Cost-effectiveness of soluble beta-glucan gel in hard-to-heal wounds: an evaluation

Objective: To evaluate the cost-effectiveness of a soluble beta-glucan-containing gel as short-term adjunct therapy in the treatment of hard-to-heal wounds in a UK community health-care setting.
Methods: A comparative clinical evaluation involving consecutive patients treated for up to eight weeks with a beta-glucan-containing gel as adjunct to standard care. This was compared with consecutive patients as retrospective controls, and using the same standard care protocol from a year previously. The inclusion criteria was wounds that were slow-healing or stalled (<40% healing in four weeks).
Results: A total of 300 patients took part. Complete follow-up at 24 weeks was available for 144 patients in the beta-glucan group, and 136 patients in the standard care group. At 24 weeks, the beta-glucan group had a 96% healing rate compared with 75% in the standard care group (p<0.001). The improvement in healing was associated with a reduction in the mean number of weeks of treatment per patient (7.2 and 10.7 for beta-glucan and standard care, respectively), and a reduction in the mean cost of treatment (£576 versus £685 for beta-glucan and standard care, respectively). Treatment costs included nursing time, prescription medications and dressings. In a subset of ulcer wounds (50% of the full sample), at 24 weeks the beta-glucan group had a 92% healing rate compared with 46% in the standard care group (p<0.001). Mean weeks of treatment were 10.4 versus 17.6, leading to a reduction in treatment cost of £388 per patient (£1227 versus £839) over 24 weeks.
Conclusion: The results of this evaluation suggest that short-term use of the beta-glucan gel as an adjunct to standard care on slow-healing wounds can shorten healing times and reduce NHS costs.
Declaration of interest: SH works for a UK primary care health-care provider. SH, FE and JP provide consulting services to pharmaceutical and medical device manufacturers, including but not limited to, Biotec Beta Glucans A/S.

beta-glucan gel • cost-effectiveness • hard-to-heal • wounds • ulcers

The treatment of wounds represents a significant resource cost to the UK's National Health Service (NHS) and chronic, hard-to-heal wounds severely impact on the quality of life (QoL) of patients.[1] A retrospective cohort analysis of data from The Health Improvement Network (THIN) database estimated that the NHS treats more than two million patients with a wound annually, at a cost of £4.5–£5.1 billion at 2013/14 prices.[2] Most wounds are managed in the community by nurses and general practitioners (GPs), and a majority heal without problems. However, in the THIN analysis, 39% of wounds were not healed within the one-year study period. The costs of treating these hard-to-heal wounds ranged from £1719 to £5976 per patient, on average 135% higher than the cost of treating wounds that healed within the study period.[2]

The ability of beta-glucans to stimulate wound healing was first described by Leibovich and Danon in 1980.[3] They observed faster re-epithilialisation and earlier onset of fibroplasia mediated by increased macrophage activity and fewer polymorphonuclear neutrophils in the wound bed during the inflammatory stage of repair.[3] In a recent randomised, placebo-controlled trial, 60 patients with type 1 or type 2 diabetes and lower extremity ulcers received a soluble beta-glucan gel (SBG) or a comparator gel (methycellulose) for up to 12 weeks.[4] Ulcers had to be present for at least four weeks at recruitment. At 12 weeks, the proportion of ulcers healed was 56% in the SBG group compared with 37% in the placebo group (p=0.09). The study also showed a tendency towards shorter healing time. The median time to healing in the SBG group was 36 days, compared with 63 days in the placebo group (p=0.13).[4] In a separate economic analysis developed alongside the clinical trial, a Markov cohort simulation model was developed to extrapolate outcomes over a 12-month period by applying transition probabilities derived from the trial to a series of health states reflecting response to treatment. Expected healing rates at 12 months were 94% (SBG) versus 78% (control), and mean weeks of treatment were 17.63 (SBG) versus 27.35 (control).[5]

The previous randomised control trial (RCT) provided evidence for SBG in treating lower limb ulcers in patients with diabetes.[4] In order to evaluate the effect on a wider range of wound types, a clinical evaluation was carried out in four primary care practices in England. The evaluation recruited patients with a

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Table 1. Average cost per visit by contact type at 2013/14 prices, adapted from Guest et al. 2017[2]

