Clinical efficacy of biocellulose, carboxymethyl cellulose and normal saline dressing in epidermolysis bullosa

Objective: To evaluate the efficacy of a biocellulose, a carboxymethyl cellulose and a normal saline wound dressing in the wound care management of epidermolysis bullosa (EB) skin wounds.
Methods: This was a single-blind, randomised controlled trial involving wounds from patients with EB. Wounds were divided into three groups: group I with biocellulose wound dressing, group II with carboxymethyl cellulose wound dressing and group III with normal saline wound dressing as a control. All dressing changes and wound parameters were recorded. Observations were conducted every three days until complete wound closure or up to one month.
Results: The outcomes of treatment of 36 wounds from four patients were evaluated in this study. Mean healing time in group I was seven days, eight days in group II and 14 days in group III. There were significant differences in healing times between group I and group III (p=0.0001) and between group II and III (p=0.001). The results showed a significant reduction in the percentage of wounds area on day three for each group: 51.7% in group I, 51.9% in group II, and 26% for group III. All wounds in groups I and II had healed at day 12 (100%) and at day 24 (100%) in group III. There were significant differences in the reduction of percentage wound area between group I and group III at day three (p=0.044) and day six (p=0.000), and between group II and III at day six (p=0.003).
Conclusion: The study demonstrates that both the biocellulose and the carboxymethyl cellulose wound dressings significantly reduced percentage wound areas and complete healing times compared with the normal saline wound dressing in EB skin wounds, demonstrating they are both equally good for wound care management in EB patients.
Declaration of interest: The authors have no conflicts of interest.

biocellulose • carboxymethyl cellulose • epidermolysis bullosa • normal saline • wound dressing

Epidermolysis bullosa (EB) is a rare inherited mechanobullous blistering disorder, characterised by fragile skin and mucous membrane. The cause of EB is a mutation of various structural proteins in the skin resulting in various levels of tissue separation within the dermal-epidermal basement membrane zone.[1] The presence of chronic multiple wounds makes the management of EB difficult and complex.[2] In the absence of a cure, supportive wound care management is a mainstay of treating patients with EB. Patients with EB require a non-adherent dressing to avoid trauma and bleeding to the skin on removal. To date, there is a consensus about wound care management in EB, but no specific guidelines that address the wound care challenges faced by people with EB.[1]

Traditionally, gauze soaked with normal saline (also known as normal saline wound dressing, NSWD) has been used to treat wounds. Modern wound dressings create a moist environment to provide the optimal conditions for wound healing.[3,4] The ideal dressing should be able to maintain humidity at the wound-dressing interface, remove excess exudate, permit the exchange of gases between the wounded tissue and the environment, provide thermal insulation, be impermeable to microorganisms, be biocompatible, non-toxic and be removable without causing trauma to the wound.[3] Such dressings include those formed of biocellulose and carboxymethyl cellulose.[3] Adequate moisture balance promotes keratinocyte and fibroblast migration that support the wound healing process.[5]

The aim of this study was to compare the efficacy of a biocellulose wound dressing, a carboxymethyl cellulose wound dressing, and a normal saline wound dressing on the wound care management in patients with EB.

Method

This study was a single-blind, randomised controlled trial that took place between December 2018 and March 2019. Participants were patients in the Paediatric Dermatology Clinics of Dr. Hasan Sadikin Hospital, Bandung, Indonesia. Inclusion criteria in this study were non-infected EB wounds with a minimal size of 2cm^2. The exclusion criteria were patients who were receiving wound care (topical or systemic antibiotic or corticosteroid, or traditional or modern wound dressing), hypersensitivity to carboxymethyl cellulose and/or biocellulose, and a haemoglobin level <8g/dl.

