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ARTICLE

Surgical management of hand deformities in patients with recessive dystrophic epidermolysis bullosa

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ABSTRACT

Recessive dystrophic epidermolysis bullosa (RDEB) is a congenital disease caused by a mutation in the *COL7A1* gene and frequently results in hand contractures and pseudosyndactyly. Although multiple treatments exist that can improve the hand malformations, there are currently still no radical cures for this disease because of its high recurrence rate. The present study reports our experiences on how to improve hand deformities in 11 RDEB patients with surgical management and postoperative skin dressings. Hand function was substantially improved after complete release of pseudosyndactyly and achievement of favorable digital web spaces. Patients were followed up for two years, and nine of which showed slight decrease in hand function characterized by re-narrowed web spaces, digit adhesion and flexed metacarpophalangeal (MP) and interphalangeal (IP) joints, while the last two patients underwent hand reoperation one year after their initial surgery because of recurrence. In conclusion, our results show that surgical correction followed by skin dressing changes is an effective approach to improving mitten-hand malformations in RDEB patients.

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Recessive dystrophic epidermolysis bullosa; surgical management; hand deformity; wound dressing

Introduction

Epidermolysis bullosa (EB) is a group of rare genetic disorders characterized by increased skin fragility, blistering and scarring in response to minor mechanical injury [1]. Based on the location of the fragility and the level of skin cleavage, EB is classified into four major types: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB) and Kindler syndrome [2]. DEB is caused by a mutation in the *COL7A1* gene. This gene encodes type VII collagen, which makes up the anchoring fibrils in the sublamina densa. The defective anchoring fibrils allow easy epidermal detachment from the dermis, thus resulting in blisters [3,4]. DEB is categorized into two main subtypes: autosomal dominant DEB (DDEB) and recessive DEB (RDEB). These two subtypes are further mainly classified into DDEB generalized, DDEB acral, DDEB pretibial, DDEB pruriginosa, RDEB generalized severe, RDEB generalized intermediate, RDEB inversa, RDEB localized, RDEB pretibial and RDEB pruriginosa [2,5]. For DEB patients, mortality rates during infancy or early childhood are low if meticulous pediatric and dermatologic intensive care was provided.

RDEB individuals present with clinical symptoms at birth, including generalized blisters, ulceration of the mucous membranes, and atrophic scars. These symptoms gradually deteriorate with disease progress and can cause chronic blood loss, recurrent infections and malnutrition. This can result in anemia, delayed puberty and osteoporosis [6,7]. RDEB generalized patients who survive past childhood frequently develop metastatic squamous cell carcinoma (SCC), which often leads to death [8,9].

Due to daily use, the hands of RDEB patients are subjected to repeated cycles of blistering, ulceration and healing, which may lead to chronic scarring. This can also provoke chain-linked inflammation. Inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and transforming growth factor-β1 (TGF-β1) can promote the development of chronic wounds and tissue fibrosis. Severe fibrosis can specifically induce finger contractures [10], progressive digital fusion (pseudosyndactyly), flexion contractures and adduction contractures in the thumbs. In some cases, sever mitten-like deformities can cause significant dysfunction that leads to the loss of ability to perform even the most basic daily tasks [11]. These hand deformities are known as 'cocoon hands' [12].

Currently, treatments such as allogeneic fibroblast injections [13], bone marrow [14], mesenchymal cells [15] and skin substitutes [16,17] show favorable efficacy in improving RDEB symptoms. However, they are not radical cures for RDEB [18] and generally, recurrence is inevitable. In order to regain hand function, most RDEB patients choose to undergo hand surgeries. Therefore, we decided to investigate the outcomes of using reconstructive surgical methods to improve hand function and appearance. Although deformities still recur postoperatively, our results show that temporarily improved hand function and appearance still lead to a better quality of life (QoL) [19] which satisfied both the patients and their parents.

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Patients and methods

This work was approved by the institutional review boards of the Shanghai Ninth People's Hospital affiliated with Shanghai Jiaotong University School of Medicine. This retrospective study was conducted in accordance with their ethical standards, as well as the Helsinki declaration.

