Woundox® Irrigation Solution: a case series study

KEY WORDS
- Antimicrobial cleanser
- Bioburden
- Wound healing

Biofilm-based solutions are an important part of the management of chronic wounds and preventing infection, combining wound cleansing with debridement and application of topical antimicrobials (Wolcott and Fletcher, 2014). Water and saline are not antimicrobial and do not actively promote wound healing, while highly reactive solutions and commercially available products do little to control wound bacteria and may interfere with natural healing (Fernandez et al, 2010). This study evaluated the clinical efficacy, cost-effectiveness, and tolerability of Woundox, a powerful antimicrobial cleanser, in patients with complex venous leg ulcers and diabetic foot ulcers. Improvement and progression towards healing were noted in 4 weeks in both aetiologies.

NICKY IVINS
Clinical Research Director, Welsh Wound Innovation Centre, Cardiff; Clinical Trials Manager, Cardiff University

DR SALMA KHURAIBET
Diabetic Foot and Wound Care Specialist Surgeon, Mubarak Al-Kabeer Hospital, Kuwait

Diagnosis and management of infection are particularly challenging in chronic compared with acute wounds, as the former are less likely to display classic signs of infection (Wounds UK, 2014), and more likely to be colonised by microorganisms that form biofilms. Biofilms are complex structures that protect bacteria and block the penetration of antibodies and other immune responses (Wolcott and Fletcher, 2014). The presence of biofilm can impair epithelialisation and granulation tissue formation and reduce the effectiveness of systemic antibiotics (Hurlow, 2015). A study using electron microscopy found that biofilm was present in 60% of chronic wounds (James et al, 2008). Where increased bioburden is suspected, wound cleansing/irrigation should be combined with debridement and application of topical antimicrobial agents (e.g. wound cleansers and dressings), to break up the biofilm and prevent its reformation (Wolcott and Fletcher, 2014).

Wound cleansing

Wound cleansing is *'the use of fluids to remove loosely adherent debris and necrotic tissue from the wound surface'* (Fernandez et al, 2010) and to *'remove surface contaminants, bacteria and remnants of previous dressings from the wound surface and its surrounding skin'* (Rodeheaver and Ratliff, 2007). The broad categories of solutions that can be used are: saline and water; highly reactive solutions; and minimally or non-cytotoxic antimicrobial-containing solutions.

Although water and saline have been standards of non-cytotoxicity, neither have antimicrobial properties. They have not been found to be harmful, but neither do they actively promote wound healing (Cutting, 2010). The Cochrane review of water and saline as irrigation agents found no evidence that their use to cleanse wounds increases infection (Fernandez et al, 2010); however, the review found no strong evidence that cleansing with water and saline is better than not cleansing, noting that water can become colonised with microbes, which may cause infection. It also found that highly reactive solutions (e.g. peroxide and iodine) and commercially available products (e.g. foams, soaps, wipes and solutions containing surfactants) have little effect in terms of controlling wound bacteria and may, in fact, interfere with natural healing mechanisms (Fernandez et al, 2010).

Woundox Irrigation Solution

Woundox Irrigation Solution (Woundox) is an antimicrobial solution indicated for use in acute and chronic wounds (Martindale Pharma, UK); the active substance of this solution is hypochlorous acid (HOCl), a naturally occurring substance produced by leukocytes during phagocytosis to kill pathogens and fight infection (Wang et al, 2007). Antimicrobial solutions have been

found to be effective while having a minimally toxic effect when used in low concentrations, and can reduce bioburden, while disrupting and preventing biofilm formation (Wolcott and Fletcher, 2014). Woundox has low toxicity and *in vitro* testing has demonstrated it has a rapid onset of action and broad-spectrum antimicrobial action against the bacterial species commonly found in chronic wounds. When Woundox was used to treat 24-hour and 72-hour pre-formed *S. aureus* for 30 seconds, 5 minutes and 10 minutes, no viable material was recovered; in addition, no viable material was recovered against 24-hour and 72-hour pre-formed *P. auruginosa* at 5 minutes and 10 minutes. When 72-hour pre-formed *S. aureus* (2 minutes), *P. auruginosa* and *C. albicans* (2 minutes) biofilms were treated with Woundox, no viable organisms were recovered post-treatment. Throughout this study, Woundox demonstrated equivalence or better responses compared with other test products (Martindale, data on file).