Participants were divided into three groups:

Reiva Farah Dwiyana,[1] MD, PhD; **Yuri Yogya**,[1] MD; *__Srie Prihianti Gondokaryono__,[1] MD, PhD; **Inne Arline Diana**,[1] MD; **Oki Suwarsa**,[1] MD, PhD; **Lies Marlysa Ramali**,[1] MD; **Eva Krishna Sutedja**,[1] MD; **July Iriani Rahardja**,[1] MD; **Hendra Gunawan**,[1] MD, PhD
***Corresponding author email:** prihianti@gmail.com
1 Department of Dermatology and Venereology, Faculty of Medicine, Universitas Padjadjaran – Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

Table 1. Baseline characteristic of wound size

Wound size (cm^2)	Treatment*			Comparisons*,†		
	Group I	Group II	Group III	Group I vs III	Group II vs III	Group I vs II
Mean±SD	7.34±6.77	5.94±3.16	4.37±1.95	NS‡	NS‡	NS‡
Median	5.2	4.80	3.52			
Range	2.00—25.62	2.52—12.16	2.09—7.48			

*Group I—biocellulose wound dressing; Group II—carboxymethyl cellulose wound dressing; Group III—normal saline wound dressing; vs—versus; SD—standard deviation; † p-levels of significance (p<0.05) of difference are given; NS—not significant; ‡Mann-Whitney U-test

Table 2. Comparison of complete healing times between groups

Days to complete wound healing	Treatment*			Comparisons*,†		
	Group I	Group II	Group III	Group I vs III	Group II vs III	Group I vs II
Mean±SD	7.00±2.335	8.00±2.662	14.00±4.670	p=0.0001‡	p=0.001‡	NS‡
Median	6.00	9.00	13.50			
Range	3.00—12.00	3.00—12.00	9.00—24.00			

*Group I—biocellulose wound dressing; Group II—carboxymethyl cellulose wound dressing; Group III—normal saline wound dressing; vs—versus; SD—standard deviation; † p-levels of significance (p<0.05) of difference are given; NS—not significant; ‡Mann-Whitney U-test

- Group I treated with a biocellulose wound dressing (Cuticell Epigraft, Essity formally BSN Medical, Germany) (12 wounds)
- Group II treated with a carboxymethyl cellulose wound dressing (Cutimed Hydro L, Essity formally BSN Medical, Germany) (12 wounds)
- Group III treated with a normal saline wound dressing (12 wounds) as a control.

The study was conducted by two researchers: one researcher applied and removed the dressing, the other, blinded to the dressing used, assessed and measured the wound area.

Each wound in each group was treated with one piece of dressing, applied in a single layer in direct contact with the wound base. After application, the dressing was protected with an elastic bandage (Elastomull, BSN Medical, Germany). No adhesive plasters were used. After removal of the dressings, normal saline and gauze were used as appropriate (that is, if there was any residue in the wound after the dressing removal). Dressing changes in group I were every six days, group II was every three days, and group III was three times daily (each procedure was performed at 10-minute intervals, for a period of one hour). Dressing changes continued until complete wound closure was achieved. Observations were conducted every three days for all groups (the transparent appearance of the biocellulose allowed the measuring of the wound without the need to change the dressing) until complete wound closure or for up to one month.

Efficacy was measured by complete healing times and the percentage of wound closure at each three day timepoint. The method to measure the wound area was the longest length x widest width (based on a consensus approach to wound care in EB by Pope et al.,[1] which has an advantage in that it can easily measure irregular wounds.

Ethical approval

The study protocol was approved by the local ethical committee of scientific research. Patient consent was obtained, including for the taking and use of photographs. The study was performed according to the Declaration of Helsinki.

Results

This study included 36 wounds from four patients with EB (each patient had nine wounds which were subsequently divided across the three groups). All of the patients were male. Mean age of patients was 10.25 years (range: 1–23 years). EB types included simplex (n=1) and dystrophic (n=3). All patients had anaemia, three had hypoalbuminaemia, two had low ferritin, and one patient had a low serum zinc level.

The mean wound size in group I was 7.34±6.77cm^2, group II was 5.94±3.16cm^2, and group III was 4.37±1.95cm^2. There was no significant difference in wound size among the three groups (Table 1).

The comparison of complete healing times between groups is shown in Table 2. Healing times showed a significant result for group I (mean: 7.0±2.3 days, range: 3–12 days) compared with group III as a control (mean: 14.0±4.6 days, range: 9–24 days) (p=0.0001). Group II (mean: 8.00±2.6 days, range: 3–12 days) also showed a significant result compared with group III (p=0.001). There was no significant result for group I compared with group II (p=0.347).