Patients

Eleven patients, including eight males and three females (average age, 8.7 years; ranging from 4 to 24 years-old), were included in this study. Medical histories were reviewed for RDEB disease from August 2007 to December 2014. RDEB diagnosis was made based on the gene mutational test results, medical histories and clinical features. All patients received the gene mutational tests from gene companies (Peking Kangso Medical Inspection Company, Peking University First Hospital affiliated Medical Inspection Company, Beijing, China) before they came to seek further medical treatment in our hospital. Patients typically showed multiple skin bullae and generalized wounds, with extremities most severely affected. The bimanual malfunctions in all patients consisted of varying degrees of contracture and pseudosyndactyly, especially in the metacarpophalangeal (MP) and interphalangeal (IP) joints. Evaluation and scoring of preoperative and postoperative hand scars were based on the 'Birmingham Epidermolysis Bullosa Severity Score Sheet' (BEBSS) [20]. According to BEBSS, six grades indicating different degree of hand malfunction are included 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 4 and 5 = mitten formation with fingers all fused. Clinical features and preoperative hand scar evaluations are shown in Table 1.

Anesthesia

Due to the presence of oral and airway blisters, we used combined intravenous-inhalational anesthesia with a face mask instead of an endotracheal tube. All instruments were in indirect contact with the defected skin or mucosa to avoid further damage.

Preoperative protection

Before starting the surgery, special precautions in daily care were implemented to prevent frictional trauma; for example, patient were recommended to use an air-cushion bed and receive a semi-liquid diet. Patients' parents also participated in an educational program. All patients were then scrupulously evaluated using physical, biochemical and imaging examinations. We found that in addition to multiple skin lesions, cornea and oral mucosal ulcers and hand deformities, these patients also had varying degrees of malnutrition, anemia, hypoalbuminemia, osteoporosis and poor dentition. Therefore, a multi-disciplinary team of specialists were involved in the perioperative period, including dermatologists, anesthetists, pediatricians, psychologists and rehabilitation therapists. Careful pre-plan sand preparation procedures were carried out in order to reduce operational risk. Total parenteral nutrition and systemic antibiotics were used to provide preoperative support and routine operative blood transfusions were prepared.

Table 1. Patients' clinical characteristics and preoperative hand scar evaluation with BEBSS.

Patient no.	1	2	3	4	5	6	7	8	9	10	11
Age (years)/gender	4/M	7/M	6/M	11/M	24/F	7/M	10/M	5/F	13/M	4/M	5/F
Clinical features	These patients exhibit poor growth with comparative short height, malnutrition, muscular dystrophy, osteoporosis, sparse hair, anemia and dental abnormalities. Skin, mucosa blisters and erosions are obvious.										
Gene diagnosis	Mutation in the gene *COL7A1*										
Primary/secondary surgery	Primary surgery										
Severity score of hands scar[a]	R L 4 3	R L 5 4	R L 5 5	R L 5 5	R L 5 5	R L 3 4	R L 5 4	R L 3 3	R L 5 5	R L 5 4	R L 3 3

R: right hand; L: left hand.
[a]Birmingham Epidermolysis Bullosa Severity Score (BEBSS): 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 4 and 5 = mitten formation with fingers all fused.

Surgical management

The surgical procedures were performed under electro-pneumatic tourniquet control (50–70 mmHg), which was applied indirectly to the skin with a silicone dressing pad to protect the supper arm skin. The hands were disinfected gently using betadine solution instead of conventional frictional scrubbing. The procedure began with local injection of tumescent solution (200 ml normal saline + 10 ml 5% lidocaine solution + 0.5 ml 0.1% epinephrine solution) in the subcutaneous tissue of the hand to facilitate dissection and reduce bleeding. Using the magnifying head-loupe, the 'cocoon' epidermis (Figure 1(A)) at the curled digits was gently removed. The epidermal degloving of the deformed hand clearly revealed the dermal 'glued' junction between the contracted digits, which made it easy to confirm the web spaces in this type of pseudosyndactyly. First, the skin adhesion between digit tips and palms was separated. Then, parallel vertical incisions and blunt dissection were progressed in the web spaces between the involved individual digits all the way to the level of the MP joints. These steps created the first web space and achieved restoration in every digit interval.