Here, we report findings of a case series investigating the cost- and clinical effectiveness and tolerability of Woundox as a part of a standard treatment regimen for patients with venous leg ulcers (VLUs) and diabetic foot ulcers (DFUs). The data are presented for both aetiologies at Week 4 interim analysis, with supporting case studies. This work follows on from the Woundox In-Market Evaluations (data on file), which were conducted in 170 patients in both acute and primary care settings, and demonstrated encouraging progression through to healing and improvements in various quality of life parameters.

METHOD

Aim

This study evaluated Woundox as part of a standard treatment regimen in patients with chronic VLUs and DFUs, for whom tap water, normal saline or another cleansing product had previously been used as a wound cleanser for at least 1 month.

Objectives

Primary

The primary objective of this study was to investigate the effect of Woundox used in conjunction with standard care on wound size in patients with VLUs or DFUs.

Secondary

This study had a number of secondary objectives:

- To assess changes in wound healing parameters such as wound bed appearance, exudate levels, presence of odour and condition of surrounding skin
- To monitor for increased and decreased levels of bioburden and pain
- To evaluate safety and tolerability
- To gain patient and clinician perspective on ease of use
- To determine cost-effectiveness.

Eligibility

Inclusion criteria

- Adult patients (aged ≥18 years) who were able to give informed consent for study participation and wound photography
- Patient had a VLU located below the knee joint or a DFU located below the malleolus that had been present for ≥6 weeks and required routine wound cleansing
- Infected or non-infected wounds
- Ulcer surface area of ≥2cm^2.

Exclusion criteria

- Patient unable to consent
- Known sensitivity to HOCI.

METHODOLOGY

In this non-interventional, multicentre case series study, patients with VLUs or DFUs were recruited to centres in Cardiff, UK, and Kuwait, respectively. Patients were treated with Woundox for up to 12 weeks; patients could be discontinued at any time if goals of treatment had been achieved, and were to be followed up 1 week after discontinuation and at 12 weeks. A protocol was put in place in order to standardise data collection across the two study centres.

The treatment procedure included cleansing the wound bed and surrounding skin with Woundox, which should remain in contact with the skin for 3–5 minutes; application of an appropriate primary dressing (as per local protocol); use of a secondary dressing to secure the primary dressing; and use of appropriate conjunctive therapy, such as compression bandaging for VLUs and offloading for DFUs.

