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Moist dressing coverage supports proliferation and migration of transplanted skin micrografts in full-thickness porcine wounds

Florian Hackl, Elizabeth Kiwanuka, Justin Philip, Philipp Gerner, Pejman Aflaki, J. Rodrigo Diaz-Siso, Geoffroy Sisk, E.J. Caterson, Johan P.E. Junker, Elof Eriksson *

Division of Plastic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

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ABSTRACT

Transplantation of skin micrografts in a 1:100 ratio regenerate the epidermis of full-thickness wounds in pigs within 14 days in a wet environment. The aim of the current study was to combine micrografts and commercially available moist dressings. We hypothesized that micrografts regenerate the epidermis when covered with a moist dressing. 5 cm × 5 cm and 10 cm × 10 cm full-thickness wounds were created on the backs of pigs. Wounds were transplanted with 0.8 mm × 0.8 mm micrografts created from a split-thickness skin graft in a 1:100 ratio. 5 cm × 5 cm wounds were treated with wound chambers, moist dressings or dry gauze (non-transplanted control group). 10 cm × 10 cm wounds were compared to non-transplanted wounds, both covered with moist dressings. Reepithelialization was assessed in biopsies from day 10, 14 and 18 post-transplantation. 5 cm × 5 cm transplanted wounds covered with moist dressings showed 69.5 ± 20.6% reepithelialization by day 14 and 90.5 ± 10.4% by day 18, similar to wounds covered with a wound chamber (63.9 ± 16.7 and 86.2 ± 11.9%, respectively). 18 days post-transplantation, 10 cm × 10 cm transplanted wounds covered with moist dressings showed 66.1 ± 10.3% reepithelialization, whereas nontransplanted wounds covered with moist dressings were 40.6 ± 6.6% reepithelialized. We conclude that micrografts combined with clinically available moist dressings regenerate the epidermis of full-thickness wounds.

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1. Introduction

Extensive burns and large wounds represent major treatment challenges. Split-thickness skin grafting is the standard of care in these difficult scenarios. However, in large burns, donor sites will have to be used multiple times and may increase the risk of wound infection and add to patient mortality [1,2]. Current skin expansion ratios at a maximum of 1:6 are often times not sufficient [3,4].

Cultured epithelial autografts provide an expansion ratio of up to 1000 times [5]. However, the cell culture process takes up to weeks, requires special laboratory facilities and puts the patient at additional risk [6,7].

Early skin grafting techniques were developed by Reverdin [8], Thiersch [9], Pagett [10] and Brown [11]. In 1958, Meek [12] described a technique for expanding a small piece of skin with a microdermatome. Using this technique an expansion ratio of 1:10 could be achieved [12,13]. However, the Meek technique required the skin pieces to be transplanted with the dermal

* Corresponding author at: Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, United States. Tel.: +1 617 732 7409; fax: +1 617 732 6387.

E-mail address: eeriksson@partners.org (E. Eriksson).
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side down to ensure dermis to dermis contact, and survival of the grafts. This made the technique extremely cumbersome [4].

Several attempts have been made to modify Meek's technique utilizing micrografts of different sizes [14-17]. The modified postage stamp graft technique (also known as the Flypaper technique) has been widely used in burn patients, especially in Asia [18-20]. However, these methods all provide similar expansion ratios as compared to the original Meek technique and still remain labor-intensive and costly [4,21,22].

Previously we have described a simple technique to create skin micrografts from an autologous split-thickness skin graft (STSG) using a handheld mincing device. The micrografts were transplanted in a 1:100 ratio and were able to regenerate full-thickness porcine wounds in healthy as well as diabetic pigs [23]. The wounds were treated in a wet environment utilizing a polyurethane wound chamber that has been tested extensively in previous experiments [24,25]. The wet environment enabled the skin micrografts to migrate and proliferate independent of orientation, which has been demonstrated in our previous work [23,26].

In this study, in order to translate the micrografting technique into a clinically applicable setting we used a common moist dressing (hydrogel and foam) in place of the wound chamber. The hypothesis of this study was that micrografts will survive and regenerate the epidermis of full-thickness porcine wounds, independent of orientation, when covered with a clinically available moist dressing.

