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METHODS

SkinDot: A modified full-skin transplantation technique

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ABSTRACT

Existing epidermal transplantation procedures applied in burn surgery or wound treatment, such as mesh grafting or the Meek method, do not lead to a restoration of all the skin layers. Dermal skin layers are indispensable in ensuring the quality and function of the transplanted skin as a frictional surface and a carrier of skin appendages such as hair, sweat glands, and sebaceous glands, as well as nerve receptors for detecting pressure, vibration, and temperature. Because of the restricted skin surface area that can be provided by the donor, full-skin transplants cannot be transplanted over a large area. Cultured skin procedures, based on skin cells cultivated in a laboratory, have not yet reached a stage of development where a complex full epidermal transplantation is possible. In particular, the introduction of skin appendages with a functional cell-to-cell communication has not been observed thus far in cultivated skin. Based on the Reverdin transplantation method, in which concave skin islands with epidermal and dermal parts are transplanted, Davis in 1910 described the transplantation of multiple 2–5 mm sized full-skin islands as a new method for the treatment of skin lesions. Further modifying this 100-year-old procedure, we developed a miniaturization and automation of the Davis transplantation method that started in 2011 and called it “SkinDot”. In the following article we describe the effectiveness of the full-skin island transplant procedure in two patients. The transplantation of single 2–3 mm full-skin islands results in a full-skin equivalent without any limits on donor area and with a reduced donor morbidity.

1. Introduction

Due to restrictions on the size of donor skin, split-skin transplantation remains the state-of-the-art method when treating patients with large area burns (Smolle et al., 2017). A maximum of 2–3 percent of the body surface can be transplanted using autologous full-skin, while larger areas can only be transplanted after a complex and lengthy expansion process (Motamed et al., 2008). However, split-skin transplantation does not result in a replacement of a dermal skin layer and cannot achieve an ideal result for the patient, especially where skin appendages are also absent. The use of allogenic and alloplastic dermal replacement matrices has significantly improved the quality of transplanted split skin in recent years, but remains costly, fragile, and expensive, especially with a two-stage application (Debels et al., 2015). In the years 1975 through 1979, Rheinwald and Green described the first clinical outcomes of the transplantation of in vitro cultured epidermal cells cultured (Rheinwald and Green, 1975). Since 1981, cultured epidermal autografts (CEA) have been routinely used in the treatment of severely burned patients (Still et al., 1994). However, only the work of Cuono in 1987 and Hickersen in 1994, which additionally described allogeneic dermis in the wound bed before CEA transplantation, improved the take rate of transplantation of laboratory cultured keratinocytes (Cuono et al., 1986; Hickerson et al., 1994). In the meantime, bilaminar skin replacement matrices based on keratinocytes and fibroblasts have become commercially available, while tri- and multilaminar constructs of cultured cells for skin transplantation are currently being researched worldwide. Such tissue engineering procedures have inspired the term “skingineering”, a term describing the various means of creating and implanting bio-engineered human skin (Hartmann and Ottomann, 2016). Other dermal-engineered matrices and engineered dermo-epidermal matrices may become available for transplantation in the future. Nevertheless, the results of CEA transplantations have

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fallen way short of expectations: even 40 years after the results presented by Rheinwald and Green, multiple skin cell layers are not yet available for use in CEA procedures, as the complex nature of skin as an organ making use of side-by-side and consecutive cell-to-cell communication was completely underestimated (Atiyeh and Costagliola, 2007). Another approach for transplanting dermal layers or full-skin segments has been to further miniaturize the method of Reverdin and Davis. Inspired by the transplantation method of the French dermatologist Jaques-Louis Reverdin from 1869, J.S. Davis, the father and pioneer of American plastic surgery, described a novel full skin transplantation method he called "The Small Deep Graft" (Reverdin, 1874). Davis successfully transplanted 2–5 mm skin islets individually into the wound. The islands were obtained using cannulae, which rendered his full-skin transplantation method a time-consuming procedure (Davis, 1914). Because of the limited technological capabilities at the beginning of the 20th century to accelerate the procedure with a device, Davis chose a spacing of up to 0.75 cm between the individual full-skin islets. However, this method did not produce cosmetically favorable results when compared with the full-skin equivalent. Therefore, we developed devices that allow the automated transplantation of 1–3 mm full skin islets. In order to demonstrate the effectiveness of our full-skin islet transplantation method, we performed our newly developd full-skin transplantation technique "Skindot" on two patients with the approval by the Ethics Committee of the University of Lübeck (AZ 18-189). Here, we present for the first time the technique and results from these first two operations.