Declaration of interest
This paper was funded by Martindale Pharma

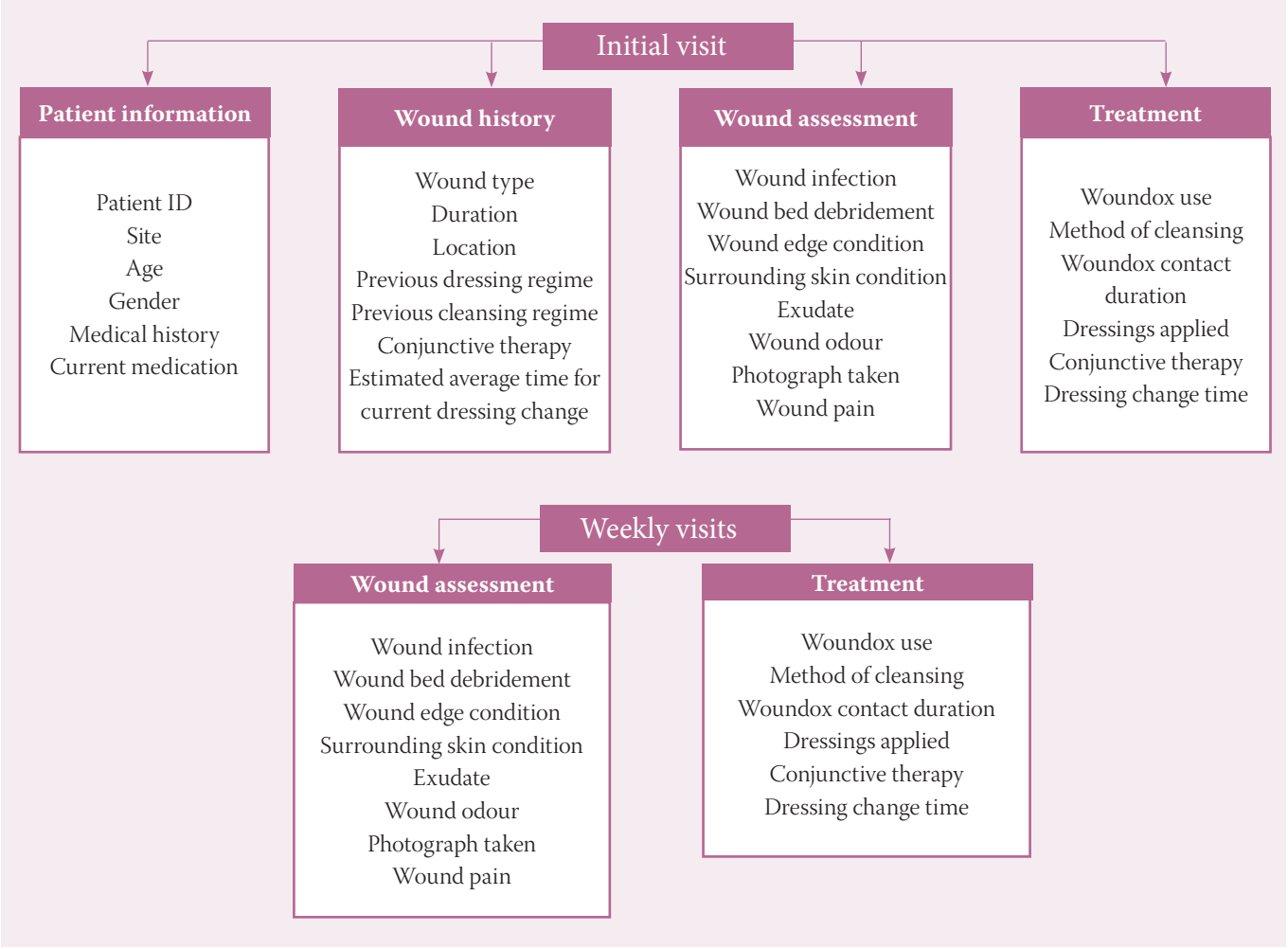


Figure 1: Wound assessment and treatment information taken at initial visit and subsequent visits

At the initial study visit, patients were asked to sign a written consent form for study participation and for anonymised photographs to be taken. At this visit, full patient information, wound assessment and treatment information were recorded (*Figure 1*). Thereafter, patients underwent weekly reviews consisting of wound and treatment assessments, with results recorded in data assessment forms.

This case series was considered to be a service evaluation/post-marketing surveillance, so no formal ethical approval was required. Photographs taken in the wound assessments were entered into the Elixr Wound Assessment programme to provide objective measurements and tissue analysis regarding progression to healing (see *Case Studies*). The accuracy of these measurements was reviewed by an independent assessor.

RESULTS

Patient population

A total of 30 participants were recruited to this case series study: 11 patients with VLUs and 19 patients with DFUs. The study population consisted of 21 male patients (70%), the mean age was 61.5 years (range: 18–89 years; age data were not available for two patients), and the mean ulcer duration was 22.5 months (range: 1–208 months; ulcer duration data were not available for one patient). Details of wound treatment history are presented in Table 1; measurements taken at baseline for patients with VLUs and DFUs are provided in *Tables 2* (page 100) and *3* (page 101), respectively.

A total of 11 patients with VLUs provided data at baseline. Most patients had used tap water as their cleansing method (n=7) and silver was the most common dressing type (n=7). Patients had frequent dressing changes and cleansing, at