2. Materials and methods

2.1. Animals

All experiments were approved by the Harvard Medical Area Standing Committee on Animals. Female Yorkshire pigs (Parson's Farm, Hadley, MA) weighing 50-60 kg were used for experiments. Pigs were allowed to acclimatize for 1 week prior to experiments. A total of 6 animals were used in this study: $n = 4$ in experiments including $5 \text{ cm} \times 5 \text{ cm}$ wounds; $n = 2$ in experiments including $10 \text{ cm} \times 10 \text{ cm}$ wounds. At the end of the experiment pigs were euthanized using intravenous injection of 8 ml barbiturate (Euthasol, Virbac AH, Fort Worth, TX).

2.2. Skin graft collection

Under general anesthesia the skin was depilated and cleaned with soap, 10% povidone iodine scrub (Betadine; Purdue

Products LP, Stamford, CT) and 70% isopropanol. A STSG (0.35 mm thick) including epidermis and upper dermis was harvested from the back of each pig using a pneumatic dermatome (Zimmer, Dover, OH).

2.3. Surgical mincing of split-thickness skin grafts

STSGs were washed twice in Dulbecco's modified Eagle's medium (DMEM) (Sigma-Aldrich, Steinheim, Germany) before mincing and transplantation. The mincing device consists of 24 parallel rotating cutting disks 0.8 mm apart (Xpansion Micrografting System, Wright Medical Inc., Arlington, TN) (Fig. 1A). Using the device, the graft was cut twice, with the direction of the second cut perpendicular to the first. Micrografts measuring $0.8 \text{ mm} \times 0.8 \text{ mm} \times 0.35 \text{ mm}$ were obtained (Fig. 1B).

2.4. Wounding

Wounds were randomized according to treatment and location on the back of the pigs using the online tool Research Randomizer (<http://www.randomizer.org>). The same number of wounds belonging to each group and time point were present on each pig. After marking wound locations in two parallel paraspinal stripes on the dorsum of the pig, outlines were tattooed with black ink using an electric tattoo marker (Spaulding & Rogers, Voorheesville, NY). Full-thickness wounds down to the panniculus carnosus were excised. Wounds were separated by at least 4 cm of unwounded skin.

2.4.1. $5 \text{ cm} \times 5 \text{ cm}$ wound model

A total of 12 wounds measuring $5 \text{ cm} \times 5 \text{ cm}$ were outlined and excised as described above. Hemostasis was achieved using electrocautery. A total of 39 micrografts, each measuring $0.8 \text{ mm} \times 0.8 \text{ mm}$ (total surface area of 24.96 mm^2), were transplanted and spread evenly over the wound bed in $5 \text{ cm} \times 5 \text{ cm}$ wounds, without regard to orientation (dermal side up or down) (Fig. 2B).

The transplanted wounds were covered with either a moist dressing (Fig. 2A) consisting of hydrogel (Tegaderm™ Hydrogel, 3M Health Care, St. Paul, MN) and foam (Tegaderm™ Foam, 3M Health Care, St. Paul, MN) or polyurethane wound chambers. The wound chamber model has been validated extensively in previous studies [23,24]. Non-transplanted wounds covered with dry gauze dressings served as controls. Micrografts were allowed to adhere to the wound bed for 30 min before the dressings were applied.



Fig. 1 – Creation of skin micrografts. (A) Mincing device consisting of 24 parallel rotating cutting disks spaced 0.8 mm apart. (B) $0.8 \text{ mm} \times 0.8 \text{ mm}$ micrografts obtained from a split-thickness skin graft by two perpendicular cuts using the device.