Next, transverse volar or Z-plasty incisions at the level of flexion creases in the flexion contractures fingers were made. Contracted scars in the skin and subcutaneous tissues were released using scissors. While performing deep incisions, attempts were made to avoid the direct exposure of bilateral neurovascular bundles. If exposure was inevitable due to intraoperative tendon readjustments, local fat flaps or skin flaps were designed to cover those neurovascular bundles. In severe cases, if the thumb adduction contracture involved the adductor pollicis brevis and the first dorsal interosseous muscle, the hand function would be largely restricted and the adducted thumbs must be thoroughly released. This requires a long incision from the base of the web at the level of the thenar eminence and mid-palm up to the dorsal palm. To separate the metacarpal muscle head of the first dorsal interosseous muscle, an exterior manual force was used to lengthen the adductor pollicis brevis and flexor policis brevis muscle, thus creating a new first web space. To completely release and lengthen the severely contracted second to fifth digits, it was necessary to cut off the musculus flexor digitorum superficialis. Additional releases of the palm prints and the medial margin of the hypothenar eminence were necessary if the patients had severe palm flexed contracture (Figure 1(B)). The Kirschner wires (Smith & Nephew Company, Memphis, TN) were used to secure and maintain the fingers in specific position: the thumb was fixed in an opposed position and the other digits were fixed in the functional position crossing the IP joints. In four patients, wire fixation was unnecessary because their digit flexion contracture was not severe enough.

Wound dressings

The soft silicone-coated dressing Mepitale (Mölnlycke Health Care Company, Gothenburg, Sweden) was used instead of the skin grafts to cover the secondary hand wounds in all patients. The digits, palm and wrist were covered with a silicone-coated