Table 1.Wound treatment history		
Type of dressing, *n* (%)	Silver	23 (77)
	Hydrofiber	3 (10)
	Iodine	3 (10)
	Non-adherent	1 (3)
Dressing change frequency, *n* (%)	Daily	4 (13)
	Alternate days	17 (57)
	Twice weekly	2 (7)
	Three times weekly	7 (23)
Estimated weekly cost of dressings, mean (range)		£12.96 (£0.66 – 33.74)
Cleansing method, *n* (%)	Soak	16 (53)
	Irrigation	14 (47)
Cleanser type, *n* (%)	Saline	11 (37)
	Tap water	7 (23)
	Betadine®	5 (17)
	Microsafe®	3 (10)
	Permitabs®	1 (3.5)
	Prontosan®	1 (3.5)
	Not determined	2 (7)
Cleansing frequency, *n* (%)	Daily	7 (23)
	Alternate days	15 (50)
	Twice weekly	4 (13)
	Three times weekly	4 (23)
Estimated weekly cost of cleansing, mean (range)		£5.06 (£0.00 – 13.65)
Estimated weekly cost of dressing + cleansing, mean (range)		£17.68 (£0.99 – 46.48)

a minimum of twice a week (*n*=5; *n*=3) and a maximum frequency of daily (*n*=1; *n*=1). In total, 19 patients with DFUs provided data at baseline. Nine patients had used saline as their previous cleansing solution, three had used Microsafe, and five had used another cleansing method (two patients did not provide data). Silver was the most common dressing type (*n*=16), with three patients using iodine. Most patients underwent dressing changes and cleansing on alternate days (*n*=14; *n*=12).

Week 4 interim results

NB: These interim results are derived from 10 of 11 patients with VLUs and 16 of 19 patients with DFUs (who attended follow-up at Week 4).

Patients with VLUs

Wound size: Mean wound length had decreased from 6.1cm (baseline) to 5.8cm, and mean wound width from 4.2cm to 3.2cm. No decrease was seen in mean wound area or mean wound depth.

Wound bed condition: Decreased levels of slough were observed. One patient reported slough (20% of the wound) compared with two patients at baseline (45% of the wound [mean]). Mean percentage of granulation tissue in the wound had increased from 44.3% at baseline (seven patients) to 72% (10 patients); the number of patients reporting epithelium had risen from three at baseline (11.6% of the wound [mean]) to six (15.8% [mean]); and the number of patients

Table 2: Baseline measurements for patients with VLUs (*n*=11)

Mean costs	Dressings	£11.54
	Cleanser	£1.19
	Combined treatment cost	£12.73
Wound size	Area (mean)	19.5 cm^2 (range: 2.05–52.81)
	Length (mean)	6.1 cm
	Width (mean)	4.2 cm
	Depth (mean)	0.1 cm
Debridement required (no of patients)		0
Malodour present (no of patients)		3
Wound bed appearance	Epithelium (mean % of wound reported, no of patients)	11.6%, 3
	Granulation (mean % of wound reported, no of patients)	44.3%, 7
	Slough (mean % of wound reported, no of patients)	45%, 2
	Fibrin (mean % of wound reported, no of patients)	21.6%, 3
	Necrotic eschar (mean % of wound, no of patients)	0%, 0
Surrounding skin	Erythema (no of patients)	11
	Maceration (no of patients)	0
	Oedema (no of patients)	9
	Dry/flaky skin (no of patients)	11
	Eczema (no of patients)	9
	Atrophe blanche (no of patients)	0
Exudate levels	Mild (no of patients)	1
	Moderate (no of patients)	8
	High (no of patients)	2
	No exudate (no of patients)	0
Wound edge	Epithelialising (no of patients, % of total population)	3, 27.3%
	Static (no of patients, % of total population)	8, 72.8%
	Callus (no of patients, % of total population)	0, 0%
Infection status	Localised (no of patients)	5
	Spreading (no of patients)	3
	Receiving antibiotics (no of patients)	3
Mean pain scores	Pre-dressing change	4.3
	During dressing change	1.5

reporting fibrin had increased from three (21.6% of the wound [mean]) to seven (20.7% [mean]). One patient required debridement.

Exudate levels: Six patients reported mild exudate (60%) compared with one at baseline (9.1%). Only three patients (30%) and one patient (10%) had moderate and heavy levels of exudate, respectively, compared with eight (72.7%) and two patients (18.2%) at baseline.

Malodour: No patients reported malodour, compared with three at baseline (27.3%).