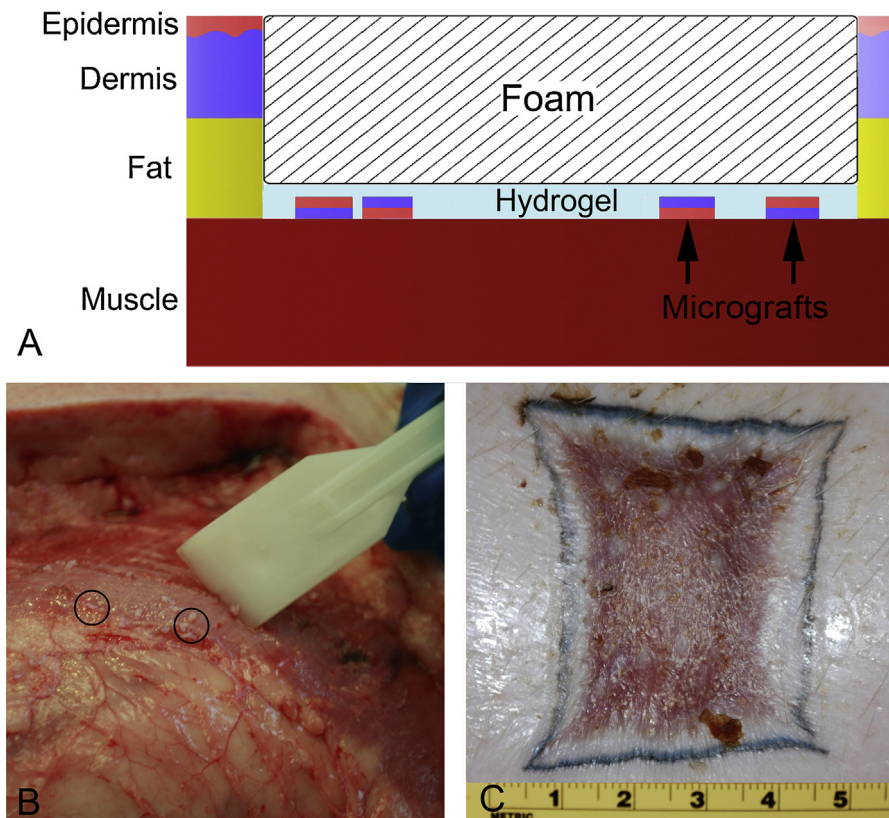


Fig. 2 – Transplantation of micrografts to porcine full-thickness wounds. (A) Illustration of wound with micrografts transplanted independent of orientation, covered with a moist dressing (hydrogel and Tegaderm™). (B) 5 cm × 5 cm wound immediately after wound creation. A sterile spatula is used to evenly spread the micrografts (circles). (C) Macroscopic picture of a fully epithelialized wound 18 days post transplantation.

In the moist dressing group, 5 cc of hydrogel were directly applied to the wound (Fig. 2A). The dressing was secured with sutures (3-0 Ethilon, Ethicon, San Angelo, TX). Moist dressings were changed on post-operative days 6, 10 and 14. Diagonal full-thickness biopsies were taken on post-operative days 10, 14 and 18. Once biopsied, wounds were excluded from further evaluation.

In the wound chamber group, a thin layer of medical adhesive (Hollister Inc., Libertyville, IL) was applied directly onto the skin surrounding the wounds, and a polyurethane wound chamber (Corium International, Grand Rapids, MI) was applied to cover each wound. 1.5 ml of keratinocyte medium (Epilife®, Invitrogen, Grand Island, NY; containing human keratinocyte growth supplement, calcium-depleted serum, gentamicin, amphotericin, penicillin and streptomycin) was added to the wound chamber via an injectable port. The wound fluid was aspirated and replaced every 24 h with 1.5 ml of saline (0.9% NaCl injection, USP, Baxter) containing 100 U/ml penicillin and 100 µl/ml streptomycin.

2.4.2. 10 cm × 10 cm wound model

A total of 10 wounds measuring 10 cm × 10 cm was outlined in two paraspinal stripes on the dorsum of the pig. Wounds were separated by at least 4 cm of unwounded skin. Full-thickness wounds down to the panniculus carnosus were excised. Hemostasis was achieved using electrocautery. A total of 156 micrografts, each measuring 0.8 mm × 0.8 mm (total surface

area of 99.84 mm²), were transplanted and spread evenly over the wound bed without regard to orientation (dermal side up or down).

A total of 20 cc of hydrogel was directly applied to each wound. The dressing was secured with sutures (3-0 Ethilon, Ethicon, San Angelo, TX). Moist dressings were changed on post-operative days 6, 10 and 14. Diagonal full-thickness biopsies were obtained at the end of the experiment on post-operative day 18. Non-transplanted wounds covered with moist dressing served as controls.

2.5. Histological evaluation

Biopsies were fixed in 10% formalin solution, embedded in paraffin, and cut into 6 µm thick sections. After rehydration, slides were stained with hematoxylin and eosin or Masson's trichrome for routine histology. Re-epithelialization was evaluated in hematoxylin and eosin stained slides using an ECLIPSE E400 light microscope (4×/0.10, 10×/0.25, 40×/0.65), DIGITAL SIGHT camera and NIS-Elements D3.0 digital image analysis system (Nikon Corporation, Kanagawa, Japan). Re-epithelialization was expressed as percent epithelialized length over total length of the wound cross-section.

