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Clinical evaluation of a bioactive beta-glucan gel in the treatment of 'hard-to-heal' wounds

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Objective: The aim of this evaluation is to assess the effects of a wound healing gel in a wounds of different aetiologies.
Method: Data was recorded on the wound surface area, tissue type, and patient level of wound pain at baseline (0) and at weeks 1, 2, 3, 4, and 8.
Results: Of the total 39 patients enrolled in the study, 26 patients who complied with the protocol criteria completed the minimum four-week study period. During the 12-week evaluation period, seven of the 26 wounds fully healed and an additional eight wounds showed a reduction in size of more than 50 %. Of the remaining 11, five wounds showed moderate healing progression and six wounds did not respond to treatment. Following the 12 week evaluation time point clinicians reported that a further three wounds healed—a 38 % healing rate.
Conclusion: The results give promise that this advanced gel, containing a macrophage activating substance, can be a tool in re-activating healing in stalled wounds where standard of care is no longer giving the desired healing progression.
Declaration of interest: Biotec Pharmacon provided supplies of Woulgan Biogel and the authors received an honorarium for their participation in the evaluation.

beta-glucan gel • restart healing • hard-to-heal wounds • inflammation • macrophage

Wound repair is a natural process that is initiated following damage to living tissue. This natural repair mechanism is reliant on an orchestrated, complex cascade of cellular and biochemical events that directs the wound through different stages of healing.[1,2] The initial release of chemical messengers in response to damaged blood cells results in haemostasis and a time-limited inflammatory response to ensure the cells required for wound repair are directed to the wound bed.[3] In the presence of certain comorbidities and medication this normal inflammatory response may be affected or reduced.

A stalled wound can be defined as one where if the wound has not decreased in size by 40% in a four week period using standard therapy.[4] The management of 'hard-to-heal' wounds calls for relevant supportive evidence where innovative wound management products have been used to regulate and promote healing.

There are a number of different wound aetiologies and these are traditionally classified, as acute or chronic. Acute wounds are usually described as being the result of an insult or injury to the skin and underlying tissues from an external force, and include: surgical incisions, lacerations, traumatic injuries and burns that usually heal within the anticipated time frame. It is anticipated that an acute wound should heal with minimal intervention, as the body's natural ability to repair damaged tissue is invoked. Conversely, chronic wounds such as, leg ulcers (LUs), diabetic foot ulcers (DFUs), fungating wounds, or pressure ulcers (PUs), result from an underlying altered physiology and have an unpredictable and extended healing trajectory. It is essential that the underlying aetiology of a chronic wound is identified and addressed so that appropriate remedial intervention can be delivered. Historically, these chronic wounds have earned the label of 'hard-to-heal'.

'Hard-to-heal' wounds

Wound healing is often interrupted due to a breakdown in the normal orchestrated cascade of cellular events involved in wound repair. In some patients, such as those with diabetes there is a poor inflammatory response with an aberrant biochemical reaction required for appropriate cellular activity.[5] In others, there is often a tendency for an abnormally prolonged inflammatory response, which becomes self-destructive to tissue and may cause extracellular matrix breakdown and inhibit generation of new blood vessels. However, interruption to wound healing can also occur in an acute wound. Any wound of over four weeks' duration and where healing is stalled has been termed chronic.[6]

Woulgan Biogel is a wound healing product containing an ancillary medicinal substance soluble beta-glucan (SBG). The novel part of the product is the component SBG, which has the ability to activate macrophage

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Table 1. Participants withdrawn from the analysis

Reason for withdrawal from analysis	Time of discontinuation* from study	Number of patients
Infected wound and concurrent antimicrobials not used. Four-week data not available	Week 1 Week 3	3 1
Wound malodorous, probably infected and concurrent antimicrobials not used. Four-week data not available	Week 1 Week 2	2 1
Deterioration in wound, pain probably due to infection and no antimicrobials used. Four-week data not available	Week 2	1
Unexplained bleed into the wound—not product related. Four-week data not available	Week 1	1
Inappropriate use of SBG gel, protocol violation	Week 1	2
Non-adherent. Four-week data not available	Week 3	1
Patient died. Four-week data not available	Week 1	1

*The decision to discontinue a participant was made by the attending clinician

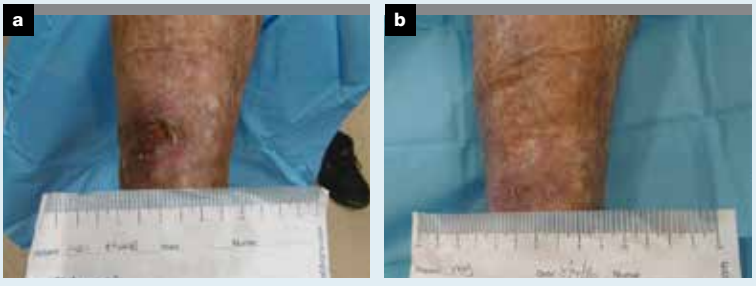
functions in the wound bed. The gel formulation also provides typical hydrogel properties, being at least 80% water, offering a moist wound healing environment that rehydrates necrotic tissue and aids in autolytic debridement.