Surrounding skin condition: A decrease was seen in erythema, from 11 patients at baseline (100%) to eight at Week 4 (80%). An increase in the percentage of patients reporting oedema was seen (81.8% to 90%), while a small decrease was seen

Table 3: Baseline measurements for patients with DFUs (*n*=19)		
Mean costs	Dressings	£13.78
	Cleanser	£7.56 (ND in 2 patients)
	Combined treatment cost	£20.54
Wound size	Area (mean)	15.02 cm^2 (range: 1.97–71.56)
	Length (mean)	5.3 cm (ND in 4 patients)
	Width (mean)	3.4 cm
	Depth (mean)	0.4 cm (ND in 4 patients)
Debridement required (no of patients)		6 (ND in 2 patients)
Malodour present (no of patients)		5 (ND in 2 patients)
Wound bed appearance	Epithelium (mean % of wound reported, no of patients)	1.6%, 5 (ND in 1 patient)
	Granulation (mean % of wound reported, no of patients)	87.8%, 18 (ND in 1 patient)
	Slough (mean % of wound reported, no of patients)	5.4%, 18 (ND in 1 patient)
	Fibrin (mean % of wound reported, no of patients)	2.8%, 17 (ND in 1 patient)
	Necrotic eschar (mean % of wound reported, no of patients)	0.2%, 17 (ND in 1 patient)
Surrounding skin	Erythema (no of patients)	0
	Maceration (no of patients)	6
	Oedema (no of patients)	0
	Dry/flaky skin (no of patients)	0
	Eczema (no of patients)	0
	Atrophe blanche (no of patients)	0
Exudate levels	Mild (no of patients)	17
	Moderate (no of patients)	2
	High (no of patients)	0
	No exudate (no of patients)	0
Wound edge	Epithelialising (no of patients, % of total population)	13, 68.4%
	Static (no of patients, % of total population)	5, 26.3%
	Callus (no of patients, % of total population)	1, 5.3%
Infection status	Localised (no of patients)	5
	Spreading (no of patients)	3
	Receiving antibiotics (no of patients)	5
Mean pain scores	Pre-dressing change	1
	During dressing change	0.4

ND: No data

in patients reporting eczema (81.8% to 80%). All patients had dry or flaky skin (10 patients).

Wound edge: Seven wounds were epithelialising and three were static, representing an increase in epithelialising wounds (27.3% to 70%) and a decrease in static wounds (72.8% to 30%).

Infection status: No patients reported infection, compared with eight patients at baseline (72.7%).

Pain levels: A small decrease in mean pain levels pre-dressing change was seen compared with baseline, from 4.3 to 4.1. However, a very small increase in pain levels was seen post-dressing change, from 1.5 to 2.

Safety and toxicity: Three patients reported

stinging during soaking. There were three discontinuations of Woundox at Week 4. However, three patients experienced no stinging or burning with Woundox.

Patients with DFUs

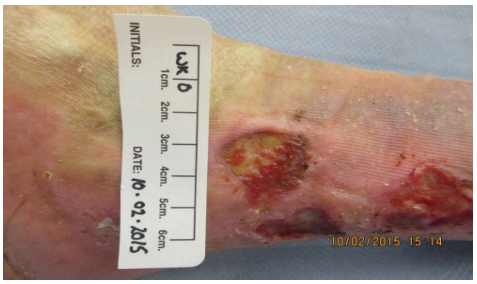
Wound size: A decrease in mean wound area was seen from 15.0 cm^2 at baseline to 14.3 cm^2. Decreases were also seen in mean wound length (5.3 cm to 4.8 cm), width (3.4 cm to 2.8 cm), and depth (0.4 cm to 0.2 cm).

Wound bed condition: Decreased levels of both slough and necrotic eschar were observed. Two patients at Week 4 reported slough (10% of the wound [mean]) compared with six at baseline (16.3% [mean]). Mean percentage of granulation tissue in

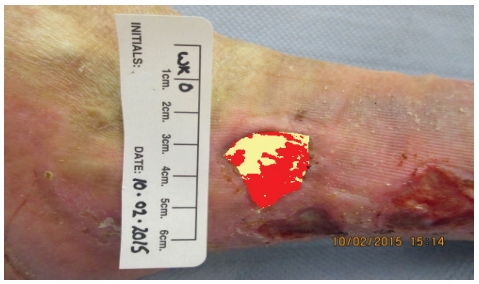
CASE STUDY 1

This was a 89-year-old male with a VLU of 22 months' duration. Despite discontinuing treatment at Week 4, the wound had reduced substantially in size by Week 12.

