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Original Research Article

Autologous skin micro-grafts and allogenic skin allograft for mitten hand deformity treatment in epidermolysis bullosa

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ABSTRACT

Background: In the genetic skin blistering disorder dystrophic epidermolysis bullosa recurrent blisters and erosions on mechanically stressed areas, as the hands, result in subsequent scarring and development of pseudosyndactylies and contractures. In its most severe form, all fingers are constrained into a fist of scarred ("mitten-hand"-deformity). No causative therapy exists and only a surgical release of the fingers is possible. Hereby, the development of large skin defects is inevitable; the lack of healthy autologous skin for grafting remains a difficult challenge.
Methods: We propose a new technique: It adopts a treatment strategy from the therapy of large extent burns and consists of a combination of autogenic and allogenic skin grafting.
Results: We present a beneficial outcome in 18 mitten hand deformities treated with this technique. In all patients, the initial functional outcome was improved. Nearly all patients got a considerably widened grip span and durable skin conditions post-operatively. Mean follow-up was 3 years. Typically, recurrence of the scarring occurred from 6 months to 2 years after operation.
Conclusions: This is the first report on the use of the combination of autogenous pinch skin grafts with allogenic (parental) skin overlay for skin defects in EB. It provides undisturbed wound healing under a "biological dressing", furthermore, a temporary take of the parental skin was visible. Defects were permanently covered with skin of increased mechanical stability, hand function improved remarkably.
However, long term follow-up showed beginning recurrence in most of the patients comparable to recurrence rates described in the literature.

Keywords: Epidermolysis bullosa, Soft-tissue defects, Treatment of mitten hand deformity, Combined auto-/allo-skin graft, Skin transplantation

INTRODUCTION

The genetic skin fragility disorder epidermolysis bullosa (EB) remains a scourge for those who suffer from this rare, incurable disease, in particular from its severe generalized recessive dystrophic form.[1] It is characterized by blistering of the skin and mucosa after minor trauma resulting from an inadequate connection of the skin layers due to mutations in the gene encoding for collagen VII. Healing of the blisters is associated with scarring, which on the hand leads to development of pseudo-syndactylies, where the fingers are trapped in a cocoon of scarred tissue. Along with esophageal strictures, the mitten-like hand deformity is causing a maximal functional impairment in these severely affected patients.[2]

Numerous concepts for the surgical treatment of the mitten-hand-deformity have been suggested. Most of them aim at separating and straightening all fingers, however with different degrees of invasiveness, ranging from blunt separation and corrective dressings to complete surgical division of all pseudo-syndactylies, open arthrolysis and internal K-Wire fixation of the phalanges.[3]

The major difficulty in the surgical treatment of EB-associated mitten deformities is the lack of intact autologous skin graft donor sites to resurface the resulting soft tissue defects. Some authors favor secondary wound healing for the skin defects, while other authors use full or split skin grafts from less affected areas of the patient or acellular dermal matrices.[4-7]

Similar to the treatment of extensive burn wounds, the predicament of defect coverage in surgical EB-treatment is the incongruity between the need for an optimal i.e., healthy autologous– skin for immediate and permanent wound coverage and the lack thereof due to the extent of injury or the primary disease, respectively. To overcome the shortcomings of the current concepts, we suggest a new treatment option based on an established one for large-area burn wounds: The "Chinese intermingled technique introduced in 1980, and its modification by Alexander et al. known as the "sandwich technique", respectively.[8,9] Both techniques combine the advantages of autogenous and autologous skin transplantation by covering large burn wounds with autogenous skin that is widely meshed or harvested as single "pinch grafts", measuring only a few mm² each, thus minimizing donor site morbidity.[8,10] A second layer of allogenic (i.e. glycerol preserved cadaveric) skin is placed above, serving as "biological dressing"; furthermore a long term incorporation of dermal components has been described.[11] There is evidence that matrix and even cellular components of the allografts are integrated into the recipient site long term.[11]

In our experience, especially the parents of the underaged patients dislike the idea of using allogenic cadaveric skin for wound dressing on their children and are frequently very pleased to be able to donate for their children.

We therefore modified this approach using a skin graft donated by the patient's parents instead of cadaveric skin and experienced encouraging results with regard to healing time, postoperative pain and hand function.

