing (Mepilex®, Molnlycke Health Care, Erkrath, Germany) in accelerating the aesthetic benefit in healing of split thickness skin graft donor sites.

Split thickness skin was grafted in patients as part of complex surgical treatment. Grafting was performed in the typical way (Fig. 1a) and resulted in individual wound areas of different sizes in the upper leg (Fig. 1b).

The graft wound areas in the upper leg were divided into two equal halves, one proximal and one distal site. Decided by randomization, one site was treated with triterpene and the other with moist dressing (Fig. 1c).

Triterpene treatment was applied to the wound at every change of dressing with the ointment (100 mg/cm^2) protected by a dressing, the remainder of the site by this dressing alone. Treatment was continued for 14 days after surgery.

Evaluation of the healing was performed by two experts who assessed photographs of the wounds at another institution, having been blinded to which area of each wound had been treated with the triterpene ointment. Photographs were taken by the surgeons 14 days after the end of treatment (Fig. 1d, presenting the case of patient 01), 3 month after treatment (Fig. 1e, same patient) and 1 year after treatment (Fig. 1f, same patient) and sent to the experts (Fig. 1g) for evaluation (Fig. 1h). The code of blinding was opened after evaluation by the surgeons (Fig. 1i, using “oleogel” as study name for OG-S10).

The criterion for evaluation of the two sites was similarity of the wound area to the surrounding skin in terms of colour and texture. The three questions for the distant experts were: which of the two sites, the proximal or the distal, is aesthetically superior in normal skin appearance after 14 days of treatment? Which site is superior after 3 month of follow up? Which of the two sites is looking more similar 1 year after treatment?

The number of patients within this descriptive comparison was initially intended to a maximum of 80. The power of at least 80% reached performed after an adaptive interim analysis after 14 days of treatment finally reduced the number to 24 patients.

Patients were able to participate in this study if they were requiring skin grafting due to surgical removal of malignancies, were aged 18–95 years and prepared to comply with all the study requirements including written informed consent. Exclusion criteria were the following: patients with uncontrolled diabetes, patients who had received treatment with systemic steroids during

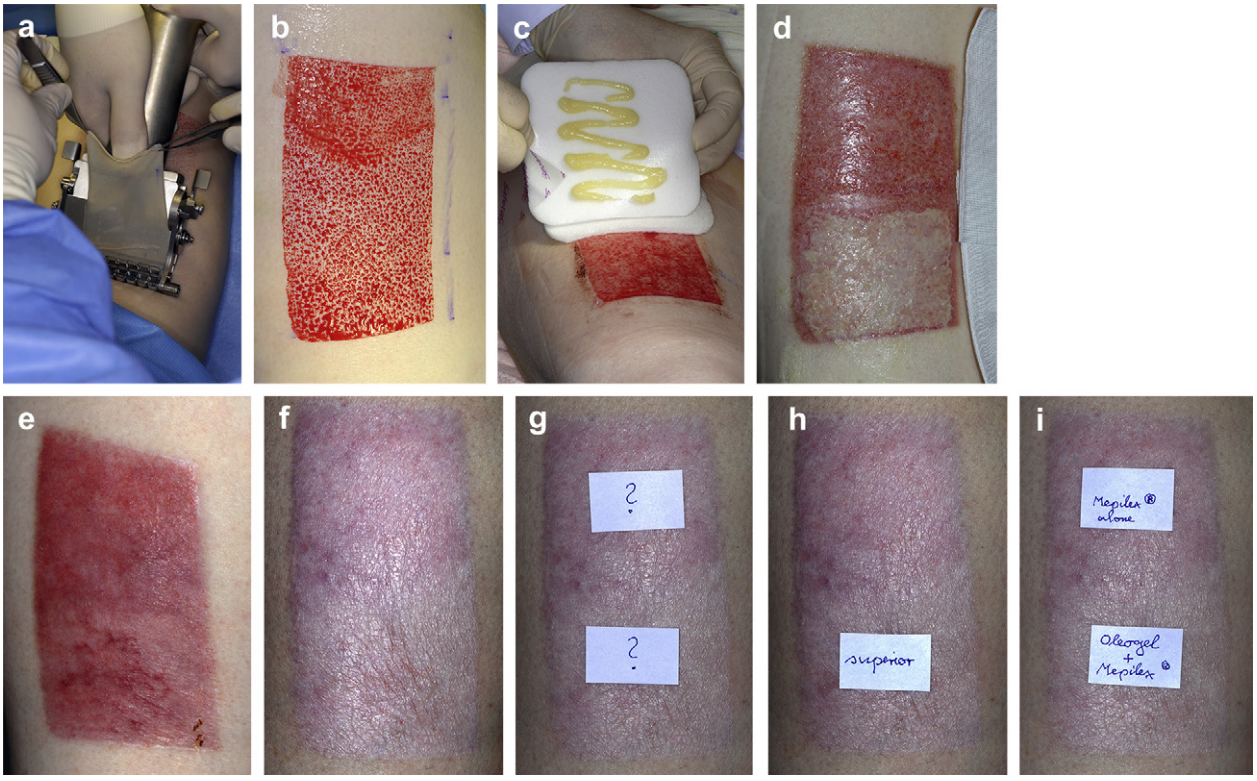

Fig. 1. Method of study. (a) Standard surgical procedure of split thickness skin grafting by using a dermatome. (b) Split thickness skin graft donor site as model wound of the study. (c) Just covering the lower half of the wound with the triterpene ointment, that is spread upon a moist wound dressing surface, while the comparative wound dressing without triterpene is already in place at the upper half of the wound. (d) Status of wound healing after 14 days of treatment. (e) Status of wound healing after 3 month. (f) Status of wound healing after 1 year. (g) Photo of the treatment result sent to the distant experts blindly, that means without letting the experts know, which of the sites has been treated with triterpene and which not. (h) Decision of the expert about superiority of aesthetic outcome. (i) Decoding of the randomization.