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Debriding effect of amino acid-buffered hypochlorite on hard-to-heal wounds covered by devitalised tissue: pilot study

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Objective: Wounds such as lower extremity ulcers are serious, costly and frequently hard to heal. Guidelines conclude that new dressings and treatments generally fail to show superiority compared with standard of care. Several mechanisms are probably responsible for impaired healing of hard-to-heal wounds, including inflammation and infection. Amino acid-buffered hypochlorite has presumed antiseptic and antibacterial properties and has been shown to be useful in the treatment of diabetic foot ulcers (DFUs). We evaluated the debriding effect of amino acid-buffered hypochlorite (ChloraSolv) on full skin hard-to-heal lower extremity ulcers covered with devitalised tissue (≥50%), with six applications over 5 weeks and follow-up at 12 weeks.

Method: This was an open-label, single-arm, multicentre, pre-market pilot investigation. We recruited subjects with a lower extremity ulcer, covered with devitalised tissue (≥50%), who were candidates for cleansing and debridement/desloughing. There was a weekly application of the investigational device for five weeks. Follow-up for wound status evaluation was performed at 12 weeks from baseline.

Results: We evaluated 57 subjects (33 males, 24 females, median age 73 years, range 51–90 years) (intention-to-treat). Of these, 61.4% had a leg ulcer and 38.6% a foot ulcer. The median wound size at baseline was 7.7cm^2 (range 2.1–52cm^2) with devitalised tissue coverage of 76.5%. After 5 weeks, a decrease of 72.7% in devitalised tissue was seen, and 71.4% of the subjects showed a decrease in devitalised tissue of ≥50% (evaluated independently using PictZar). At 12 weeks' follow-up the decrease in devitalised tissue was 84.4%. Wound-related pain was reported by ten subjects, resulting in 17 adverse events (AEs). Among these, 12 AEs from eight subjects were recorded as possibly or probably related to the investigational device and one AE was reported to have a causal relationship with the investigational device.

Conclusion: This clinical study suggests that amino acid-buffered hypochlorite can be effective and well tolerated in the treatment of hard-to-heal lower extremity ulcers to dissolve and remove devitalised tissue.

Declaration of interest: The sponsor of this clinical investigation is RLS Global AB, Sweden. The authors have no other conflicts of interest to declare.

buffered hypochlorite • chronic lower leg ulcer • clinical study • devitalised tissue • debridement • diabetes • hard-to-heal • necrotic tissue • ulcer • wound

Hard-to-heal wounds, such as lower extremity ulcers, are a major healthcare problem globally. They frequently occur in individuals with vascular disease or diabetes mellitus and are attributed to chronic venous insufficiency, arterial angiopathy, mechanical trauma or neuropathy.[1] A hard-to-heal wound is characterised by prolonged or excessive inflammation, persistent infections, formation of drug-resistant microbial biofilm and the presence of senescent cell populations that are unresponsive to wound healing signals, irrespective of the wound aetiology.[2–4] Hard-to-heal wounds are complex because, historically, chronicity has been related to the duration of the wound. However, reports have indicated that chronicity can occur even in ulcers with shorter duration, and rather reflect the condition of the wound.[4]

The underlying mechanisms cause a continuous growth of necrotic tissue, and regular debridement is necessary to reduce the necrotic burden and achieve healthy granulation tissue.[5] Debridement is a natural process that occurs spontaneously in wounds in healthy individuals, and is a prerequisite for healing, but assisted debridement speeds up the wound healing process, and is consequently essential in wound management. Debridement also reduces wound contamination and therefore assists in reducing tissue destruction.

Assisted debridement may be achieved using different techniques. Autolytic, enzymatic, mechanical, surgical, sharp, biologic and chemical debridement have been described.[6] The relative efficacy of these methods is not well established. The choice of debridement technique depends on the clinical status of the wound, general health of the patient and the skill and qualification of

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the healthcare personnel.[7–9] Consequently, there is a need for efficient debridement techniques that can minimise tissue loss to avoid deep tissue exposure such as bone, joint and tendons, particularly in wounds with decreased perfusion or a limited extent of soft tissue (skin, subcutaneous tissue).[4,6,10]

Amino acid-buffered hypochlorite (ChloraSolv® (RLS Global AB, Sweden)) is a wound bed preparation gel developed for cleansing and debridement/desloughing of wounds. In a recent study, treatment with amino acid-buffered hypochlorite suggested a more rapid transformation from black or yellow necrosis/devitalised tissue in the ulcers to purulence and red granulation tissue than standard of care.[11] There is also a lack of studies performed with debridement capacity as a primary endpoint and its role in wound healing. The primary objective of the current study was therefore to evaluate the debriding effect of amino acid-buffered hypochlorite on hard-to-heal leg ulcers, with a full skin ulcer at least 50% covered by devitalised tissue, during six weekly treatments. The secondary objectives were to evaluate change in devitalised tissue, change in wound area, pain during treatment, condition of the wound, need for sharp debridement, and an overall evaluation of the product and safety variables.

Method

Study design

This was an open-label, single-arm, multicentre, pre-market pilot investigation in 59 patients with hard-to-heal wounds who were admitted to and treated by primary care units and hospital-based wound care centres.