Wound type	Practise nurse visits	Community nurse visit	Specialist nurse	Cost per nurse visit	GP visits	Allied health care visits	Hospital outpatient visits	All contact types (excluding admissions)
Abscess	£13.01	£66.12	£63.01	£27.56	£49.46	£54.53	£121.68	£41.39
Burn	£13.07	£69.44	—	£22.29	£32.38	£72.70	£126.79	£36.82
Diabetic foot ulcer	£12.98	£58.16	£85.51	£37.38	£48.78	£57.07	£130.50	£51.94
Leg ulcer – arterial	£12.85	£63.76	—	£36.24	£40.50	£59.07	£126.12	£38.07
Leg ulcer – mixed arterial and venous	£13.14	£67.58	—	£43.29	£43.94	£47.71	—	£42.34
Leg ulcer – venous	£13.00	£62.51	£60.76	£28.45	£49.25	£64.98	£124.74	£36.35
Pressure ulcer	£13.11	£55.27	£61.51	£47.40	£56.61	£76.94	£126.51	£55.91
Surgical wound	£12.98	£63.87	£58.51	£28.69	£44.10	£46.49	£116.89	£41.21
Trauma	£12.94	£68.74	—	£27.20	£46.20	£69.67	£111.61	£41.59
Unspecified/other	£13.01	£66.33	—	£33.39	£45.73	£93.44	£112.69	£45.96
Average case-weighted cost per clinical contact in current data				£35.08				£46.26

wound of any aetiology and compared outcomes associated with standard care and standard care plus adjunctive beta-glucan-containing gel applied for a maximum of eight weeks, with 24-weeks follow-up.

This paper reports a costing analysis of the clinical evaluation designed to assess the cost-effectiveness of adjunctive beta-glucan gel compared with standard care. Cost-effectiveness was assessed by comparing the incremental cost of the intervention with the difference in outcomes. Clinical outcomes of this evaluation are reported in detail elsewhere.[6] Outcomes were measured by the number of wounds healed and the incremental cost-effectiveness ratio (ICER) was defined as the incremental cost per additional wound healed.

Methods

The clinical evaluation was carried out across four community general practitioner (GP) practices. Patients presented with wounds that were slow-healing or stalled despite standard of care to address the wound and any underlying health conditions (healing <40% after four weeks of standard care).[6] Diagnosis and treatment was coordinated by an experienced advanced nurse practitioner. The evaluation recruited patients with a wide variety of wounds typical of those presenting to community healthcare services: burn, surgical, trauma, donor site wound, pressure ulcer, leg ulcer or foot ulcer. All of the wounds were open, including surgical wounds. There were no exclusions for any comorbidities.

The protocol and the evaluation design were approved by the institutional review board overseeing the participating clinics. All participants were verbally and electronically documented consented patients/carers.

Patients

The beta-glucan intervention group consisted of the first 150 presenting patients meeting the inclusion criteria from 31 July to 31 October 2017. Patients were treated with standard care plus the beta-glucan gel (Woulgan Gel, Biotec Betaglucans, Norway) applied twice-weekly for up to eight weeks or until healed. Data were collected to 24 weeks follow-up.

A retrospective control group was constructed by selecting the first 150 patients meeting the same inclusion criteria outlined above presenting at the same GP practices from 31 July to 31 October 2016. Outcomes for these patients up to 24 weeks from first presentation were extracted retrospectively from patient notes. These patients were treated with the same standard care protocol as the intervention group, but without the beta-glucan gel. Standard care encourages the wound dressing regimen to be adjusted in accordance with the changing needs of the wound. The primary outcome was complete wound healing.

The size of the evaluation sample was determined based on the outcomes identified in a trial by Zykova et al,[4] while allowing for the considerably higher variability in healing outcomes from wounds of any aetiology expected in a real world context. The sample size also allowed for a planned subgroup analysis of ulcer-type wounds (leg ulcers, pressure ulcers and diabetic foot ulcers). The evaluation was not powered to allow comparison for any particular chronic wound type separately.

A total of 264 patients were reviewed for inclusion in the beta-glucan intervention group and 258 patients for the standard care control group to complete the enrolment target of 150 patients in each group. Of the patients who did not meet enrolment criteria, 213 were patients with a wound area reduction of ≥40% in the