The SBG gel has a slightly acidic pH of around six, which facilitates wound healing, inhibits excessive protease activity and has been found to activate macrophages to produce signal molecules and growth factors resulting in cell proliferation, angiogenesis and wound contraction.[7]

The positive effects of SBG gel in the treatment of DFUs has been studied in a randomised double blind comparator-controlled clinical trial. The results showed that 15/27 (56%) of wounds that received the SBG gel treatment healed by week 12, compared with 11/30 (37%) wounds that were dressed with methylcellulose gel (p=0.094).[8]

The mode of action of SBG has been investigated in several diabetic mouse models where overall healing, wound contraction, cell proliferation and angiogenesis were studied. In these studies, the SBG gel was compared with a gel without the active component SBG, mimicking regular commercially available hydrogels. SBG had positive impact on all the studied parameters and significantly outperformed existing products and treatment options in this model.[7] The enhanced cell proliferation and angiogenesis may be explained by activation of macrophages following SBG stimulation.

Fig 1. Wound images from case 1 (leg ulcer mixed disease) week 0 (**a**) week 8 (**b**)



Aim

The aim of the evaluation was to record wound progress in a non-randomised cohort of participants with stalled wounds following intervention with the SBG gel.

The primary outcome measure was to assess the ability of the SBG gel to restart the wound healing process measured as reduction in wound surface area. The secondary outcome measure was to record the number of healed wounds.

Methods

Patients whose wounds had been stalled for four weeks or more were identified from five different centres in the Hull and Humber (north-east England) region and invited to take part in the clinical evaluation of SBG gel.

Patients were provided with an information sheet and consent was obtained following screening and application of the prescribed inclusion/exclusion criteria.

Inclusion criteria:

- The patient or guardian understands the purpose of the evaluation and has provided written informed consent that includes permission to take photographs of the wound and dressing
- The patient had a wound between 0.5 cm^2 and 45 cm^2
- The patient's wound has been assessed as dry or producing low to moderate levels of exudate
- The patients wound has been assessed as free from the classical signs of acute infection (redness, swelling, heat and pain)
- The patient can be monitored for a minimum of four weeks
- The patient will comply with compression bandaging or offloading device when required.

Exclusion criteria

- The subject has dementia or learning difficulties and is unable to give informed consent
- The subject has a co-existing infection, such as a urinary tract or upper respiratory tract infection
- The subject is receiving immunosuppressant or steroid therapy
- If diabetic, the subject has HbA1c greater than 10% (>86 mmol/mol)
- The subject has been diagnosed with a chronic (but active) skin condition such as eczema or psoriasis.

As this was a clinical evaluation where the data gathered did not exceed that of conventional record

Table 2. Study subjects

Male subjects		16
Female subjects		10
Mean age (range)		71 years (27–93 years)
Leg ulcers		21
Diabetic foot ulcers		4
Pressure ulcers		1
Wound age	4–11 weeks	2
	12–15 weeks	3
	16–52 weeks	15
	>52 weeks	6
Wound size average (range)		8.1 cm^2 (0.5–45 cm^2)

keeping and there was no control group and ethical approval was not required.

Data collection

Patients were coded by centre and each case numbered; there were no patient identifiable data recorded on the data collection tools. Baseline data recorded before the use of SBG gel included patient age, gender, significant medical history, current medication and adjunct therapies. Furthermore, the wound type, anatomical location, duration, previous episodes of wounds at the same site, wound size, appearance and exudate levels were recorded. If the wound type was venous ulceration, it was noted if the patient was being treated with graduated compression therapy.

Details of the dressing regime used before the SBG gel evaluation was captured, along with the frequency of dressing change, the ease of existing dressing removal and the wound response to the current dressing (either static or worsening). Images were taken before beginning treatment and at each subsequent evaluation. All clinicians involved in the evaluation had been provided with a camera and advice on best practice when taking photographs to increase reliability of the image.

At the assessment visit, all wounds had SBG gel applied directly to the wound bed and covered with a secondary dressing. The choice of secondary dressing was at the discretion of the clinician, or Kliniderm Foam was used.

