Keratin gel in the management of Epidermolysis bullosa

• **Objective:** Epidermolysis bullosa (EB) describes a number of genetically inherited conditions which cause skin fragility and minor trauma leading to skin damage, skin loss and wounding. Owing to the fragility of the skin and requirement for frequent dressing changes, at present, the optimal dressing(s) is not clear. Our objective was to assess the use of a keratin gel in the management of wounds in patients with different forms of EB.

• **Method:** We treated patients with different types of EB and a range of wounds with a novel keratin gel. In a convenience sample of consecutive patients, we introduced the keratin gel into their treatment regimen maintaining other aspects of their care.

• **Results:** Patients reported faster healing and more resilient healed skin. Of the ten patients treated in this pilot study, six found the gel effective; two found it ineffective; and in two patients, it caused itching leading to discontinuation of the treatment.

• **Conclusion:** The results of this case study series suggest that keratin gel can be useful in the management of EB and are consistent with previous published experiences.

• **Declaration of interest:** Clive Marsh is an employee of Keraplast Research, Robert Kirsner is a consultant to Keraplast Research and Jackie Denyer has no conflict of interest.

epidermolysis bullosa; keratin gel; chronic wound; skin fragility

J. Denyer,[1] EB Clinical Nurse Specialist;
C. Marsh,[2] Wound Care Business Manager;
R. S. Kirsner,[3] Professor and Interim Chair;
1 Great Ormond Street Hospital, London, UK
2 Keraplast Research, Christchurch, New Zealand
3 Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, USA.

Email: Rkirsner@miami.edu

Epidermolysis bullosa (EB) is used to describe a number of genetically inherited conditions which cause skin fragility such that minor trauma leads to skin damage, skin loss and wounding.[1] Patients with EB develop erosions and ulcers in the sites of trauma, suffer significant morbidity from painful wounds and are at risk of infection and, in some cases, malignant transformation. The skin and mucous membranes blister and/or strip away in response to minimal everyday friction and trauma. Outcomes vary depending on the type of EB with disability, scarring and reduced life expectancy in those with severe forms of recessively inherited EB. Wound products which are atraumatic when applied to normal skin can be damaging to the skin of those affected, thus limiting clinician choice. Despite current management, a proportion of wounds in older children and adults become recalcitrant. Therefore, alternative solutions are needed, such as a keratin-rich gel (keragelT, Keraplast Technologies, USA) that accelerates acute wound healing and upregulates keratin gene expression.[2] A study of the keratin gel was conducted in New Zealand in the community by an EB specialist health professional, in patients with severe generalised dystrophic EB.[3,4] In the first case, a chronically wounded area (duration >5 years) on the back of an 11-year-old patient's neck was healed in approximately four months, and after six months the skin no longer required protective dressings to prevent new wound formation.[3] In the second case report, the left hand and foot on an eight-month old infant were treated with keratin gel and the right hand and foot treated with ongoing standard care. Faster healing of new wounds was observed in the keratin-treated side along with reduced formation of blisters on the treated areas.[4]

In EB, gene defects lead to absent or diminished coding of structural proteins that reduce the tensile strength of the skin. Key proteins which are affected and their subsequent physical location in the skin dictate disease severity.[1] Epidermal forms of EB involve defects in keratin proteins (KRT5 & KRT14),[1] while Junctional EB (JEB) involves defects in laminin proteins and collagen XVII[1] and dystrophic forms involve defects in collagen VII.[1] Depending on the EB subtype, the effects of EB vary between painful blistering of the hands and feet in localised EB simplex, to progressive disability from repeated scarring in those with severe forms of dystrophic EB. Dystrophic EB is associated with increased mortality from squamous cell carcinoma later in life while early death in infancy in seen in children affected by JEB generalised severe.[1] While research is progressing toward a potential cure and effective treatments, current daily management focuses on prevention of trauma, management of acute and chronic wounds, optimising nutrition, pain control, prevention of disability and psychological support.

A variety of products are used for wound management at the institution of one of the authors (JD). Experience has shown each type of EB to have different requirements for dressings.[5] Those with milder forms of EBS tend to use fewer, lighter dressings or sheet hydrogels, as blistering is exacerbated by

Fig 1. Patient 1

Before treatment

After 4 weeks gel treatment. Epithelialisation is observed at the wound margins and the wound area is reducing

After 20 weeks treatment, the wounds are almost completely epithelialisied

heat. Children with severe forms of junctional and dystrophic EB have a tendency to develop chronic wounds and are prone to bacterial colonisation and infection. Extensive dressings are often required and dressing changes are prolonged and traumatic for the child, family and caregivers.[6] Healing of these chronic wounds is difficult in the presence of poor nutrition, anaemia, and additional tissue damage from destructive pruritus and resultant trauma from scratching. Cleansing of individual wounds often results in pain and is subsequently refused due to anticipatory fear.