Table 2. Patient baseline characteristics

	Beta-glucan gel (n=150)	Standard care (n=150)	p-value
Age, years (mean, minimum–maximum)	57 (7–98)	52 (6–96)	0.05
Wound duration, months (mean, minimum–maximum)	2.5 (1–6)	2.3 (1–6)	0.13
Median	1.8	2.1	
Wound size, cm^2 (mean, minimum–maximum)	31.4 (0.98–895)	23.9 (0.39–236)	0.27
Median	12.6	14.1	
Wound aetiology (n=300)			0.85*
Trauma	37	47	
Pressure ulcer	30	26	
Venous leg ulcer	21	23	
Diabetic foot ulcer	18	21	
Burn	15	11	
Post-surgery	13	10	
Donor site	9	7	
Arterial leg ulcer	7	5	
Total	150	150	
Compression, n, % venous leg ulcer	16 (76%)	18 (78%)	0.87*
Offloading, n, % diabetic foot ulcer	15 (83%)	11 (52%)	0.04*
Notable events to week 12 (to week 24)			
Deaths	4 (4)	11 (11)	
Amputations	0 (0)	1 (1)	
Patient weeks with infection	0 (0)	8 (8)	
Loss of follow-up	2 (2)	0 (2)	
Recurrences	0 (1)	0 (0)	
Primary dressing, top 10 most frequently used			
Mepilex border (Mölnlycke) 7x7.5cm	31	40	
Aquacel foam adhesive (Convatec) 8x8cm	27	30	
Mepilex border (Mölnlycke) 10x12.5cm	22	9	0.02*
Aquacel foam adhesive (Convatec) 10x10cm	19	12	
Inadine (Systagenix) 5x5cm	0	21	<0.01*
Mepilex border sacrum (Mölnlycke) 18x18cm	5	9	
Aquacel foam adhesive (Convatec) 12.5x12.5cm	3	9	
Mepilex border lite (Mölnlycke) 4x5cm	7	2	
Mepilex border (Mölnlycke) 10x20cm	5	4	
Aqualcel ribbon (Convatec) 1x45cm	4	2	
Other dressings	27	12	0.02*
Primary dressings used in first week	150	150	

Statistics are two-tailed t-test unless specified; *Chi-square test

four-week run-in period and nine patients were excluded for other reasons: four due to an inability to consent due to dementia or cognitive deficit, three due to such high exudate levels that they were unsuitable for the beta-glucan gel, one due to an infected wound at baseline (the beta-glucan gel is not indicated for infected or highly exuding wounds), and one patient was excluded because he did not have a wound, but rather a persistent shingles rash. No patient with a wound which had remained unhealed for more than six months was available for inclusion in the evaluation, because these patients were referred to secondary care.

Table 3. Clinical outcomes

	All chronic wounds			Chronic ulcers only		
	Beta-glucan gel	Standard		Beta-glucan gel	Standard	
Healing response rate			% difference			% difference
>40% reduction by week four	80%	62%	**18%‡**	60%	27%	**33%‡**
	(116/145)	(91/146)		(43/72)	(19/71)	
Size reduction versus baseline§						
Week 1	–25%	–19%	**–6%**	–8%	–2%	**–5%**
Week 2	–51%	–38%	**–13%†**	–25%	–10%	**–15%†**
Week 3	–69%	–51%	**–18%‡**	–46%	–16%	**–30%‡**
Week 4	–79%	–59%	**–21%‡**	–61%	–20%	**–41%‡**
Wounds healed, by week, %§						
Week 4	49%	35%	**14%†**	19%	15%	**4%**
Week 8	80%	66%	**14%‡**	61%	30%	**31%‡**
Week 12	81%	66%	**15%‡**	62%	30%	**32%‡**
Week 16	88%	68%	**21%‡**	77%	31%	**46%‡**
Week 20	95%	70%	**25%‡**	90%	34%	**56%‡**
Week 24	96%	75%	**21%‡**	92%	46%	**46%‡**

*Statistically significant p<0.1, †p<0.05, ‡p<0.01; §Percent for wound with follow-up to that week or longer

Table 4. Cost-effectiveness outcomes

	Healed n, %	Treatment weeks/patient	Cost/patient £*	Incremental cost £/patient	ICER† £/additional week healed
Observed outcomes at 24 weeks, all wound types, baseline costs of care estimates					
Beta-glucan gel	138/144 (96%)	7.2	£576	–£109	Dominant†
Standard care	102/136 (75%)	10.7	£685		
Observed outcomes at 24 weeks, ulcer type wounds only, baseline cost of care estimates					
Beta-glucan gel	65/71 (92%)	10.4	£839	–£388	Dominant†
Standard care	28/61 (46%)	17.6	£1,227		

*Including nursing, dressings, prescriptions for pain and antimicrobials, and any wound procedures; ICER—incremental cost-effectiveness ratio; †Dominant means reduced time to complete healing at a lower total cost of care

Data were collected from the regular medical records for each patient. Information was recorded on all relevant wound attributes at each clinical contact and transferred to a case record form with weekly entries for the four-week run-in period and the first eight weeks from baseline, and then at least monthly up to week 24. Healing, adverse events, and any changes in wound care regimen were recorded weekly for both groups.