All patients who had previously been treated with graduated compression therapy continued to have this applied to treat the underlying venous hypertension. The difficulty in removal of the existing dressing was recorded, along with the ease of application of SBG gel. It was recommended that the SBG gel should be applied, as required at dressing change with an optimum of twice-weekly applications, but frequency of dressing changes varied depending on the wound aetiology and clinical need. A formal

Fig 2. Wound images from case 2 (neuropathic diabetic ulcer) week 0 (**a**) week 8 (**b**) (completely healed at week 12)

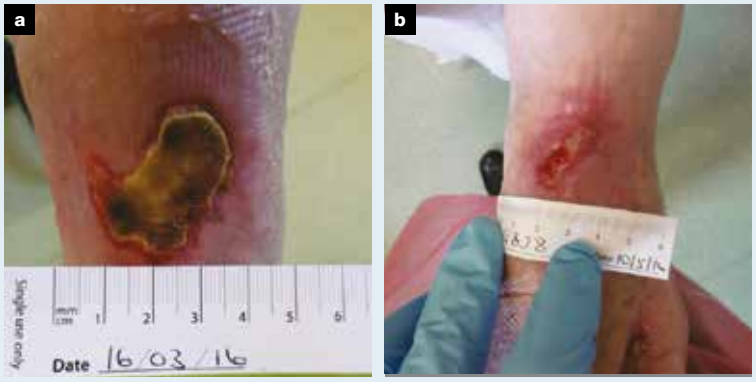


Fig 3. Wound images of case 3 (orthopaedic surgical incision site) week 0 (**a**) week 6 (**b**)

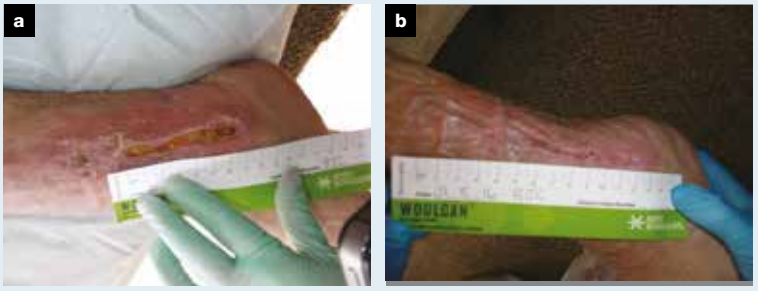


Fig 4. Wound images of case 4 (pretibial laceration) week 0 (**a**) week 7 (**b**)

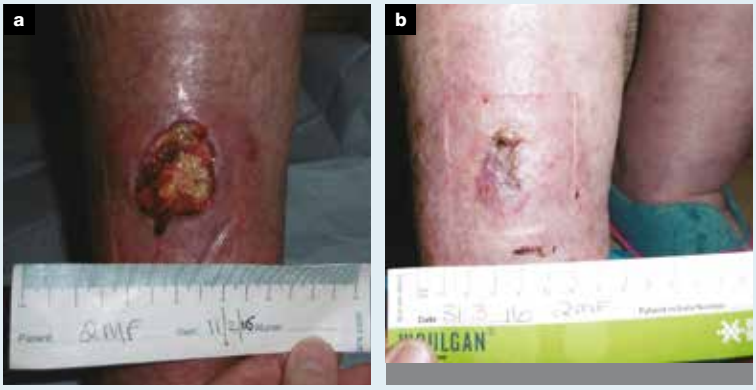


Fig 5. Wound images of case 5 (diabetic foot wound) week 0 (**a**) week 2 (**b**)

Table 3. Average wound size at start, week four, eight and twelve

Time	Average size of ulcer in cm^2	Range	Number of wounds
Start	8.1 cm^2	0.5–45 cm^2	26*
Week 4	5.7 cm^2	0 –45 cm^2	24
Week 8	3.4 cm^2	0–24.8 cm^2	12
Week 12	0.4 cm^2	0–4.0 cm^2	12

*One wound healed in two weeks

Table 4. Wound size progression during the 12 week assessment period

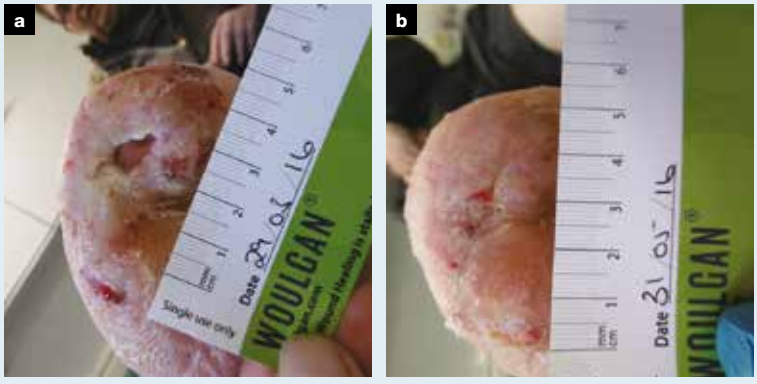
Healing status	Fully healed	>50 % reduction	10–50 % reduction	No progression
Number of wounds	7	8	5	6