The objective of this study is to describe and evaluate this technique.

METHODS

Between 2012 and 2019, all patients with mitten hand deformities suffering of dystrophic epidermolysis bullosa (DEB) (Figure 1A) were treated as presented below.

Preoperative workup

The diagnosis dystrophic EB was molecularly confirmed in all patients with pseudo-syndactylies and they underwent complete workup for the EB-related systemic manifestations.[12]

Operative procedure

All operations were performed by a highly-experienced specialist. A complete separation of all digits with reconstitution of the web spaces -in particular the first one- was performed, followed by straightening of the digits with release of the contract scars around the joints and arthrolysis. The development of extensive soft tissue defects with partial exposure of functional hand structures was inevitable, in order to achieve a maximum grip span. For defect coverage, a full-thickness skin graft was harvested from one of the parents from a location, where an incision can be inconspicuously placed and closed primarily under local anesthesia such as the groin, the medial aspect of the upper arm or the lower abdomen. Preoperatively, donor blood testing for HIV, HBV, HCV and Treponema pallidum was routinely carried out. The procedure was carried out with approval of the competent authority (25-5483/2, Regierungspräsidium Freiburg, Germany) and conducted in accordance with the relevant legislation (§20d AMG) and the Helsinki Declaration. The graft was tailored according to the defect dimensions, slit multiply with the scalpel and fixed in the defect with 6-0 polyamide interrupted sutures. The slits were then used to evenly distribute pinch autografts harvested from macroscopically intact skin with a needle and a scissor (Figure 1 B) from the patient's thigh, groin or scapular region underneath the allograft cover (Figure 1 C). Finally, fibrin glue was applied for direct tissue contact and to prevent dislocation of the layers. The hand was immobilized by a custom-made external fixation device consisting of K-wires which were placed longitudinally in the digits and connected by a frame of (polymethylmethacrylate) PMMA-bone-cement (Palacos®; Heraeus Medical GmbH Germany). Dressings consisted of greased gauze and moistened cellulose pads, which can be accurately modelled onto the surface, followed by normal gauze dressings. Dressing changes were carried out weekly, the first three times usually under analgesic sedation.

The K-wires were removed 4 weeks after the surgery followed by immediate intensive physiotherapy; at night a custom-made silicone extension splint was applied.

Immunofluorescence for detection of collagen VII

Skin biopsies were taken pre-operatively and during dressing changes und anesthesia 2 and 4 weeks after operation. The LH7.2 antibody was used to stain collagen VII expression in the operated area and to visualize rejection of the parental skin graft, whereas DAPI stained the nuclei.

Retrospective analyses

All patients who underwent operation of mitten hand deformity between 2012 and 2019 were analyzed retrospectively.

All data were collected with the clinical internal documentary systems according to the ethical approval by the ethics committee of University Freiburg. Special attention was paid for complications, post-operative functional outcome and local recurrence free time.

To evaluate the operative outcome, we quantified the adduction contracture of the thumb by measuring the angle between metacarpal bone 1 and 2 pre- and post-operatively.

To evaluate the soft tissue situation, we compared score item scarring of hands of Birmingham epidermolysis bullosa severity score (BEBSS) pre-and post-operatively.[13] According BEBSS, involvement of hand is classified as follows: 0=no scarring, 1=milia and/or atrophic scars, 2=just detectable contractures or webbing, 3=obvious contractures or proximal webbing, 4=between 3 and 5 and 5=mitten formation with fingers all fused.

RESULTS

From 2012 to 2019, in total 18 mitten hand deformities of 14 patients suffering from DEB were treated. Average age of the patients was 9 years [range 3-26 years]. 11 male and 3 female patients were operated.

Seven hands were classified as BEBSS of 5 (mitten hand) 8 times as BEBSS of 4 and 3 times as BEBSS of 3.

The 12 operations were performed on the right and 6 operations on the left hand. In 9 times the mother and in the other 9 times father donated their skin as an allograft. Donor site was chosen 15× groin, 2× abdomen and 1× upper arm. On average, an overall 12.6×5.5 cm skin graft (ranging from 9×5 to 20×9 cm) was transplanted.