Advances in the understanding of the role of keratin in cell biology, in particular the importance of keratin in cell differentiation and protein synthesis, have provided a rationale for use. For example, following injury, keratin-17 is upregulated, and in studies involving keratin-17 knock-out mice, delayed healing was observed.[7] *In vitro* keratin-based products stimulate cellular migration and *in vivo* studies of porcine partial-thickness wounds found keratin dressings to speed healing compared to air exposed wounds and those treated with polyurethane film dressing.[2,8] Molecular analyses found upregulation of keratin gene expression.

The aim of this study was to examine keratin gel on a wider range of EB and wound types under the guidance of a different EB specialist health professional in another geographic region.

Materials and methods

The patients are all cared for under the guidance of a multi-disciplinary specialist EB team based at Great Ormond Street Hospital (GOSH), London, UK—a service that typically provides care in the community. Patients with refractory or recurrent wounds or those in areas of constant friction where wound management was challenging were invited to enrol. This was a convenience sample and no willing participants were excluded. Guidance on the use of the keratin gel was given to the patients and/or their carer (sometimes the parent/guardian) by the EB specialist health professionals in accordance with the manufacturer's instructions.[4] Feedback, including photographs, was given by the patient/carer to the EB specialist. In analysing efficacy, the following aspects were measured:

- Ease of use
- Patient tolerance and acceptability
- Speed of wound healing (measured in days)
- Strength of healed skin, measured as likelihood to re-blister
- Overall impact on the patient's quality of life.

The overall impact on a patient's quality of life, including performance of activities of daily living, were assessed through questioning.

Results

There were ten patients treated, one was an inpatient receiving palliative care for gut failure and the

References

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4 Kirsner, R.S., Cassidy, S., Marsh, C. et al. Use of a

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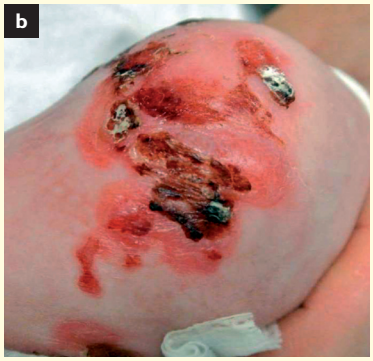
Fig 2. Patient 3

Before treatment



After 4 days' treatment, the wound showed significant improvement. The area resolved fully within 16 days