At days three and six, 51.7% and 89.5% of wounds in group I were completely closed, compared with 26% and 46.7% of wounds in group III. This distribution in

Table 3. Mean of percentage of complete wound closure at days 3—12

Percentage of wound closure (%)	Treatment*			Comparisons*,†		
	Group I	Group II	Group III	Group I vs III	Group II vs III	Group I vs II
Day 3	51.7	51.9	26	p=0.044§	NS	NS
Day 6	89.5	84.3	46.7	p=0.000‡	p=0.003‡	NS
Day 9	97.2	89.9	75.8	NS	NS	NS
Day 12	100	100	77.4	NS	NS	NS

*Group I—biocellulose wound dressing; Group II—carboxymethyl cellulose wound dressing; Group III—normal saline wound dressing; vs—versus; † p-levels of significance (p<0.05) of difference are given; NS—not significant; ‡Mann-Whitney U-test; § Unequal Variance T-test

favour of the biocellulose wound dressing was statistically significant at p<0.05 (Table 3).

At day six, 84.3% of wounds in group II were completely closed, compared with 46.7% of wounds in group III. This distribution in favour of a biocellulose wound dressing was statistically significant at p<0.05 (Table 3).

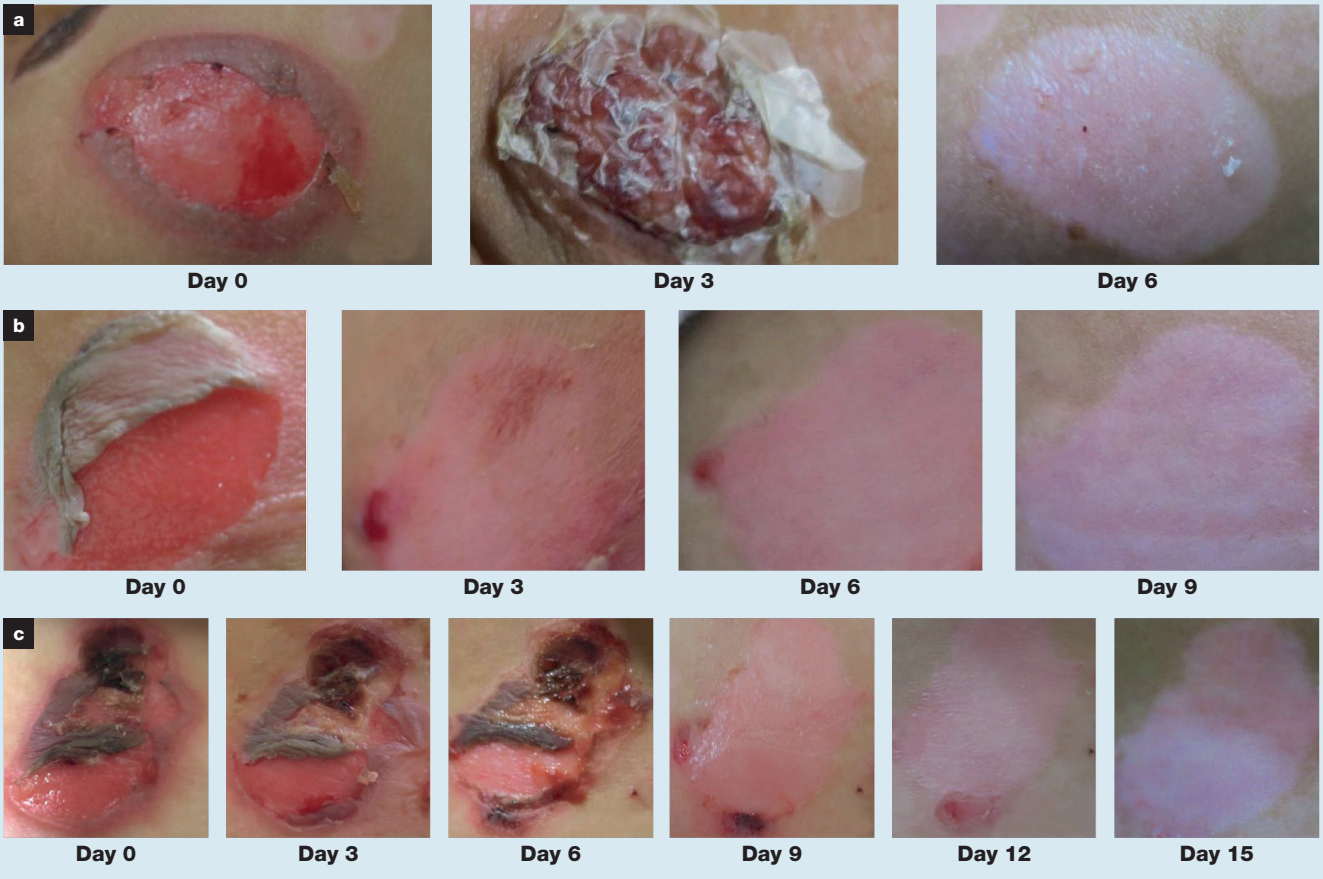
There was no significant difference between group I and group II. All lesions completely healed at day 12 in both groups. All wounds in group III were completely closed at day 24 (Fig 1).