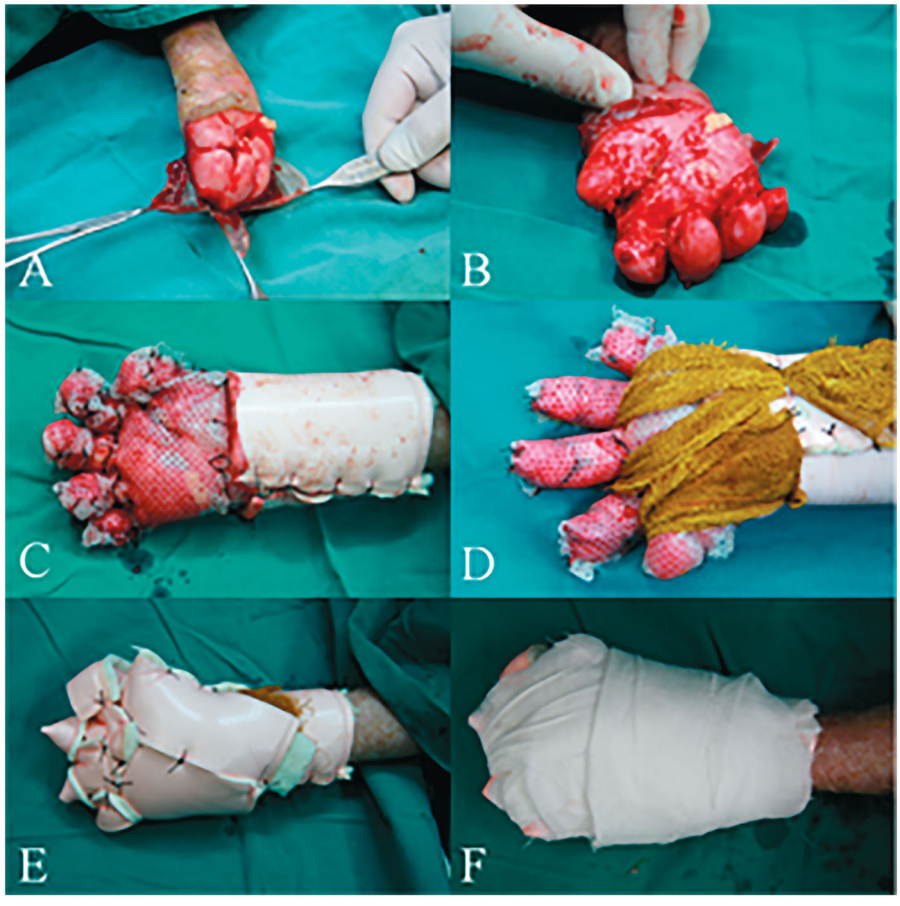

Figure 1. The surgical management for the malformed right hand. (A) The epidermis degloving in the hand revealed the dermal 'glued' junction of contracted digits. (B) The contractures of the palm and all digits were released, web spaces were deepened, and digit was lengthened. (C) The secondary hand wounds were covered with silicone dressing. (D) Silver nanoparticle antibacterial tulle was inserted in each web space to separate the fingers. (E) Alginate and polyurethane foam dressing were used to wrap up the palm and fingers. (F) Multilayer large gauze and bandages were applied as an outer layer.

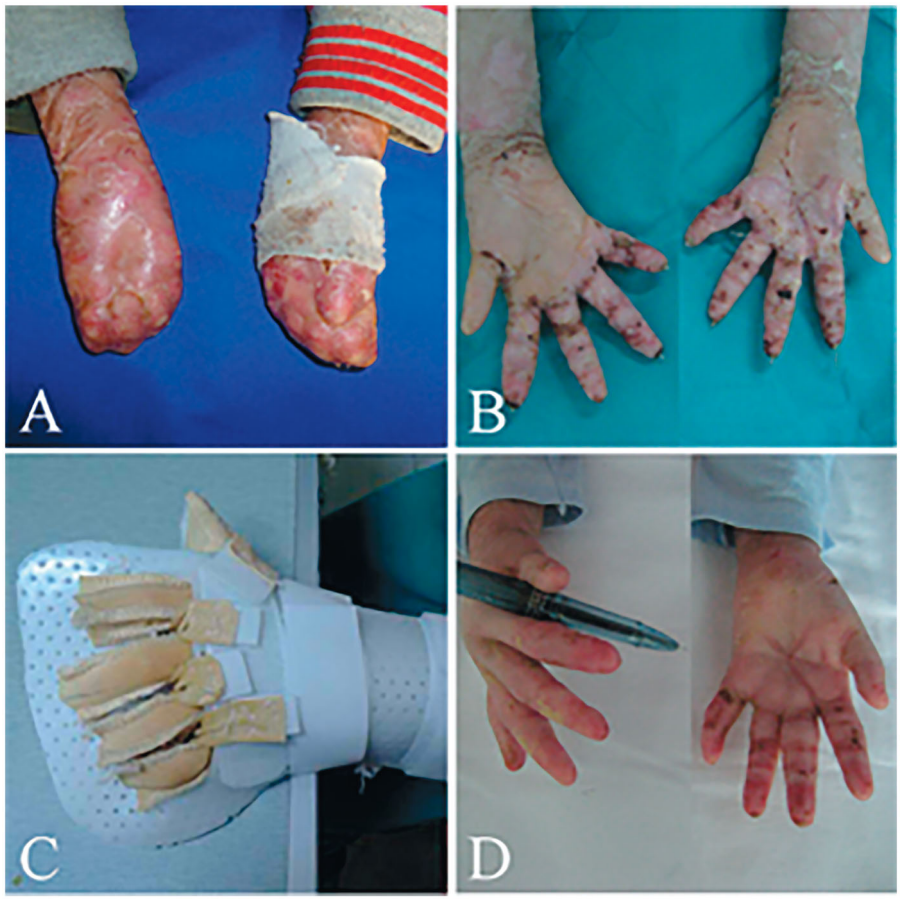

Figure 2. Transforming the 'cocoon hands' into functional ones using our surgical management and skin dressings. (A) Flexion contracture of all digits, adduction contracture of the thumb and pseudosyndactyly in digits 2–5 in both hands. (B) The hand wound healed 5 weeks postoperatively and Kirschner wires were then removed. (C) A thermoplastic splint, soft elastic glove and cotton strip were used for daily functional training to prevent re-contracture. (D) Single-handed control used to grasp a pen with greatly improved hand function 8 weeks postoperatively.