Week 0: Normal

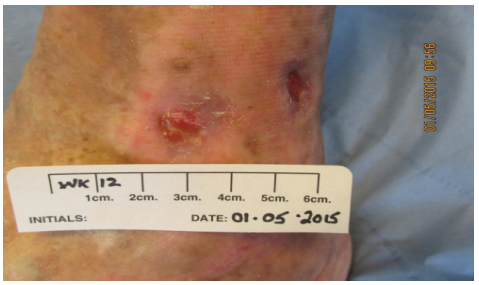


Week 0: Tissue viability

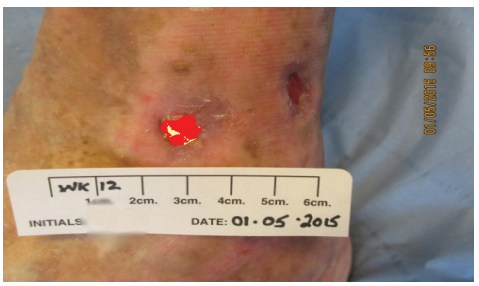


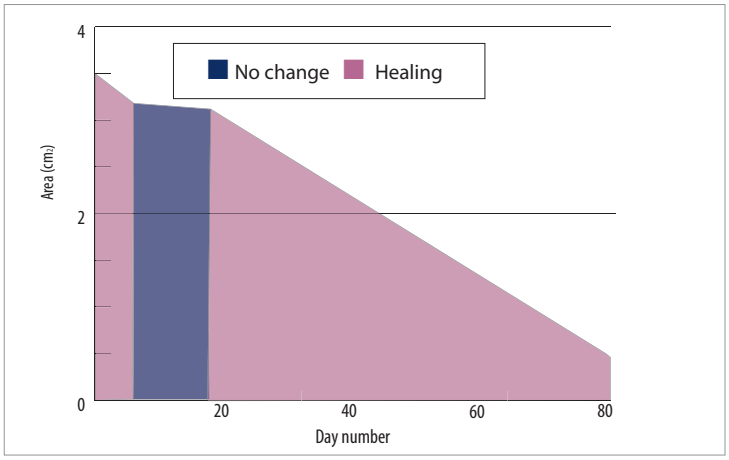
Elixr photographs

Week 12: Normal

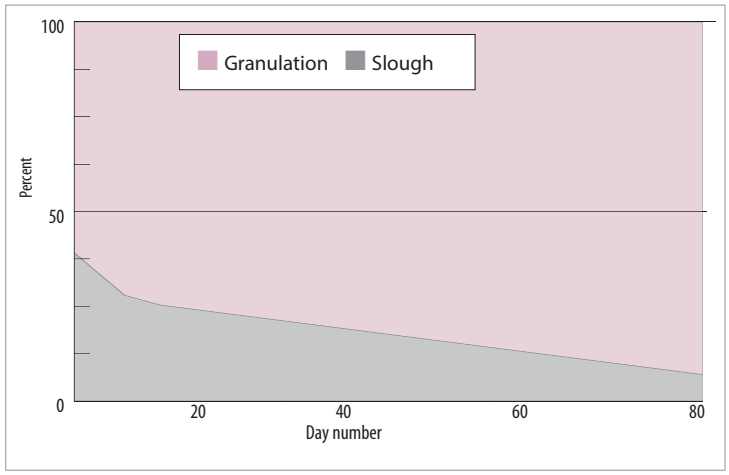


Week 12: Tissue viability





Wound measurements.



Tissue analysis.

the wound had increased from 87.8% at baseline (18 patients) to 96% (16 patients). One patient required debridement, compared with six at baseline.

Exudate levels: Reductions were seen in the percentage of patients with mild and moderate exudate levels, from 89.5% (17 patients) at baseline to 81.2% (13 patients), and 10.5% (two patients) to 0% (0 patients), respectively. Furthermore, three patients reported no exudate (18.8%), an increase from no patients at baseline.