2. Methods

Based on the observation that 2–3 mm punch biopsies cause barely visible, minimal scars or textural changes, and offer full-skin islets containing all the skin appendages, this new transplant procedure renders an immediate autologous intraoperative wound closure possible, and is equivalent to a consecutive full-skin transplant. The procedural improvement lies in the currently technical facilities, which were not possible in the olden days of Reverdin and Davis. While Davis transplanted the 2–3 mm full skin islands with a gap of up to 0,5 cm with consecutive sub-optimal cosmetic results, our improved technique is founded in a 1–3 mm full skin island transplantation with a distance of 0,1–0,2 cm.

The autologous full-skin islands are taken with a 2 or 3 mm punch biopsy and integrated into a collagen matrix (Integra® and Matriderm®), so that different skin layers and skin appendages are allowed to migrate into the gaps between the implemented full-skin islets and the surrounding tissue (Fig. 1).

Patient 1: Non-secondary closable wound after lateral dermatofasciotomy for compartment syndrome of the lower leg. Transplantation of 100 × 3 mm full-skin islets from the left thigh, with explantation using 3 mm punch biopsy skin punches (KAI Europe). Integration of the 3 mm sized islets into an Integra Single Layer Matrix® consisting of bovine collagen and hyaluronic acid. Transplantation of the matrix with the 100 embedded 3 mm islets onto the NPWT-conditioned wound on the left lower leg. Bandaging with Mepithel® and NPWT (100 mmHg, for 7 days, continuous mode).

Patient 2: Secondary wound healing after dermatofasciotomy of the lower leg for compartment syndrome with only an incomplete secondary wound closure. Transplantation of 100 × 2 mm full-skin islets. Explantation from the right thigh using 2 mm punch biopsy skin punches (KAI Europe). Integration of the 2 mm sized islets into a custom-made 4 mm Matriderm Matrix® consisting of bovine collagen. Transplantation of the Matriderm Matrix® with the 100 embedded 2 mm islets onto the NPWT conditioned wound on the right lower leg. Bandaging with Suprathel®, fatty gauze, and NPWT (100 mmHg, for 7 days, continuous mode).

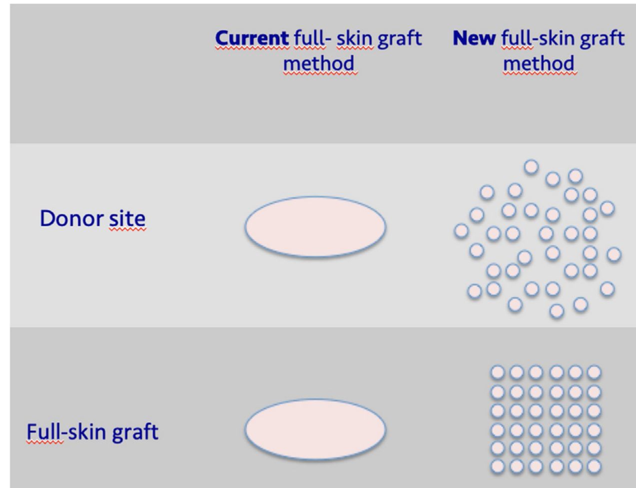

Fig. 1. This diagram shows the principle of established and modified full-skin explantation and full-skin transplantation.