Treatment costs

A treatment cost profile was constructed for each patient from information on the number and type of clinical contacts, dressings and other materials used for debridement and dressing changes, and prescriptions for analgesics and antibiotics. Any costs incurred before wounds became chronic/before enrolment were not included, such as all costs for offloading device support, for example, boots, offloading mattresses or seat cushions. Unit prices of dressings, prescriptions and other materials were derived from the NHS electronic drug tariff at January 2018 prices.[7] No mark-up to cover pharmacy or dispensing fees was added. Non-sterile water used for rinsing a wound was assumed at zero cost. Where no drug tariff price was available, a locally negotiated price was used. The cost of soluble beta-glucan gel was based on the tariff price at £20 per tube, assuming single use per tube, in line with the manufacturer's instructions for use. Representative NHS

Table 5. Sensitivity analysis for average total cost of care per patient to 24 weeks

	All chronic wounds			Ulcer-type wounds		
	Beta-glucan gel	Standard	Difference	Beta-glucan gel	Standard	Difference
Guest et al.[2] cost per average community wound specific contact cost (weighted mean £46.26)	£689	£889	–£200	£973	£1,546	–£573
Guest et al cost per average community wound specific contact cost; nursing only (weighted mean £35.08)	£576	£685	–£109	£839	£1,227	–£388
National Schedule of Reference Costs 2016–2017 per face-to-face district nursing contact; lower quartile (£29.39)	£518	£583	–£65	£707	£983	–£275

costs for procedures (such as debridement) were taken from the NHS National Schedule of Reference Costs.[8]

The costs of clinical contacts were based on details of the resource use associated with wound care in the NHS in 2012/13 derived from an analysis of The Health Improvement Network (THIN) database.[2] The THIN database contains information on patient contacts with the NHS, prescriptions and diagnostic tests recorded by 562 GP practices in the UK. No patients in the current evaluation required specialist referral or a hospital outpatient visit, and clinical contacts were valued at a weighted average of practice nurse, community nurse and specialist nurse time (£35.08) (Table 1).

Results

A total of 300 patients were recruited into the evaluation. There were no significant differences between the evaluation groups at baseline, with the exception of patient age (Table 2). Patients in the beta-glucan group were older (mean 57 years versus 52 years; p=0.05). The two groups were similar in terms of wound duration, wound area and wound type. In both evaluation groups, approximately 50% of wounds (n=76 and n=75 in the beta-glucan and standard care groups, respectively) were ulcers (pressure ulcers, leg ulcers or foot ulcers). A similar proportion of patients with a venous leg ulcer were receiving compression (76% (beta-glucan) and 78% (standard care)). The proportion of patients with offloading devices for a foot ulcer was significantly lower in the standard care group at 52% versus 83% for the beta-glucan group (p=0.04) (Table 2).

In the beta-glucan group, six patients were lost to follow-up (four deaths and two for other reasons) and 14 in the standard care group (11 deaths, one amputation and two for other reasons). Hence, complete 24-week follow-up data were available for 280 patients: 144 and 136 in the beta-glucan and standard care groups, respectively. After adjusting for losses to follow-up, there were more ulcer-type wounds in the beta-glucan group than in the standard care group (71 versus 61, respectively).

At 24 weeks follow-up, 138/144 (96%) of wounds had healed completely in the beta-glucan group compared with 102/136 (75%) in the standard care group (p<0.001) (Table 3). A proportional hazards regression for time to healing was estimated, controlling for baseline wound area, prior duration of the wound, patient age, healing trajectory (wound condition static or improving) and wound type (ulcer or other). This showed a statistically significant effect of the beta-glucan (p<0.001), with more than a threefold greater weekly chance of healing (β=3.15; 95% Confidence Interval (CI) 2.37–4.20) compared with standard care, negative effects on healing associated with longer prior wound duration (p=0.008) and larger baseline wound area (p<0.001). Ulcer-type wounds had a significantly lower chance of healing (β=0.490: p<0.001; 95% CI 0.41–0.59).

The higher rate of wound healing in the beta-glucan group implies that patients treated with the intervention enjoyed, on average, more weeks with a healed wound and fewer weeks of treatment. After 24 weeks, patients in the beta-glucan group had a mean of 16.8 weeks healed compared with 13.3 weeks in the standard care group. Total treatment costs were £576 and £685 per patient in the beta-glucan and standard care groups, respectively (Table 4). Most of the lower cost was due to fewer clinical contacts. Because improved outcomes are achieved at a lower cost, the intervention is judged to be a dominant option. The ICER in this case is negative.