2.5.1. Evaluation of wound contraction

Before creating the 5 cm × 5 cm wounds, borders were tattooed with India ink. The initial surface area of the wounds

was 25 cm². At day 10, 14 and 18, the surface area of all wounds was measured using computer planimetry (NIS-Elements D3.0 digital image analysis system, Nikon Corp., Kanagawa, Japan). Contraction was expressed as percent of original wound surface area.

2.6. Statistical analysis

Statistical analyses were performed using 2-way ANOVA with Bonferroni correction to compare 5 cm × 5 cm wounds in regards to re-epithelialization and contraction. A Student's *t*-test was used to evaluate re-epithelialization in 10 cm × 10 cm wounds. All results are given as mean ± SD. A *p* value of less than 0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism 5.0 (GraphPad Software Inc., LaJolla, CA).

3. Results

3.1. Reepithelialization 5 cm × 5 cm wounds following micrograft transplantation in a 1:100 ratio

Reepithelialization was assessed in diagonal full-thickness biopsies from day 10, 14 and 18 post-transplantation. Transplanted wounds treated with a hydrogel and foam dressing showed 36.1 ± 10.8% reepithelialization by day 10, 74.3 ± 18.9% by day 14 and 90.5 ± 10.4% by day 18, similar to wounds enclosed in a wound chamber with 47.9 ± 17.3%, 63.9 ± 16.7 and 86.2 ± 12.0%, respectively. No statistical difference was observed between the two transplanted groups at any time point. Gauze covered control wounds were 39.3 ± 6.6% epithelialized on day 14, and 58.6 ± 18.3% on day 18, significantly lower than both transplanted groups (*p* < 0.05 and 0.01, respectively) (Fig. 3A).

3.2. Reepithelialization 10 cm × 10 cm wounds following micrograft transplantation in a 1:100 ratio

Reepithelialization was evaluated on day 10 post-transplantation in diagonal full-thickness biopsies. Transplanted wounds showed significantly greater reepithelialization with 66.1 ± 10.3% compared to non-transplanted wounds with 40.6 ± 6.6% (*p* < 0.005) (Fig. 3B).

3.3. Histological and macroscopic evaluation of transplanted micrographs

Transplanted micrografts proliferated and migrated to the surface of the wounds within 10 days post-transplantation in both 5 cm × 5 cm and 10 cm × 10 cm wounds. The original stratum corneum was expelled once the micrografts reached the wound surface (Fig. 4A and B). Islands of newly formed epithelium were evident upon macroscopic observation in wounds starting on day 10 post-transplantation (Fig. 2C). At day 18 post-transplantation, the wounds were close to full reepithelialization (Fig. 4C).

3.4. Wound contraction

On day 10 post wounding, the surface area of 5 cm × 5 cm wounds treated with micrografts and moist dressings, micrografts and wound chambers, and dry controls were 71.5 ± 10.5%, 60.0 ± 13.0% and 86.2 ± 13.7% of the original wound surface area, respectively. Both groups treated with micrografts showed significantly reduced surface area compared to dry controls (*p* > 0.01). On day 14, wounds covered with moist dressings, wound chambers and dry controls were 58.4 ± 8.6%, 51.1 ± 10.7% and 71.1 ± 6.2%, respectively. The wound chamber treated group showed a significantly reduced surface area compared to dry controls (*p* > 0.01). On day 18,