dressing that was tailored to form a glove based on the size of the reconstructed hand [21]. The wrist was then covered with an Alginate dressing (Smith & Nephew Company, London, UK) and non-adhesive polyurethane foam dressing (Allevyn, Smith & Nephew Company, London, UK) (Figure 1(C)). To separate the web spaces between digits, a silver nanoparticle antibacterial tulle (Anson Company, Shenzhen, China) was placed in each web space and stitched to the wrist dressing (Figure 1(D)). Alginate and polyurethane foam dressings were also used to wrap the palm and digits and were placed in the first web space to maintain the thumb in an abducted position (Figure 1(E)). Finally, the hands were wrapped in polyurethane foam dressing and multiple layers of gauze (Figure 1(F)). Antibiotics were administered prophylactically for three days postoperation. The Mepitale dressing was changed one-week postoperation. The hands were carefully washed with benzalkonium chloride and betadine solutions under general anesthesia. Then silicone-coated dressing, alginate dressing, non-adhesive polyurethane foam dressing and silver nanoparticle antibacterial tulle were used to wrap the hands, according to the procedure described above. Dressings were changed weekly. Three to four weeks later, the completely dysfunctional 'cocoon' hand (Figure 2(A)) wounds gradually healed and the Kirschner wires were removed (Figure 2(B)). A soft elastic glove and cotton strip were used to maintain the interdigital spaces after the removal of the Kirschner wires (Figure 2(C)). Furthermore, a thermoplastic splint was used to immobilize the palm side and facilitate thumb abduction and digit extension, thus beneficiating the surgical outcomes. The splint required appropriate adjustments after each dressing replacement.

Postoperative hand management and functional training

The goals for postoperative treatment were to maintain optimal ranges of motions in the palm and digits and postpone the recurrence of deformity. The functional hand training activities resumed with help from the rehabilitation therapist, psychologist and patients' parents. Parents and psychologists helped encourage patients to overcome the fear and pain of performing basic daily tasks because it is vital for the patients to regain self-confidence. According to the experiences of Formsma et al. [22], the rehabilitation therapist instructed parents to help their kids to perform functional exercises such as flexor tendon-gliding, a finger flexion exercise. These exercises help improve joint mobility and avoid joint contractures and stiffness after Kirschner wire removal and were required three times a day for three continuous months. Afterwards, parents were asked to help the patients with performing daily life activities such as writing, dressing, holding spoons, opening caps and playing ping-pong. Patients were recommended to wear the static splints, soft elastic gloves and cotton strips for three months after the removal of Kirschner wire. Three months later, daily activities could be carried out without the help of the splints, soft elastic gloves and cotton strips, but patients were still required to wear them at night for another three months.

Results

Seven patients with severe hand contracture received the local fat flaps or skin flaps reconstruction with extended incisions. Skin wounds completely healed 7–8 weeks postoperatively without complications other than the newly formed bullae caused by the unavoidable abrade to the wrist and forearm areas during dressing changes. Digit function was restored quickly with physical therapy exercises from the help of rehabilitation therapists after removal of the Kirschner wire. Hand function was remarkably improved within 2 months which was demonstrated by the capability of grasping and pinching large objects such as cups, spoons and pens using unilateral hand (Figure 2(D)). Functional and rest positions can be freely switched after the surgical management. Younger patients without joint disease achieved better surgical results than older ones who had long-standing hand deformities and secondary damage to the MP and IP joints. After surgical management, the range of flexion and extension of the MP joint was between 0° and 70°. Flexion and extension of the proximal and distal IP joints ranged from 0° to 60°. Each digit could perform adduction and outreach in coordination. The restored thumb in particular achieved much increased flexibility. Results from the two-year follow-up showed that the majority of patients achieved good functional and cosmetic outcomes 2–6 months postoperation in the early stage (Table 2). Contracture and pseudosyndactyly, especially in the right hand, were observed in two younger patients. At 12 months postoperation, the favorable functional and cosmetic results continued (the severity score was ranged from 0 to 1) for all except two patients who suffered serious recurrence in the right (dominant) hands scoring from 4 to 5. These patients received a second hand operation. The other nine patients displayed slightly decreased hand function characterized by mild loss of web spaces, recurred adhesion in the separated digits, and mild flexion in both MP and IP joints 12–18 months postoperation. The right hands in three patients showed obvious contracture (scored 3) 24 months after the initial surgery; however, further reconstructive surgeries were turned down by their parents (Table 2).