Wound healing both in donor and recipient was without major complications. Whereas the parental donor site healed per primam within 2 weeks, healing in the children passed through several stages: Initially, the wounds showed no signs of irritation, the skin transplants showed an incremental ingrowth: At the second dressings change on the 9th postoperative day, clinically viable skin allografts could be observed (Figure 1 D). The 14 days postoperatively, a mixture of viable skin areas and an incipient rejection of the graft was detectable. After removal of the skin debris, an advanced stage of secondary wound healing became apparent with re-epithelisation originating from the wound margins, as well from multiple islands within the wounds, arisen from the autologous pinch grafts (Figure 1 E). Immediately after the four-week immobilization period, intensive physio-and occupational therapy exercises were carried out, leading to substantial improvement of gross and fine motor skills (Figure 2 A-C).

Figure 1 (A-E): Maximum finger spread/extension preoperatively, harvesting of pinch grafts from a less affected area of the patient, situation intraoperatively before dressing, 2nd change of dressings 9 days postoperatively 3rd change of dressings 2 weeks postoperatively.

Because of post-operative dislocation of K-wires, the external fixation had to be removed prematurely after 3 weeks in one patient.

Immunofluorescence

In accordance with the clinical observation, immunofluorescence 2 weeks postoperatively (Figure 3 C) showed a regular expression of collagen VII in comparison to control staining's from healthy patients (Figure 3 A), whereas this anchoring molecule was completely absent in the patient preoperatively (Figure 3 B). Figure 3 C shows the loss of the epidermal layer at this point of time (asterisk mark). At the latest 2 weeks after operation, the parental skin grafts were rejected. Nonetheless, 4 weeks after the operation there was still collagen VII detectable in the dermis of the transplanted area (Figure 3 D).

Outcome

Mean follow up was 3 years (ranging from 6 months to 6 years). Three foreign patients were lost to follow up.

In all patients, the initial functional outcome was improved. Nearly all patients got a considerably widened grip span and durable skin conditions (Figure 2 A-C) post-operatively. In 2 patients clenching fist was hampered due to persisting stiffness of fingers. Even in these cases, pinch grip of thumb by releasing adduction contracture was possible/ improved after surgery.

The angle between the metacarpal bone 1 and 2, as expression of the adduction contracture, improved substantially in all cases (Table 1).

The BEBS score showed directly after surgery a clear improvement for all cases achieving category one for scarring of the hand. These results were not maintained in the patients over time. While seven patients remained without recurrence of the scarring of the hand until end of follow up as shown in the Tablet 1, eight operated hands showed a relapse of different degrees of severity. Four of them developed a web creep and some mild contractures of the fingers (BEBSS 2). The other four patients had a complete relapse of the mitten hand deformity (BEBSS four and five). Typically, recurrence of the scarring occurred from six months to the two years after operation.

Figure 2 (A-C): The 10 months postoperatively: Stable skin conditions and substantial increase in grip span and functionality.