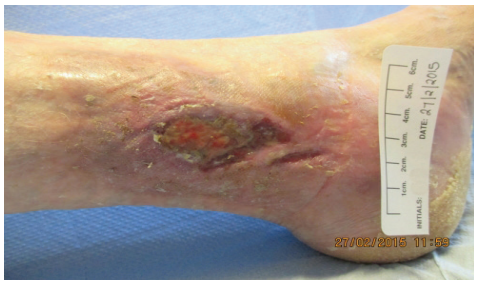
Malodour: No patients reported malodour, compared with five at baseline (26.3%).

Wound edge: At Week 4, 14 wounds were epithelialising, one was static, and one had callus, representing an increase in epithelialising wounds (68.4% versus 87.5% at baseline) and a decrease in static wounds (26.3% versus 6.25%). One patient reported callus at baseline and at Week 4.

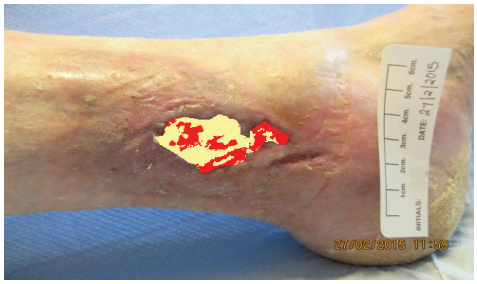
CASE STUDY 2

This was a 47-year-old female with a VLU of 12 months' duration. The wound had healed by Week 6.

Week 0: Normal

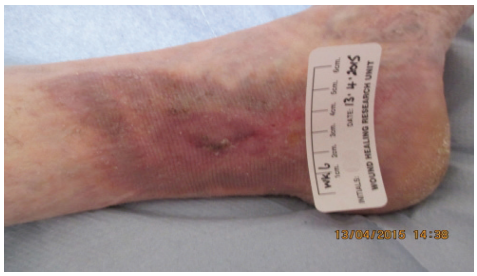


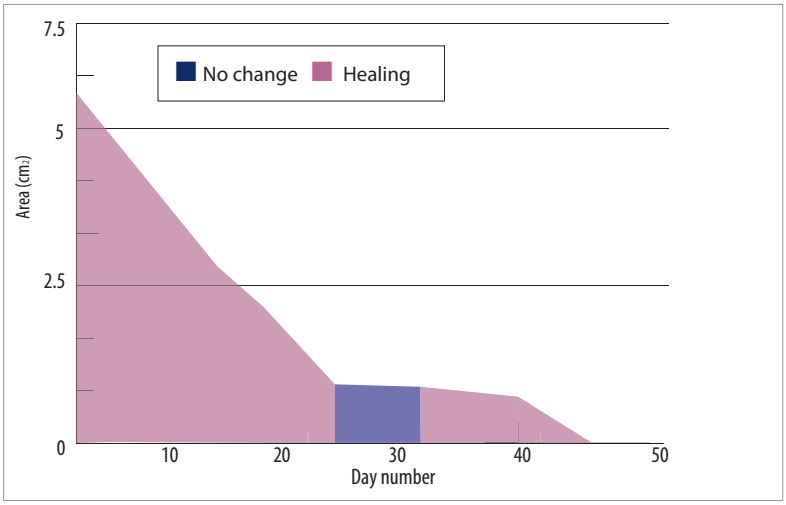
Week 0: Tissue viability



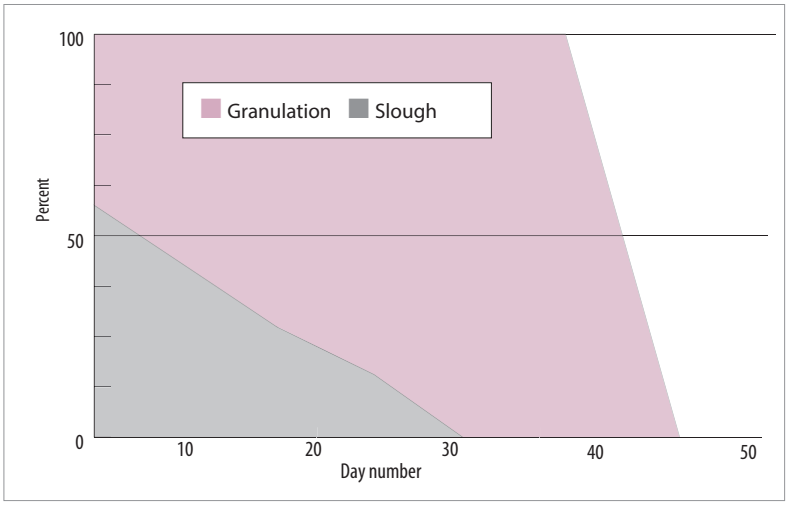
Elixr photographs

Week 6: Healed





Wound measurements.