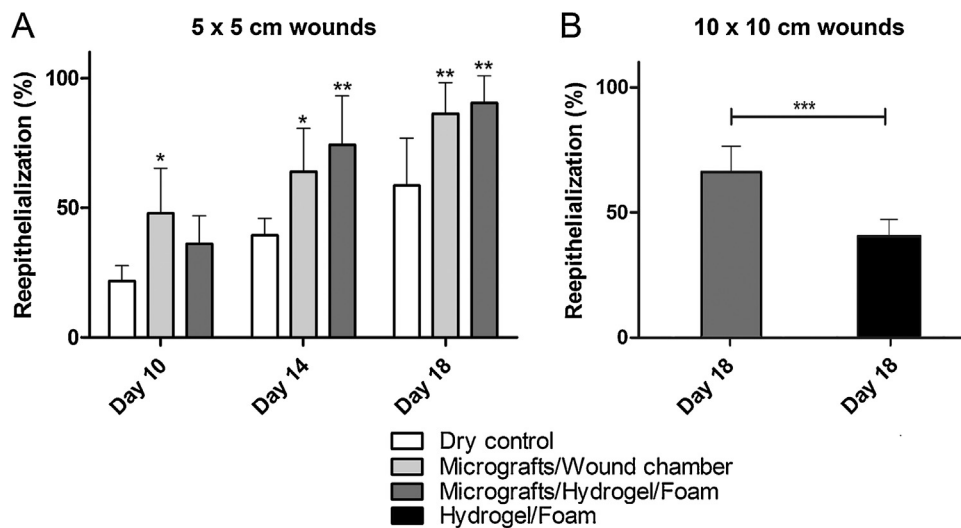


Fig. 3 – Re-epithelialization of full-thickness wounds. (A) Diagonal cross-sections of 5 cm × 5 cm wounds were evaluated with regard to reepithelialization on post-operative day 10, 14 and 18. Transplantation of micrografts resulted in a significantly higher percent reepithelialization. There were no significant differences between micrograft transplanted wounds covered with a wound chamber or moist dressings. **(B)** Diagonal cross-sections of 10 cm × 10 cm wounds were evaluated with regard to reepithelialization on post-operative day 18. Transplantation of micrografts resulted in a significantly higher percent reepithelialization. **p* < 0.05, ***p* < 0.01 ****p* < 0.005.

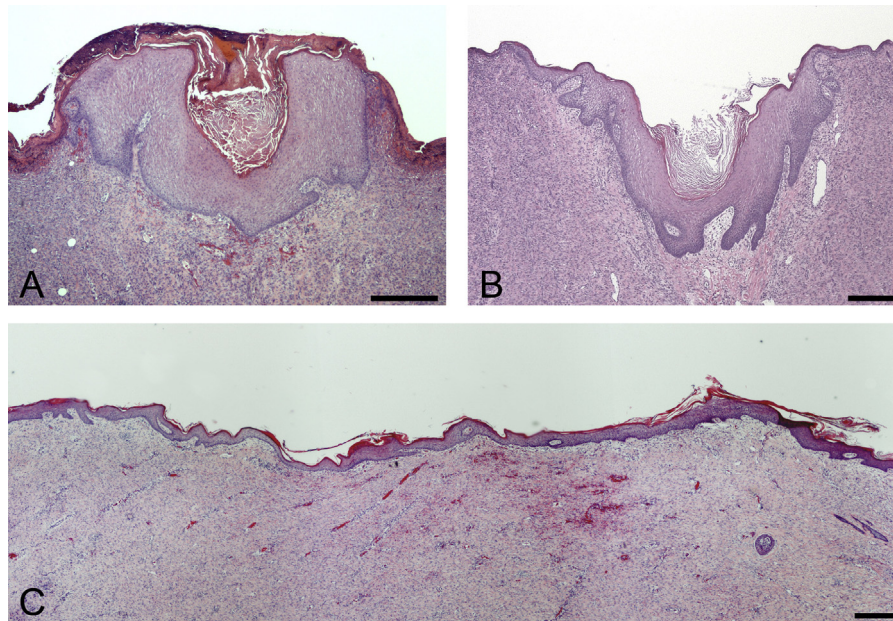


Fig. 4 – Hematoxylin–eosin staining revealing reepithelialization following micrograft transplantation of full-thickness wounds. (A) Micrografts migrated to the wound surface by postoperative day 10. (B) The stratum corneum was expelled through the wound surface after 14 days. (C) Central area of a fully healed wound 18 days post transplantation. Scale bars equals 200 μm .

wounds covered with moist dressings, wound chambers and dry controls were $54.9 \pm 9.8\%$, $44.2 \pm 9.3\%$, and $45.2 \pm 16.5\%$, respectively. There were no statistically significant differences at this time point (Fig. 5).