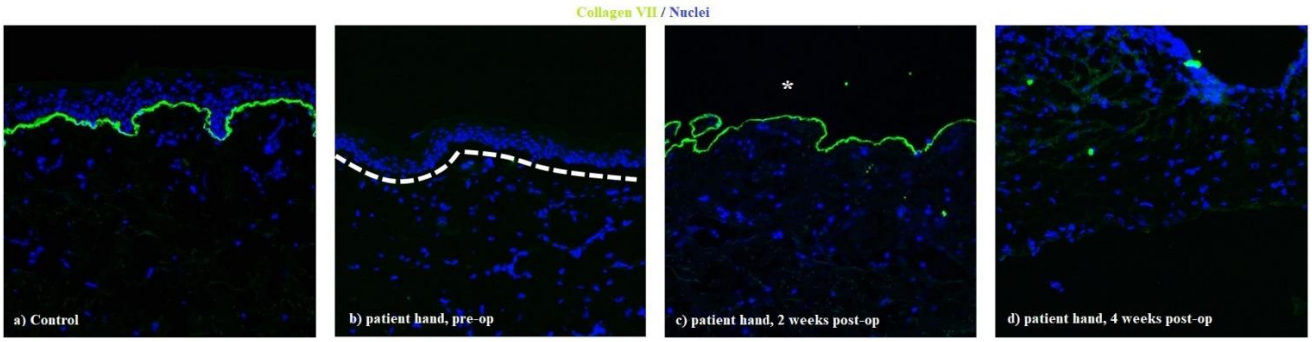

Figure 3 (A-D): Immunofluorescence analysis of skin biopsies staining cell nuclei (blue) and collagen VII (green). In the control skin, whereas in, the patient skin before operation is shown. The white interrupted line marks the dermal-epidermal junction zone, without any collagen VII expression in a severely affected patient. In a biopsy taken 2 weeks after operation, collagen VII expression is seen at the dermal-epidermal junction zone, the epidermis has already been rejected (white asterisk mark) and 4 weeks after operation collagen VII expression still can be found.

Table 1: Patient characteristics.

Patient number	Age (Years)	Sex	Side	Pre-op BEBSS	Post-op BEBSS	Pre-op thumb abduction	Post-op thumb abduction	Recurrance (months)	Follow-up (month)
1	10	M	Right	4	1	10°	60°	None	18
2	11	M	Right	5	1	5°	50°	6	24
3	15	M	Right	4	1	10°	70°	None	22
4	26	F	Left	5	1	5°	50°	None	54
5	3	M	Right	5	1	10°	50°		
6	9	M	Right	4	1	5°	50°	22	58
7	9	F	Right	3	1	20°	70°	23	60
8	7	M	Right	5	1	20°	70°	None	12
9	8	M	Left	4	1	10°	50°		
10	12	M	Left	4	1	30°	50°	None	13
11	12	M	Right	3	1	40°	70°		
12	21	M	Right	5	1	20°	50°	14	60
13	6	M	Right	4	1	20°	40°	12	36
14	6	M	Left	4	1	20°	40°	12	36
15	6	M	Right	5	1	20°	70°	8	42
16	6	M	Left	5	1	20°	70°	6	30
17	20	F	Right	3	1	30°	70°	None	6
18	7	M	Left	4	1	20°	60°	None	6

DISCUSSION

Restoration of a satisfactory hand function remains one of the major challenges in the surgical treatment of DEB and has a major impact on the patients' quality of life. Although various surgical approaches have been advocated, still no generally accepted gold standard has been established. Due to the multiform appearance of the disease, type and extent of the therapy have always to be adjusted individually. In this context, we present a new therapeutic concept for the EB-associated mitten deformities, which combines autogenous and allogenic skin transplantation for defect coverage after release of the pseudo-syndactylies and contractures of the fingers. The technique shown here presents several advantages:

The parental skin allograft serves not only as an active "biological dressing" throughout the vulnerable phase of wound healing, moreover an-at least temporary-incorporation of the graft could be observed. Adding only minimal donor site morbidity, the pinch grafts contribute to an improved re-epithelization process.

Another aspect, which must not be underestimated, is that the parents, who often feel reduced to helpless bystanders, can now participate actively in their children's treatment by donating their skin. Parental skin grafting has previously been advocated in the treatment of burns to minimize the risk of transmission of infectious diseases or for cultural/religious reasons.[14-16] The theoretical basis for this technique has been established in the treatment of severe burns: Following the pioneering work of Alexander et al., the approach of combining auto- and allogenic skin grafting underwent various adaptions and refinements: To achieve a downsizing of donor site morbidity, the autografts have been minimized from widely meshed split skin to small skin fragments placed within slits in the allograft skin overlay; the technique is referred to as the "Chinese Intermingled Technique" according to the author's provenance. Since the limited availability of intact skin is likewise an issue in severe dystrophic EB, we harvested the autologous skin in a similar "pinch graft" manner.[8-10]