Table 1. Use of gel in the management of Epidermolysis bullosa

Characteristics	Prior treatment and experience	Outcome with gel
Patient 1, 5-years old (Fig1) **Type of EB** • Severe generalised dystrophic **Comorbidities** • Typical for severe generalised dystrophic EB* **Rarer comorbidities** • Gut failure with multiple small bowel perforations **Wound size and duration** • Large, most of upper chest • 4-years' duration	The wound had not responded to daily dressings using soft, silicone-based dressings and antimicrobial products. Owing to comorbidities, this patient was an inpatient receiving palliative care and was able to be closely monitored.	The gel was applied daily to the affected area during dressing changes. After 4 weeks (Fig 1b), epithelialisation can be seen at the wound margins and the wound area is reducing. By 20 weeks (Fig 1c), the wounds are almost completely epithelialised. The gel application was continued to the scarred area with further reduction in redness seen. Reduction in tissue damage improved quality of life, reduced pain and increased mobility. Dressing changes were quicker with less distress and without opiate analgesia. Foam dressings were replaced with a lighter version, which reduced heat production with a subsequent decrease in pruritus and trauma from scratching.
Patient 2, 7-years old **Type of EB** • Severe generalised dystrophic **Comorbidities** • Typical for severe generalised dystrophic EB* **Wound size and duration** • Cluster of ~5 size, typically 50 x 50mm • 1-year duration	Extreme skin fragility with multiple areas of chronic wounding. Neck is particularly prone to break down and a difficult area to dress. Dressings increase heat production leading to pruritus and subsequent scratching which causes additional skin trauma. Management included using Mepitel (Mölnlycke Health Care) soft silicone mesh which was covered with PolyMem (Ferris).	Gel was applied to the front of the neck. This caused some pain on application, and so was diluted to 50% of its strength using Dermol 500 lotion. With daily application, the wound sizes gradually decreased. After 12 weeks, the area at the front of the patient's neck could be managed without dressings.
Patient 3, 6-months old (Fig 2) **Type of EB** EBS generalised severe **Comorbidities** • Sub-optimal nutrition • Pain **Wound size and duration** • Cluster of ~5, size, typically 20 x 20mm • 2-months' duration (1/3rd of life to date)	EB simplex generalised severe is characterised by widespread blistering typically occurring in clusters. Unlike other types of EB, the skin does not generally benefit from regular dressings as there is a tendency to blister under and around the edges of the dressing materials Management is to lance blisters and apply topical treatments such as emollients or anti-microbial ointments as required. Previous treatment involved using Flaminal Hydro (Crawford Pharma) ointment and QV ointment (Crawford Pharma).	The gel was applied to an area of persistent blistering on the upper thigh. This lesion had resulted from trauma of the edges of the patient's napkin rubbing, and as expected in this condition, blisters developed around the resulting crusts increasing the damaged area of skin. Fig 2 shows the extensive blistering typical of EBS, which is generalised severe with crusting from one blister causing breakdown of adjacent skin and the herpetic form.
Patient 4, 1-month old (Fig 3) **Type of EB** • Severe generalised dystrophic **Comorbidities** • Typical for severe generalised dystrophic EB† **Wound size and duration** • Small size: blisters on fingers • 1-month duration (since birth)	In common with all infants, the patient held her fingers and thumbs in tight fists which caused repeated blistering and wounds which were difficult to dress while allowing movement for her development. To minimise trauma caused by this behaviour, her fingers where dressed with strips of hydrofibre and secured with a simple retention bandage.	The gel was applied to the wounds and vulnerable skin on the fingers. Fig 3 shows typical breakdown before the gel treatment began. The wounds essentially healed in 14 days (Fig 3b). For the next 14 days, the gel was applied daily, but less protection was needed and carer time was reduced. After 28 days, the fingers were strong enough not to need regular protective dressings, (Fig 3c). The gel continued to be used to help to strengthen the skin, typically every 2nd day. Traumatic blistering and wounding reduced once the patient reached the developmental stage of having her hands open and was no longer persistently fisting.

Table 1. Continued

Characteristics	Previous treatment and experience	Outcome with gel
Patient 5, 15-years old (Fig 4) **Type of EB** • Dystrophic EB inversa type **Comorbidities** • None **Wound size and duration** • 2 example new blisters were studied: one on her patella and one on her elbow • Size was typically 100 x 50mm	Suffers from frequent traumatic wounds. Main problem areas of skin are the patient's back, ankles, knees and elbows.	The gel was applied daily and improvement was seen after 4 days (Fig 4). The area resolved fully within 16 days. The gel is now applied to all newly blistered areas and continued until the skin is clear.
Patient 6, 1-year old **Type of EB** JEB intermediate **Comorbidities** • Typical for JEB: intermediate‡ • Specific for patient: gastroschisis repaired at birth followed by long period of parenteral nutrition **Wound size and duration** • 2 wounds were studied: one on shoulder and a larger one on side of chest/abdomen • Both were medium size, typically 100 x 100mm	Extreme skin fragility and a risk of developing chronic wounds following the natural history of this disease. Management since birth has been dressing wounds with PolyMen (Ferris) and Flaminal Forte (Crawford Pharma). Typical healing time is 14 days.	The gel was applied to a new wound on the patient's shoulder and covered with PolyMem. There was no discomfort on application. This was repeated daily. The wound healed in 7 days and dressings were not required. The second wound (a very large blister), developed over the patient's chest and side. Following standard management, this was lanced and the blister roof left *in situ*. The gel was applied daily, and after 6 days, the area was healed. The patient's mother described this as 'healing faster than she had experienced with similar blisters'.

*Sub-optimal nutrition, anaemia of chronic disease, pain, contractures, osteoporosis
†Extreme skin fragility; prenatal and birth damage resulted in extensive wounds over both lower limbs
‡Frequent blistering and wounds, sub-optimal nutrition, pain

other nine were treated in the community. In the treatment group, three had severe generalised dystrophic EB, one dystrophic EB inversa type, two JEB generalised severe, one JEB intermediate, two had localised epidermolysis bullosa simplex (EBS) and one EBS generalised severe.