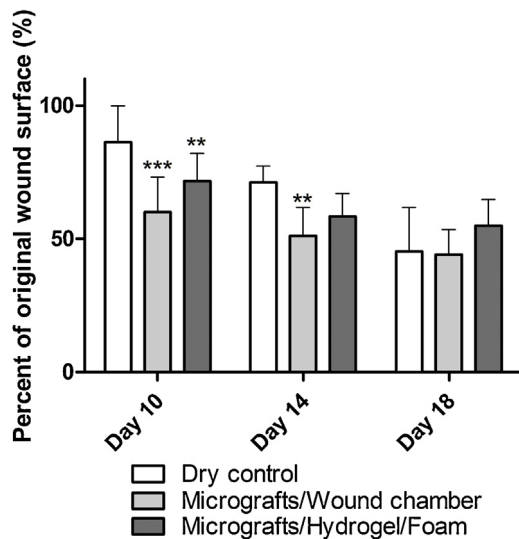


Fig. 5 – Wound contraction in 5 cm \times 5 cm wound on post-operative days 10, 14 and 18. Micrograft transplanted wounds covered with moist dressings or wound chambers displayed significantly increased contraction on postoperative day 10. At post-operative day 14, wounds covered with wound chambers showed significantly increased contraction. No significant difference between the treatment groups was observed on post-operative day 18. ** $p < 0.01$, * $p < 0.005$.**

4. Discussion

In previous studies we have shown that micrografts that are transplanted to full-thickness porcine wounds migrate and proliferate similar to cultures of single cell keratinocytes [27]. Moreover, it could be shown that transplanted micrografts can regenerate full-thickness porcine skin wounds even when transplanted in a 1:100 expansion ratio if covered with a wound chamber [23]. The wet wound chamber microenvironment allows for orientation-independent transplantation of the micrografts [23,26,28].

In a study published by Kiwanuka et al. [28], transplantation of micrografts in a full-thickness porcine wound model was compared to conventional treatment using split-thickness skin grafts (STSGs). It was found that transplantation of micrografts improve wound healing parameters such as macroscopic scar appearance, wound contraction, neoepidermal maturation, rete ridge formation, granulation tissue thickness and width, and scar tissue formation, comparable to treatment with STSGs [28].

The results obtained in this study illustrate that transplantation of micrografts in combination with a clinically available moist dressing enhance the reepithelialization of full-thickness wounds compared to non-transplanted control wounds. Furthermore, in 5 cm \times 5 cm wounds, no difference in the degree of reepithelialization between wounds covered with a moist (hydrogel and foam) or wet (wound chamber) was observed. This indicates that proliferation and migration is independent of micrograft orientation (dermal side up or down).

Wounds treated with micrografts displayed a higher degree of contraction at the early time points as compared to dry

control. By day 18 post wounding, no significant differences could be found between the treatment groups.

In order to further investigate the beneficial effects of micrograft transplantation and coverage with a moist dressing, we employed a larger wound model (10 cm × 10 cm). We feel that this represents a clinically more relevant wound size, which requires a relatively long time before spontaneous healing occurs. The results gathered from the experiments with the 10 cm × 10 cm wounds reveal that transplantation of micrografts lead to significantly faster healing as compared to moist dressing only treated wounds.

Taken together, the two experiments performed using different wound sizes illustrate that micrografts covered with a moist dressing enhances wound healing to an extent comparable to micrografts in a wet wound chamber microenvironment.

In wounds transplanted with micrografts, the healing process is driven by proliferation and migration of the keratinocytes. We hypothesize that transplanted micrografts of a certain size (0.8 mm × 0.8 mm) initially mainly survive by diffusion of wound fluid rather than neovascularization, and that this process is supported by the environment created by the moist dressing. Moreover, the micrografts survive and proliferate independent of orientation and contribute to reepithelialization of the wound. This fact makes the proposed methodology of micrograft transplantation clinically appealing, without the need of time-consuming procedures. An interface layer in combination with the moist dressing can be used to protect the micrografts and neopeidermis from disruption.

In a case report published in 2010 by Major R. Danks, a US Army surgeon, the use of skin micrografts covered with a moist dressing was employed to treat a large burn wound of a Iraqi civilian [29]. This patient has the distinction of being one of only a few patients to survive a >50% TBSA burn injury with treatment outside of a non-specialized burn center.

Micrografting is a promising method for achieving higher expansion ratios than possible with conventional split-thickness skin grafting techniques. The use of a moist dressing to cover transplanted wounds enables wide-spread clinical use of this methodology in wound care.

Conflict of interest statement

Dr. Eriksson is a member of a limited liability company that receives royalty payments on the sale of micrografting equipment.

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