For the reconstitution of a mechanically stable skin, an intact dermal-epidermal junction is essential, for which the presence of collagen VII, the major constituent of the anchoring fibrils, is needed. This is proven by the clinical picture of the dystrophic EB individuals where collagen VII is missing.[17] Histological and clinical observations have shown a beneficial coaction of combined auto- and alloskin-grafting: As well using the "Sandwich"-echnique as in combination with autologous cultured keratinocytes, a partial integration of the allodermis along with better mechanical stability in comparison to sole autografting can be observed.[18,19] Immunohistochemically, the reconstitution of a basement membrane and strong expression of collagen VII in the junctional dermo-epidermal zone was verified in burn patients -an observation which could have a major impact in the treatment of soft-tissue defects in EB.[20] In our patients, we were able to observe a persisting expression of collagen VII 14 days postoperatively (Figure 3 C) and even after 4 weeks, some collagen VII-positive cells were still found in the transplanted areas. Nevertheless, most of the cellular alloskin components are lost within 2-3 weeks 11), in particular the epidermal part; the Langerhans cells have been found to play a key role in this rejection process.[21] The dermis seems to be partially incorporated and gives rise to a new dermal layer, either

by permanent ingrowth or -more likely- by serving as a scaffold and being subjected to a "creeping" non-inflammatory replacement by host cells, thus contributing to the reconstitution of a normal skin architecture.[6,14,19,20] There is some evidence that remaining parental fibroblasts are still possible.[11] Another possibility would be that the allogeneic skin cells resulted in enhanced collagen VII expression in the patient's skin, as has been shown with the use of fibroblast injections in wounds of a DEB patient and in a DEB mouse model.[22,23] The exact mechanism of the enhanced collagen VII expression remains largely elusive, although it has been suggested to be associated with increased expression of heparin-binding epidermal growth factor-like growth factor (HB-EGF).[22] We observed that the epidermal layer of the parental skin began to be rejected between the 9th and 14th postoperative day, due to the fact that EB-patients do not suffer from immunodeficiency as burn victims. Nevertheless, it proves to be a good option for covering the wound areas after surgery. Moreover, the cadaveric alloskin, as supplied by most skin banks today, is preserved in glycerol, which already reduces its immunogenity along with its viability.[24] To allow optimal wound healing, a postponement of the onset of rejection is desirable. Whereas in large extent burns, at least for some indications a temporary immunosuppression may be debated, in EB the relatively small defect and the availability of safer treatment options do not encourage a systemic immunosuppression of the host.[25,26] However, a pre-treatment of the allograft to reduce its immunogenetic properties is an alluring option. Alsbjörn and Sørensen presented a protocol for the pre-treatment of allogenic skin with glucocorticoids and UVB-radiation, which substantially prolongated graft survival up to 6 weeks, concordant findings have been made in a porcine skin transplantation model.[24,27]

Comparing different techniques of mitten hand treatment is difficult due to heterogeneous examination criteria, the low number of reported cases and often short follow up time.[3,28] Recurrence rates are always high, which is understandable, considering that separation of pseudo-syndactylies in EB is only a symptomatic and not a causal treatment.[29,30] Nevertheless, with our technique, we show an improvement of hand function over a distinctive time possible for nearly all patients. Especially dissolving the adduction contracture of the thumb leads to a better functionality. This functionality maintains, even when recurrence of the pseudo-syndactylies has taken place.[31]

Interestingly, in one case the result was stable over a long follow up till now (6 years) without signs of recurrence. This might be due to underlying factors of EB, which aren`t completely understood yet. However, correction of mitten hand deformity in EB is typically a temporary improvement of hand function.[32] Therefore, is it important to identify the right time for operation, when the patient will have the utmost benefit for his or her motoric and social development.

Combination of autologous pinch grafts and allogenic skin grafts leads to a reliable and stable healing with collagen VII expression for several weeks, allowing early exercise, to achieve a maximum benefit within the relapse free interval.[33]

Nevertheless, the study is subject to some limitations; in particular the sample size, which is comparatively presentable when taking the low incidence of the disease into consideration, but nevertheless does not permit a conclusive statistical analysis of our cases. This is all the more relevant, since the study group itself is very inhomogeneous due to the variable manifestation of the disease.

CONCLUSION

This is the first report on the use of the combination of autogenous pinch skin grafts with allogenic (parental) skin overlay for the treatment of skin defects in EB. It provides an undisturbed wound healing under a "biological dressing", furthermore, a temporary take of the parental skin was visible. The defects were permanently covered with skin of increased mechanical stability, hand function improved remarkably as well. However, long term follow-up showed beginning recurrence in most of the patients comparable to recurrence rates described in the literature.

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