Discussion

Patients with RDEB often suffer from severe hand deformities, which results in the obviously decreased or complete loss of ability to perform daily activities. It is important to reconstruct the hands with significantly deteriorated function and appearance in order to help these patients reintegrate into society [23,24]. RDEB is a rare disease, and unfortunately there is insufficient information about the proper treatments reported in China. According to our experience, minimizing intraoperative bleeding is very important. In some studies, tourniquet use was excluded to avoid secondary skin lesions on the upper arm [6,21]. However, while shearing forces on the skin can result in new bullae, we believe that pressure applied perpendicular to the skin with the protection of silicone dressings is less likely to damage the skin. Eisenberg Llewelyn [11] and Campiglio et al. [23] both performed procedures under pneumatic tourniquet control without direct skin contact. If an electropneumatic tourniquet equipped with automatically adjustable pressure was used, bullae did not occur and bleeding was controlled without using intraoperative transfusion.

The type of wound coverage that ensures high effectiveness of treatment and low rates of recurrence continues to be debated. Some authors recommended using skin grafts for secondary surgical wounds. Luria et al. [6], Terrill et al. [25], Zarem et al. [26] and Horner et al. [27] used a variety of techniques for split-thickness skin grafts. Rees and Swinyard [28] and Ladd et al. [29] chose to graft full-thickness skin. They believed that grafted skin could protect the exposed neurovascular bundles and tendons, facilitate wound healing, and perhaps reduce the recurrence of hand contracture. However, Vozdvizhensky and Albanova [30] and Ciccarelli et al. [31] held the opposite view, suggesting that skin grafting not be used in order to avoid damage in donor-site skin, which may result in extra trauma and bullae. Ciccarelli et al. [31] showed that skin grafting is unnecessary as it does not affect the average recurrence rate. Bioengineered skin was also reported in treatment of RDEB [12] but is very costly and difficult to obtain, which curtails its application. We decided to use skin dressings to cover the exposed wounds and promote healing. Non-adhesive, silicone-coated, glove-shaped dressings were also used to protect the released fingers. These silicone dressings not only assist in the drainage of exudates from the wound, but also help avoid subsequent skin adhesions due to their good plasticity and elasticity. Moreover, the antibacterial tulle contains many silver nanoparticles which may release free radicals and induce bacterial membrane damage to prevent infections [32]. Kirschner wire fixation was used to maintain finger extension in these patients. However, depending on the severity of hand contracture, Kirschner wires sometimes can only cross the IP joints but not the MP joints. Prolonged Kirschner wire fixation can potentially cause pin-tract infection, articular cartilage damage and finger stiffness so they are often removed at an earlier rather than later stage.

Recurrence of malformed hands has always been a major issue for RDEB patients after reconstructive surgery. Studies indicate that deformity recurrence generally occurs 2–5 years after the initial surgery [11,25]. In the present study, two patients underwent re-operations one year after the initial surgery. However, our two-year follow-up period is too short to make final and confirmatory conclusions about the efficacy of our surgical treatment. As yet, there is no radical cure for RDEB. The surgical treatments to release mitten-hand only improve function temporarily and prevention of

Table 2. Postoperative hand scar evaluation with BEBSS.