No side effects were reported in any of the groups. A single bulla was reported in one patient in group II and in group III at the end of the observation period and after complete wound closure.

Discussion

Wound dressing is recommended in the wound care management of patients with EB.[2] However, there are no controlled studies for wound dressing in patients with EB, and to the best of our knowledge, no study has been found in the literature comparing the effectiveness of a

Fig 1. The appearance of wound dressing until complete healing between groups. Biocellulose wound dressing (**a**); carboxymethyl cellulose wound dressing (**b**); normal saline wound dressing (**c**)



biocellulose wound dressing, a carboxymethyl cellulose wound dressing, and NSWD in patients with EB.

Carboxymethyl cellulose is a water-soluble, non-woven, hydrocolloid dressing which has the ability to form a gel upon contact with fluid, which promotes a moist wound healing environment. These dressings provide the optimal moist wound healing environment for a variety of wound types and shapes.[6] Clinical trials on carboxymethyl cellulose wound dressings have demonstrated its ability and efficacy in children and adults in various wounds (light-to-moderately exudating wounds such as pressure ulcers, minor burn wounds and traumatic wounds). These dressings are also recommended for paediatric wound care management.[3] An open single-centre prospective non-randomised without control trial, using carboxymethyl cellulose for wound care management in patients with EB, confirmed good acceptability and efficacy for wound care management. The dressing could be changed every three to four days or when saturated.[2,7]

A biocellulose (bacterial cellulose) wound dressing is made from *Acetobacter xylinum* that produces a nanofiber, about 100 times smaller than plant cellulose. This unique nano-morphology results in a non-adherent, transparent wound dressing that allows direct inspection of the wound. It also demonstrates a high level of elasticity and water-holding capacity — up to 200 times their weight.[8] In the absence of exudate, it may stay in place for seven days, on average, without the need for replacement.[9] The need for a dressing change is based on the accumulation of fluids under the dressing.[10] The use of a biocellulose wound dressing is attractive for advanced wound management because of its favourable characteristics, such good elasticity, adaptation to wound contours without adherence to normal skin, good attachment to moving body parts, biocompatibility, non-toxicity and a high moisture content.[11] The use of biocellulose has been described by several investigators in the treatment of hard-to-heal ulcers and other wounds characterised by loss of superficial epidermal layers: in all these studies, the product showed excellent efficacy and safety.[10]

Our data showed that the average complete healing time with the biocellulose wound dressing was seven days, eight days for the carboxymethyl cellulose wound dressing, and 14 days for the normal saline wound dressing. To date, there is no study of a biocellulose wound dressing for patients with EB. Liu et al.[10] reported on use of a biocellulose wound dressing for split-thickness skin graft (STSG) donor sites in burn or reconstructive plastic surgery patients, with an average complete healing time of seven days. Our study showed that biocellulose wound dressing has good efficacy for EB wounds. Bardon et al.[7] reported that EB wounds treated with carboxymethyl cellulose wound dressing had an average complete healing time of eight days.

The wound healing process in our study of a biocellulose wound dressing and a carboxymethyl cellulose wound dressing had shorter healing times compared with the normal saline wound dressing. Brown et al.[12] reported average healing time with the NSWD was 14 days. Normal saline wound dressings may have disadvantages to patients with EB due to its effect of nonselective mechanical debridement and is considered one of the most traumatic materials for wound dressing.[13,14] Traditional dressings are typically formed by moistening cotton gauze with a solution (usually 0.9% normal saline) and placing it in the wound, allowing it to dry, then removing it dry from the wound.[4] How traditional wound dressing is performed in practice varies across health professionals.[13] Usual practice is for frequent dressing change, as much as three to four times daily.[14] Frequent dressing changes the NSWD can lead to damage of healthy granulating tissue, a drop in wound temperature, causing vasoconstriction, and a decrease in blood perfusion. Each time the dressing is changed, cooling and destruction of the wound micro-environment can lead to hypoxia, which impairs leukocyte mobility and phagocytic efficiency that may delay healing.[14]