The wounds that were studied were placed into three categories:

- Recalcitrant chronic wounds (typically of greater than 1-year duration)
- New/acute wounds occurring in areas that receive persistent trauma and are continually breaking down

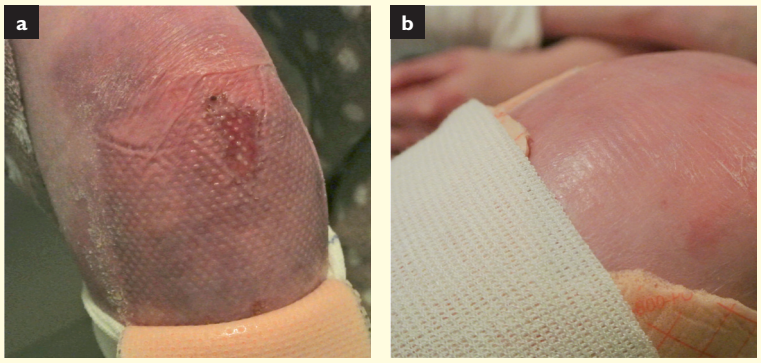
Fig 3. Patient 4

Typical breakdown before the gel treatment

After 2 weeks of treatment, the wound had essentially healed

After 4 weeks using gel the fingers were strong enough to not need regular protective dressings

Fig 4. Patient 5



Patella, pretreatment

Patella, 9 days posttreatment

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- New/acute wounds occurring in isolation, essentially as a singular event.

All patients and carers found the product easy to use and there were no adverse events reported. Owing to the sticky nature of the gel, patients and careres were told to allow time (5~10 minutes) for it to dry before putting on clothing or getting into bed. However, drying time was reduced by covering with cornflour, a practice that was adopted by three of the patients, while two patients experienced a stinging sensation which was usually overcome by diluting with a moisturiser or emollient. On clinically critically colonised wounds, the keratin gel was mixed with a topical anti-microbial agent (for example Flaminal, Crawford Healthcare).

The keratin gel was found tolerable and acceptable by 8/10 patients, however, itching occurred in two patients with JEB generalised severe who discontinued use. In contrast, the other patients, anecdotally, found it to reduce itching. Of the remaining eight, six continued long-term use of the gel until the wound healed and used it for subsequent wounds that developed as well. The localised EBS patients discontinued use after no response was seen following four weeks of treatment.

Of the six patients who found the gel to be effective, two had recalcitrant chronic wounds, two had acute wounds occurring in an area that receives persistent trauma and two had acute wounds occurring in isolation. A comprehensive summary of these six patients is given in Table 1.

In patients 1 and 2 (both severe generalised dystrophic EB), chronic (4-years' and 1-year duration, respectively) wounds healed in 20 weeks and 12 weeks, respectively. Patient 1 was an inpatient receiving palliative care. As the skin healed, fewer protective foam dressings were required which reduced heat production and thus pruritus and consequent trauma from scratching was reduced (Fig 1). Patient 2 did find that the gel stung on application. This was overcome by a 50% dilution with Dermol 500 (a moisturising lotion containing emollients and antiseptics). As the skin healed, protective dressings were gradually reduced, then discontinued without any breakdown. In 2 patients (#3 EBS generalised severe and #4 severe generalised dystrophic EB), new wounds in areas of persistent trauma and resultant breakdown were studied. In patient 3, as is typical for EBS generalised severe, no dressings were used before treatment, and after 16 days, the area had resolved (Fig 2). In patient 4, the fingers were being dressed with protective dressings before the use of the keratin gel. The dressings were gradually reduced during treatment and then discontinued as the skin healed in 2~3 weeks (Fig 3). These areas had not healed as rapidly in the past and were persistently recurring. After treatment, the skin broke down less frequently, and the patient did not need the protective dressings on the fingers (Fig 3). In two patients (#5 JEB intermediate and #6 dystrophic EB inversa type), new, isolated wounds were studied (two for each patient) and all four wounds healed in approximately seven days, (Fig 4).

Quality of life improved with increased mobility and reduction of itching, and reduced discomfort from heat was reported in the six patients who found the keratin gel to be effective.

Discussion

This case series reported the treatment with keratin gel in a wider range of EB and wound types than previously published work.[3,4] Only two patients did not tolerate the treatment due to itching. However, other patients reported an improvement in itching, possibly due to the reduction in application of thick foam dressings. Of the 8 patients who tolerated treatment, two found it to be ineffective. Both patients had localised EBS, representing all of the treated patients with localised EBS in this study. Whether the superficial nature of these wounds results in differing efficacy is not known. However, there have been anecdotal unpublished reports of it being effective for localised EBS. In two patients, chronic wounds which had not healed in the previous six months, healed; thus, the keratin gel appears to have facilitated healing.

Owing to the small number of patients with this disorder and the different variation in the types of EB and the wounds, it would be difficult to perform large-scale studies.

Conclusion

In the six patients in whom the keratin gel was effective, the healing times were faster and consistent with those in previously published reports.[3,4] In this series, quality of life improvements were observed, which are of significant value to the patient. These results suggest this keratin gel can play a useful role in the management of EB. ■