	Patient no.	1		2		3		4		5		6		7		8		9		10		11	
Severity score of hands scar[a]	Postop (M)	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
	2	0	0	0	1	1	0	0	0	1	0	0	0	0	0	1	0	0	0	1	1	0	0
	6	1	1	0	1	3	2	1	1	1	0	1	1	1	0	1	1	1	0	3	3	1	1
	12	1	1	1	1	4	3	1	1	1	1	1	1	1	1	1	1	1	1	5	4	1	1
	18	2	2	2	1	Reop		1	1	2	1	1	1	1	1	2	2	2	1	Reop		2	2
	24	3	2	2	1			2	2	2	1	2	2	2	1	3	3	2	2			3	2
Follow-up (M)		24		24		13		24		24		24		24		24		24		13		24	
Duration of function (M)		21		24		12		24		24		24		24		21		24		12		19	

Reop: reoperation; Postop: postoperation; M: months; R: right hand; L: left hand.
[a]Birmingham Epidermolysis Bullosa Severity Score (BEBSS): 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 4 and 5 = mitten formation with fingers all fused.

reoccurrence remains very difficult. Even so, patients and parents were still excited and satisfied with the opportunity to achieve a degree of independence and improve their QoL.

Conclusions

We have presented our outcomes for treating malformed hands in RDEB patients with surgical management combined with postoperative special dressings. This approach is shown to temporarily help regain good functional and cosmetic outcomes for mitten-hands. Despite the high reoccurrence rate of deformities, the temporary recovery of function and appearance in mitten-hands helps reintegrate RDEB patients into family life and society.

Disclosure statement

The authors report no conflicts of interest in relation to the content of this work.