Our data showed, at days three and six, that wounds dressed with the biocellulose wound dressing had a higher percentage of wound healing (51.7% and 89.5%) compared with the control group (26% and 46.7%). Melandri et al.[15] reported more than 90% of STSG donor site wounds completely healed at days 10–13 with a biocellulose wound dressing. On day six, the wounds dressed with the carboxymethyl cellulose wound dressing had abetter healing rate compared with the control group (46.7%). Nemeth et al.[16] reported complete closure of all wounds within two weeks after shave excision with a carboxymethyl cellulose wound dressing.

Moist wound healing has been accepted as the prominent and most advantageous principle of wound treatment modalities since George Winter's pivotal work in 1962, demonstrated that moist wounds heal 2–3 times faster than traditional wound dressings.[4] In our study, wounds healed twice as fast with use of a modern cellulose wound dressing than a traditional wound dressing. There was no significant difference between biocellulose and carboxymethyl cellulose based on a statistical study. The mean healing time differed by one day only, although this was not statistically significant.

A biocellulose wound dressing could help wound healing from the early stages of wound healing and the proliferation phase. Carboxymethyl cellulose can help wound healing from the proliferation phase. Ferreira et al.[17] reported fibroblasts displayed 70% adhesion to biocellulose after 24 hours. Carboxymethyl cellulose stimulates platelet-derived growth factor, epidermal growth factor and fibroblast growth factor after 24–78 hours.[18] Based on the mechanism of action, we could explain the difference of one day in the mean healing times. The wound area in groups I and II could not be measured every day because the application of the carboxymethyl cellulose wound dressing remains in place for up to 2–3 days and the biocellulose wound dressing for up to seven days.

The advantage of modern wound dressings is the reduction in dressing changes in patients with EB from daily to every three days or even weekly. Cowan et al.[4] reported that traditional wound dressings are more costly than other dressings and Dale et al.[19] reported a similar finding in their study. Not directly measured in our study but worth noting is the costs related to the use of the cellulose wound dressings. In our study, the total cost for treating 12 wounds with a biocellulose wound dressing was $40.53 USD, for a carboxymethyl cellulose wound dressing the cost was $5.91 USD, and for NSWD it was $17.31 USD. In our study the price of a 10x10cm biocellulose wound dressing was $55 USD and for a 10x10cm carboxymethyl cellulose wound dressing the cost was $3.50. There were no significant differences between the biocellulose wound dressing and carboxymethyl cellulose wound dressing in efficacy but the price of the carboxymethyl cellulose wound dressing was lower than that of the biocellulose wound dressing. For daily wound care management, a carboxymethyl cellulose wound dressing is a good option in terms of cost and efficacy. Biocellulose is a new material that has the potential for use as a wound dressing or as artificial skin.[11] However, despite its impressive potential for a wide range of commercial applications, biocellulose is expensive to manufacture. The synthetic media commonly used for biocellulose production is the major factor contributing to its high production costs.[20] An advantage of using a biocellulose wound dressing is that it can be used on moving body parts, such as joints, is relatively non-adherent (reducing risk of trauma and bleeding on removal), and its transparent appearance allows continuous clinical observation.

Limitations

The sample was relatively small in our study, due to the rarity of this genetic disease. A further investigation of this topic would be worthwhile to corroborate the rationale for the use of this dressing in the management of patients with EB.

Conclusion

The biocellulose wound dressing and the carboxymethyl cellulose wound dressing performed significantly better than the normal saline wound dressing on all parameters. The study demonstrated that the biocellulose wound dressing and the carboxymethyl cellulose wound dressing significantly reduced percentage wound area and the average time for complete wound closure compared with the normal saline wound dressing. The performance of the biocellulose wound dressing and the carboxymethyl cellulose wound dressing were comparable. **JWC**

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Reflective questions

- Why do modern wound dressings provide better conditions for wound healing compared with traditional wound dressings?
- Why do patients with epidermolysis bullosa need a non-adherent wound dressing?
- What are the advantages of using a biocellulose wound dressing?