Tissue analysis.

Surrounding skin condition: At Week 4, no patients reported maceration of the surrounding skin compared with six at baseline (31.6%).

Infection status: No patients reported infection, compared with eight at baseline (42.1%).

Pain levels: Patients reported no pain pre-dressing or during the dressing change, a reduction from mean scores of 4.3 at the pre-dressing change stage and 1.5 during the dressing change at baseline.

Safety and toxicity: There were no reports of adverse events. One patient reported that they experienced no pain.

DISCUSSION

The results of this real-world case series study reflect current practice and patterns of treatment, building on previous *in vitro* testing that has demonstrated Woundox's low toxicity and rapid, broad-spectrum antimicrobial action against the bacterial species found in chronic wounds (Martindale, data on file).

With some patients lost to follow-up, an interim analysis was conducted at Week 4, where data were most comprehensive. These data show a number of positive trends aligned with the treatment goals of a topical antimicrobial cleansing agent, for both VLUs and DFUs: to reduce pain, exudate and odour, reduce necrotic tissue or slough in the wound bed, reduce wound size, and encourage progression to healing (Edwards-Jones et al, 2015).

For patients with VLUs, improvements in numerous wound healing parameters were seen, including appearance of the wound bed; decreased exudate and malodour; reduced erythema in the surrounding skin; and reduced infection levels. An increase was seen in the percentage of epithelialising wounds, with a decrease in static wounds. Pre-dressing change pain also decreased. A number of patients provided feedback stating the product was easy to use when performing their own dressing changes and other patients reported no pain and no stinging on use. Patients with DFUs demonstrated decreased levels of slough and necrotic escher; increased granulation tissue; reduced exudate and malodour; reduction in number of infected wounds to zero; decreased pain levels pre- and during dressing change; and a substantial decrease in the number of static wounds. Decreases in wound size were seen in both VLUs (mean length and width) and DFUs (all parameters) at Week 4. By Week 12, five patients had reported healed wounds, with the first patient healing at Week 6.

Since the primary aims of Woundox are to remove loosely adherent tissue and any surface contaminents or bacteria, Woundox is indicated for a short period of use only. Once the wound is epitheliasing, it can be discontinued. It is important to note that the few discontinuations (i.e. due to burning or stinging) in this study took place after Woundox had cleansed the wound and effectively removed deeper debris, close to or after the Week 4 interim analysis. Importantly, limiting the use of Woundox to a short period will lead to cost savings, since less solution will be required.

This study was conducted in patients whose wounds were complex and chronic, with some patients' wounds having been present for many months prior to initiation of Woundox. Indeed, chronic wounds are a substantial economic burden on the healthcare system; according to Posnett and Franks (2008), treatment of VLUs costs at least £168–198m per year, while DFUs are estimated to cost around £300m a year. In this study, the prior average duration of wounds had been 22.5 months, whereas improvements in a number of clinical parameters were seen with Woundox within just 4 weeks, including encouraging progression towards healing. The reduction in time to healing that can be seen with Woundox is likely to have a positive impact on the cost of chronic wounds to the healthcare system.

CONCLUSION

Woundox — a powerful antimicrobial cleansing agent — encourages rapid progression to healing in wounds that have been present for often very long periods of time. Woundox is an important alternative to standard wound cleansing agents (including saline and water; highly reactive solutions; and minimally or non-cytotoxic antimicrobial-containing solutions) where a biofilm-based approach to wound care is important — that is, in complex wounds where a solution is required to effectively cleanse and debride, ensuring broad-spectrum antimicrobial action with rapid onset and low toxicity. WUK

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