Ulcer-type wounds (pressure ulcers and lower limb ulcers) were slower to heal in both treatment groups, but particularly in the standard care cohort, and were more costly to treat. After 24 weeks, 65/71 (92%) ulcers had healed completely in the beta-glucan group, compared with 28/61 (46%) in the control. Patients in the beta-glucan group with ulcer wounds had a mean of 13.6 weeks healed compared with 6.4 weeks in the standard care group. Total treatment costs were £839 and £1227 per patient in the beta-glucan and standard care groups, respectively (Table 4).

Sensitivity analysis

The average cost of a clinical contact in the base case analysis (£35.08) includes only nurse time, because patients in the evaluation were managed in the community by nursing staff, unless referral was required to secondary care. In routine NHS practice, some patients would also require consultations with a GP or other health professionals, and/or hospital outpatient

attendance. Including these costs, but excluding the costs of hospital admissions, the average cost of treating a wound as estimated by Guest et al.[2] is £46.26 per contact (Table 1). Applying this cost to the number of clinical contacts observed in the study gives an estimated total cost for all wounds of £689 and £889 for patients in the beta-glucan and standard care groups, respectively. For ulcer wounds only, total costs are £973 and £1546 for patients in the beta-glucan and standard care groups, respectively. Results are also robust to lower assumptions about the cost of nursing time (National Schedule of Reference Costs 2016/17).[8] Assuming all care contacts were delivered at the mean lowest quartile of face-to-face district nursing contact costs, at £29.39 per nursing contact (at the same overall quality of care), the beta-glucan intervention remains dominant. With the reduced average cost per contact, the overall cost of care saving is a mean £65 per patient (£275 mean saving per patient for ulcer-type wounds) (Table 5).

Discussion

The clinical evaluation recruited patients with a wide range of different wound types, including acute wounds and chronic ulcers. Significantly, more wounds were healed at 12 and 24 weeks in the beta-glucan group and resource savings were observed in the form of a reduction in nurse time, dressings and other materials, analgesics and antibiotics. A shorter time to complete wound closure also implies that patients can expect to enjoy more weeks free of a wound, with an associated improvement in QoL, as demonstrated in the literature on the QoL impact of living with a chronic wound.[9]

The evaluation also highlighted the significantly slower healing times associated with ulcer-type wounds compared with other wound types, and this effect was particularly notable in the standard care group. In this group, the proportion of ulcers healed at 24 weeks was <50%. In the beta-glucan group; the healing rate was almost the same in the ulcer cohort as in the full wound sample (92% ulcers versus 96% all wounds). In the ulcer cohort, the mean weeks of treatment was >7 weeks less in the beta-glucan group than in the standard care group.

The results of the current evaluation are consistent with the results of the previous RCT of soluble beta-glucan versus a standard care comparator.[4] The RCT recruited patients with a foot ulcer with follow-up to 12 weeks.[4] That study showed complete healing in 56% and 37% (p=0.09) of wounds in the intervention and control groups respectively. Although it is difficult to make a direct comparison between the two studies, in the present evaluation, with up to eight weeks beta-glucan treatment, the healing rates of ulcer-type wounds at 12 weeks follow-up were 62% versus 30% (p<0.01) in the beta-glucan and standard care groups, respectively (Table 3), with an estimated cost saving of £62 per patient (savings to 24 weeks shown in Table 4).

Limitations

This evaluation was not an RCT, but a review of normal clinical standards using products available on prescription within the NHS. The lack of randomisation may be a limitation. On the other hand, the two groups were well matched at baseline and patients were treated according to the same standard care protocol and by the same clinical team. A caveat here is that the proportion of patients with offloading devices for a foot ulcer was significantly lower in the standard care group at 52% versus 83% (p=0.04), with four more patients receiving offloading in the beta-glucan group versus the standard care group, and this may have affected the observed healing rates of this subgroup of ulcers. The present evaluation has the advantage that it is a reflection of actual clinical practice. Nonetheless, the evaluation was carried out in a relatively small number of GP practices in England. In other geographic areas, clinical practice and outcomes may vary.

Conclusion

The results of this study suggest that short-term use of soluble beta-glucan gel as an adjunct to standard care on slow-healing or stalled wounds has the potential to kick-start the healing process, and to reduce healing times and resource costs to the NHS. **JWC**

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Reflective questions

- How does soluble beta glucan gel promote faster healing in hard-to-heal wounds?
- What are the advantages of using soluble beta glucan gel in the treatment of hard-to-heal wounds, compared with standard care alone?
- How can use of soluble beta glucan in the treatment of hard-to-heal wounds promote cost savings?