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References

[1] Tian F, Li B, Tian LJ. Treatment of severe hand deformities caused by epidermolysis bullosa. Orthopedics. 2011;34(11): e780–e783.
[2] Fine JD, Bruckner-Tuderman L, Eady RA, et al. Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. J Am Acad Dermatol. 2014;70(6): 1103–1126.
[3] Varki R, Sadowski S, Uitto J, et al. Epidermolysis bullosa. II. Type VII collagen mutations and phenotype–genotype correlations in the dystrophic subtypes. J Med Genet. 2006; 44(3):181–192.
[4] Shinkuma S, McMillan JR, Shimizu H. Ultrastructure and molecular pathogenesis of epidermolysis bullosa. Clin Dermatol. 2011;29(4):412–419.
[5] Fine JD, Eady RA, Bauer RA, et al. The classification of inherited epidermolysis bullosa (EB): report of the third international consensus meeting on diagnosis and classification of EB. J Am Acad Dermatol. 2008;58(6):931–950.
[6] Luria S, Radwan S, Zinger G, et al. Hand surgery for dystrophic epidermolysis bullosa. J Pediatr Orthop. 2014;34(7): 710–714.
[7] Pfendner EG, Lucky AW. Dystrophic epidermolysis bullosa. NCBI bookshelf. A service of the National Library of Medicine [updated 2018 Sep 13]. National Institutes of Health; Seattle (WA), 2006. p. 21.
[8] Montaudié H, Chiaverini C, Sbidian E, et al. Inherited epidermolysis bullosa and squamous cell carcinoma: a systematic review of 117 cases. Orphanet J Rare Dis. 2016;11(1): 117–129.
[9] Hon KLE, Li JJ, Bernadette L, et al. Age and etiology of childhood epidermolysis bullosa mortality. J Dermatolog Treat. 2015;2(2):178–182.
[10] Breitenbach J, Gruber C, Klausegger A, et al. Pseudosyndactyly—an inflammatory and fibrotic wound healing disorder in recessive dystrophic epidermolysis bullosa. J Dtsch Dermatol Ges. 2015;13(12):1257–1266.
[11] Eisenberg Llewelyn MD. Surgical management of hands in children with recessive dystrophic epidermolysis bullosa: use of allogeneic composite cultured skin grafts. Br J Plast Surg. 1998;51(8):608–613.
[12] Fivenson DP, Scherschun L, Cohen LV. Apligraf in the treatment of severe mitten deformity associated with recessive dystrophic epidermolysis bullosa. Plast Reconstr Surg. 2003; 112(2):584–588.
[13] Venugopal SS, Yan W, Frew JW, et al. A phase II randomized vehicle-controlled trial of intradermal allogeneic fibroblasts for recessive dystrophic epidermolysis bullosa. J Am Acad Dermatol. 2013;69(6):898–908.
[14] Wagner JE, Ishida-Yamamoto A, McGrath JA, et al. Bone marrow transplantation for recessive dystrophic epidermolysis bullosa. N Engl J Med. 2010;363(7):629–639.
[15] Petrof G, Lwin SM, Martinez-Queipo M, et al. Potential of systemic allogeneic mesenchymal stromal cell therapy for children with recessive dystrophic epidermolysis bullosa. J Invest Dermatol. 2015;135(9):2319–2321.
[16] Falabella AF, Valencia IC, Eaglstein WH, et al. Tissue-engineered skin (Apligraf) in the healing of patients with epidermolysis bullosa wounds. Arch Dermatol. 2000;136(10): 1225–1230.
[17] Gorell ES, Leung TH, Khuu P, et al. Purified type I collagen wound matrix improves chronic wound healing in patients with recessive dystrophic epidermolysis bullosa. Pediatr Dermatol. 2015;32(2):220–225.
[18] Siprashvili Z, Nguyen NT, Gorell ES, et al. Safety and wound outcomes following genetically corrected autologous epidermal grafts in patients with recessive dystrophic epidermolysis bullosa. JAMA. 2016;316(17):1808–1817.
[19] Marín-Bertolín S, Amaya Valero JV, NeiraGiménez C, et al. Surgical management of hand contractures and pseudosyndactyly in dystrophic epidermolysis bullosa. Ann Plast Surg. 1999;43(5):555–559.
[20] Wong A, Ward R, Hadley N, et al. A scoring system for epidermolysis bullosa. Br J Dermatol. 2007;157(1):26–27.
[21] Jutkiewicz J, Noszczyk BH, Wrobel M. The use of biobrane for hand surgery in epidermolysis bullosa. J Plast Reconstr Aesthet Surg. 2010;63(8):1305–1311.
[22] Formsma SA, Maathuis CB, Robinson PH, et al. Postoperative hand treatment in children with recessive dystrophic epidermolysis bullosa. J Hand Ther. 2008;21(1):80–84.
[23] Campiglio GL, Pajardi G, Rafanelli G. A new protocol for the treatment of hand deformities in recessive dystrophic epidermolysis bullosa (13 cases). Ann Chir Main Memb Super. 1997;16(2):91–100.
[24] Rashidghamat E, McGrath JA. Novel and emerging therapies in the treatment of recessive dystrophic epidermolysis bullosa. Intractable Rare Dis Res. 2017;6(1):6–20.
[25] Terrill PJ, Mayou BJ, Pemberton J. Experience in the surgical management of the hand in dystrophic epidermolysis bullosa. Br J Plast Surg. 1992;45(6):435–442.
[26] Zarem HA, Pearson RW, Leaf N. Surgical management of hand deformities in recessive dystrophic epidermolysis bullosa. Br J Plast Surg. 1974;27(2):176–181.
[27] Horner RL, Wiedel JD, Bralliar F. Involvement of the hand in epidermolysis bullosa. J Bone Joint Surg Am. 1971;53(7): 1347–1356.
[28] Rees TD, Swinyard CA. Rehabilitative digital surgery in epidermolysis bullosa. Plast Reconstr Surg. 1967;40(2):169–174.

[29] Ladd AL, Kibele A, Gibbons S. Surgical treatment and postoperative splinting of recessive dystrophic epidermolysis bullosa. J Hand Surg Am. 1996;21(5):888–897.

[30] Vozdvizhensky SI, Albanova VI. Surgical treatment of contracture and syndactyly of children epidermolysis bullosa. Br J Plast Surg. 1993;46(4):314–316.

[31] Ciccarelli AO, Rothaus KO, Carter DM, et al. Plastic and reconstructive surgery in epidermolysis bullosa: clinical experience with 110 procedures in 25 patients. Ann Plast Surg. 1995;35(3):254–261.

[32] Kim JS, Kuk E, Yu KN, et al. Antimicrobial effects of silver nanoparticles. Nanomedicine. 2007;3(1):95–101.