Table 5. Details of healed wounds

	Wound	Wound age at start	Wound size at start	Healed at
1	LU with mixed aetiology	22 weeks	2.4 cm^2	Week 8
2	Ischaemic DFU	4 weeks	5.0 cm^2	Week 12
3	Surgical lower LU	16 weeks	3.9 cm^2	Week 6
4	LU pretibial laceration	12 weeks	12.0 cm^2	Week 7
5	DFU at dorsum	5 weeks	2.4 cm^2	Week 2
6	DFU forefoot amputation	312 weeks	0.5 cm^2	Week 9
7	LU	14 weeks	0.5 cm^2	Week 7*

* Patient treated with SBG gel in the first four weeks. LU–leg ulcer; DFU–diabetic foot ulcer; A further three wounds healed after the 12-week evaluation period. Their average baseline wound surface area was 17.7 cm^2 and their average duration before treatment with SBG gel was 54 weeks

Fig 6. Wound images of case 6 (diabetic foot amputation site) week 0 (**a**) week 9 (**b**)



evaluation with data collection was undertaken at weekly intervals for the first four weeks, then at weeks eight and twelve for patients who had ongoing evaluation. A record was kept of any adverse events, the number of tubes of SBG gel used and any changes to the secondary dressing and the rational for using a different dressing. All data collected were subject to descriptive analysis.

Results

Of the 39 patients identified, 13 were withdrawn from the analysis (Table 1). Data were included for 26 patient's wounds from five different centres in England; see Table 2 for patient and wound details. Patients ages ranged from 27–93, with an average age of 71 years. The majority of the wounds were LUs (21/29) followed by DFUs (4/29) with one PU assessed.

Of the patients with LUs, 16 of the patients were already being treated with compression therapy before beginning the treatment with the SBG gel. This included one pretibial laceration and one non-healing orthopaedic surgical wound. The DFUs included one forefoot amputation. The remaining wound was a sacral pressure ulcer over the coccyx: this patient was using pressure redistributing equipment.

All wounds had been static for four weeks or longer with 21 open for 16 weeks or longer (Table 2), six for more than one year. There were four patients reported to have diabetes mellitus, two with ischaemia and three were regular smokers.

Wound size progression

A clear reduction in the average wound size presented at four-weekly intervals from start of the evaluation and up to week 12 can be seen in Table 3. Wound size in terms of progression during the 12 week assessment period may be seen in Table 4. There was an average wound surface area reduction of 41%, one wound healed, 20 decreased in size, four remained static, and two increased in size.

Healed wounds

A summary of the seven wounds that healed during the 12 week evaluation period is seen in Table 5. The table records the wound type and the duration of the wounds (range: 4–312 weeks) together with the week in which the individual wounds healed. Fig 1–6 show 6 wounds that healed during the evaluation period. Subsequent to the conclusion of the formal 12-week evaluation period, clinicians reported that three additional wounds achieved healing. Overall, 10 wounds healed completely (38 %).

Removal and application of dressing

This was scored as: very easy, easy, difficult or very difficult. For the removal of the dressing in use before the use of SBG gel, the clinicians reported 16 cases as very easy, nine as easy and one was classed as difficult to remove. For the removal and application of SBG gel, 25 recorded this to be very easy and one easy throughout the evaluation period.

Discussion

Despite a number of patients being withdrawn from

the evaluation SBG gel demonstrated positive outcomes in seven patients achieving full wound healing; five of these wounds had been present for over 12 weeks. Furthermore, feedback from the clinical centres confirmed that three additional wounds healed following the 12-week evaluation period. This is notable as these wounds were stalled before intervention with SBG gel therapy. In some of the wounds that failed to heal during the evaluation period there were positive signs of a reduction in wound surface area as shown in Table 3.

Limitations

Case series use essentially a descriptive approach and are non-comparative, lacking a control arm. Therefore, the results cannot be compared with those who did not receive active treatment and recruitment selection bias cannot be controlled.

Conclusions

Based on the findings during the evaluation study it can be concluded that the SBG gel therapy is able to restart the healing process in a range of stalled wounds, including those that had been present for long periods. In the present study, 80% (21/26) of the wounds treated were 16 weeks or older. The study did not, however, give any answers to why some wounds did not respond, but the initial set evaluation period of four weeks was found to be too short for assessing the potential of the product, since several wounds did not respond to treatment until week six. Plans are already in place so that greater insight can be gained into why some wounds respond more rapidly than others following application of the bioactive gel.

A recommendation for use of SBG gel would be to use it on stalled wounds for up to six weeks treatment period, and discontinue its use if no progress is observed. **JWC**

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