3. Results

Patient 1: 100 full-skin islets, each with a diameter of 3 mm, were taken by a biopsy punch and integrated into the matrix before subsequent transplantation onto the wound (Fig. 2a, b). Fig. 2c shows the findings during the first dressing change after a ten-day VAC where a 100% take rate of the transplanted 3 mm full-skin islets was observed. Fig. 2d–f show the increasing confluence of the full-skin islets on their way to form a full-skin equivalent including hair growth. Fig. 2g shows the explantation area at the upper leg nine months after the operation.

Patient 2: Fig. 3a shows the Matriderm matrix® with 100 × 2 mm islets immediately before transplantation into the wound on the right lower leg after explantation of the islets from the patient's right thigh (Fig. 3b). The results of the first dressing change after ten days of negative pressure therapy at −100 mmHg are shown in Fig. 3c. Fig. 3d and e show the course of the wound closure and the re-epithelialization. Overall, a smoother skin texture of the graft was cosmetically apparent after nine months, so that the 2 mm full-skin islet transplant seemed to be superior to the 3 mm islets (Fig. 3f). After nine months, the donor area was largely free of scarring (Fig. 3g).

4. Discussion

In case of large burn wounds full coverage of the patient's wound with autologous skin transplants is still impossible due to a limited donor area. For this clinical scenario several techniques have been developed to solve this problem: Transplantation of skin grafts or keratinocytes cultured in a laboratory or split skin transplantation procedures. As the desired end product are largely differentiated, multi-layered, transplantable keratinocytes and skin appendages, these techniques often offer both functionally and aesthetically poor results. This is due to the fact that many skin appendages are required to ensure that a sufficient skin quality is achieved. The multifaceted nature of the human skin as an organ and the cell-to-cell communication based on highly complex physiological cascades contained therein were initially wholly underestimated with skin cultured in the laboratory (Zeng et al., 2018). In case of skin loss spanning over a large area, the transplantation of an

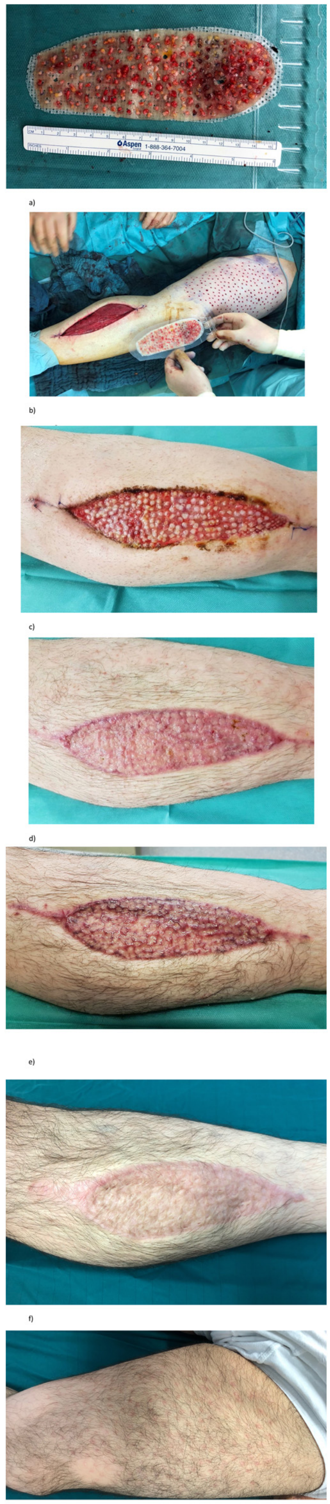

Fig. 2. a) Patient 1: 100 full-skin islets of 3 mm diameter embedded within an Integra® matrix. b) Patient 1: Transplantation of the 100 full skin islets onto the NPWT-conditioned wound on the left lower leg. c) Patient 1: Findings during the first dressing change 10 days after transplantation with the SkinDot technique showing a 100% take rate. d) Patient 1: Increasing confluence of the transplanted full-skin islets six weeks after skin transplantation with the new SkinDot technique. e) Patient 1: Findings three month after full-skin island transplantation with the new SkinDot technique. f) Patient 1: Post-operative result after nine months. g) Patient 1: Explantation area at the upper leg nine month after the operation.

Fig. 3. a) Patient 2: Harvesting of the 100 full skin islets of 2 mm diameter from the right thigh. b) Patient 2: 100 × 2 mm full-skin islets embedded in a custom-made Matriderm® matrix. c) Patient 2: Findings ten days after full-skin transplantation with the new SkinDot technique and NPWT treatment. d) Patient 2: Findings four weeks after full-skin islet transplantation (SkinDot). e) Patient 2: Findings three month after transplantation. f) Postoperative result after nine months. g) Patient 2: Findings at the donor area on the right thigh nine months after harvesting of the full-skin transplant islands.

autologous epidermal split-skin graft still therefore represents the state-of-the-art. These 0.2–0.5 mm thick transplants can not only result in cosmetically stigmatizing scarring, but can also often lead to functional losses due to scar contraction, since the dermal layer as a frictional interface is also missing. The issue of poor split-skin graft quality can be circumvented with full-skin transplantation. Due to the limited size of the donor area, even nowadays a maximum of 2–3% of the body surface can be transplanted using autologous full-skin. The new full-skin transplantation procedure presented here opens up a new therapeutic approach for large-area wound care using an intraoperatively-produced full-skin equivalent. The procedure is based on the pioneering work of Reverdin from 1869 as well as the advances described by Davis in 1910. Oddly enough, the Davis transplantation procedure was not able to assert itself and had not been further developed, although technical developments have long allowed an automation of the full-skin transplantation procedure. With the two patients depicted, we were able to demonstrate that our full-skin transplant method leads to a full-skin equivalent. The extent to which this new full-skin equivalent shall be deemed functional in a sensory and tactile sense will be validated using a Cutometer® as well as the 2-point discrimination test in future investigations. The extent to which the different skin layers can become confluent in the gaps between the full-skin islets and the surrounding tissue, or indeed poor quality tissue grows into such gaps, must be determined by histological examination. The subject of further investigations will therefore be to calibrate the spacings between each transplanted islet. This way, the level of confluence of the skin islets can be determined. The healthy tissue in the islets that have been transplanted thus far seems to encourage the idea that new dermal skin layers will become confluent in the gaps between the full-skin islets integrated within the matrix. The bonding of island and tissue is also supported by adipocutaneous stem cells attached to the islets. This should result in a full-skin equivalent, which is characterized by an improved quality and functionality of the transplanted skin compared to the previous epidermal split-skin transplantation techniques. In summary, this new technique represents a novel method for ensuring large-area autologous and immediate intraoperative wound closure with full-skin.

5. Conclusion

We have been able to apply this new full-skin islet transplantation method with two patients and have demonstrated its technical feasibility and efficacy. The results of these two transplantations are encouraging: a take rate of almost 100% was observed, and the benefits of a full-skin transplantation without a limited donor area as well as low donor morbidity were also evident.

In summary, this new technique offers the following advantages compared to earlier skin transplant procedures:

- Establishment of an autologous full skin equivalent that corresponds to the quality of full-skin
- Immediate unlimited intraoperative availability for a single-session definitive wound closure
- Higher mechanical strength due to transplantation of dermal skin layers
- Higher quality of the graft due to transplantation of the skin appendages
- Low donor morbidity with cosmetically favorable results where explantation can take place almost anywhere.

Based on these positive results, we will continue our clinical evaluation of this method. The degree of sensory and tactile function of the full-skin equivalent, and the extent to which the skin layers become confluent in the gaps between the transplanted full-skin islets remain the subject of our further research.

Ethic SkinDot

In regard to our submitted manuscript (SkinDot: A modified full-skin transplantation technique) I hereby declare that the described operations were performed in accordance to the ethical values of the Declaration of Helsinki. Moreover, we have a positive votum of the Ethics Committee of the Universities of Lübeck and Berlin.

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