Ethical approval

The study ChloraSolv01 was performed in compliance with ISO 14155:2011, Medical Device Directive (MDD) 93/42/EEC, the Declaration of Helsinki and applicable regulatory requirements. The Regional Ethics Review Board in Lund, Sweden (Dnr 2018/452) and the Swedish Medical Products Agency (Dnr 5.1-2018-74618) approved this study. The study was registered in clinicaltrials.gov (Identifier: NCT03808181).

Before enrolment in the study, all patients were given written and verbal information about the study, and signed two consent forms, one for participation and one for publishing photographs of their wounds.

Investigational device

A new technology based on amino acid-buffered hypochlorite has been developed for cleansing and debridement of hard-to-heal wounds and thus to promote natural healing.[11] The investigational device, ChloraSolv, provides a moist alkaline pH environment that helps loosen up and dissolve necrotic tissue while delivering sodium hypochlorite, which gives the device antimicrobial activity, as shown in Table 1, and the ability to further lyse necrotic tissue and thereby facilitate cleansing and debridement.[12–14] The device comprises a gel that consists of two solutions provided

Table 1. ChloraSolv has been tested in vitro to support its ancillary antimicrobial properties according to Ph Eur. 5.1.11: Determination of bacterial, fungicidal or yeasticidal activity of antiseptic medicinal products (PharmaControl, Uppsala, Sweden)

Antimicrobial effect of ChloraSolv:
>5log$_{10}$ reduction of *Staphylococcus aureus*
≥5log$_{10}$ reduction of *Pseudomonas aeruginosa*
>5log$_{10}$ reduction of *Escherichia coli*
>5log$_{10}$ reduction of *Enterococcus hirae*
≥5log$_{10}$ reduction of *Candida albicans*
=4log$_{10}$ reduction of *Aspergillus brasiliensis*

- Able and willing to follow the protocol requirements.

A subject was excluded from the participation in the investigation if he/she met any of the criteria below:

- Clinical signs of systemic infection with or without osteomyelitis
- Wound located where treatment is not possible
- Subjects not suitable for the investigation according to the investigator's judgment
- Subjects included in other ongoing clinical investigation which could interfere with this investigation, as judged by the investigator
- Known allergy/hypersensitivity to any of the components of the investigational device
- Pregnant or breast-feeding women
- Other significant medical condition that the investigator determines could interfere with compliance or study assessments
- Subjects with wounds of less than one month duration
- Wound area greater than 60cm^2.

Treatment protocol

Site personnel training was performed prior to subject enrolment, at a study site initiation visit, to ensure that the investigational device was used in accordance with the instructions for use, that protocol requirements were followed and that complications, adverse events and adverse device effects were correctly reported and investigated. Information regarding medical and surgical history was gathered and wound characteristics were described and analysed.

The mixed gel was applied to the wound with the mixer application tip. The gel was left on the wound for 2–5 minutes, after which a blunt instrument was used to help in the mechanical removal of debris and devitalised tissue, such as slough, loose fibrin, black eschar and dead tissue. The investigators were instructed to debride what could be readily removed after the treatment with the investigational device. The wound was then rinsed with water or isotonic solution and wiped dry. A second application of the investigational device was performed to further reduce the amount of devitalised tissue. Finally, the wound was dried and protected with a secondary dressing appropriate for the status of the

wound.

The investigational device was applied weekly. The first treatment was applied at baseline which means that the subjects were treated on six occasions during the five weeks. Follow-up for wound status evaluation was performed after 12 weeks from baseline, i.e. seven weeks after the last treatment.

During the study the patients maintained their initial standard basic treatment and any change during the study was recorded. The standard treatment given was according to international guidelines and recommendations with regard to lower extremity ulcers: diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs).[7,15] The ulcer was dressed according to the discretion of the investigator.

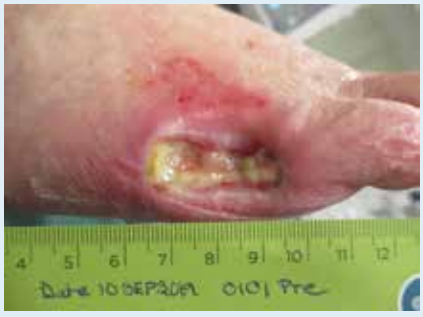
Data collection

Wound size and proportion of devitalised tissue at inclusion were estimated by the investigator and documented in the electronic case report form (eCRF) and further evaluated, calculated and confirmed by the PictZar Digital Planimetry Application 7.1 (Advanced Planimetric Services, US).[16] PictZar is a planimetry software program that is used to make measurements on digital photographs. PictZar may be used to measure wounds and other lesions that are present on the skin

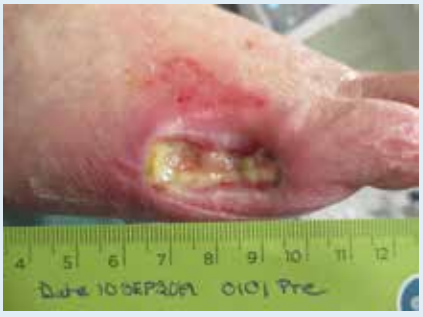
Figure 1. PictZar planimetry system provides a calibrated digital method for assessment of ulcers

ChloraSolv01
PictZar® Wound Measurement Summary Report

Patient Name: ChloraSolv01 0101 Chart ID: ChloraSolv01-0101 Wound No: ChloraSolv01-0101-1 Location:



Baseline Image
Initial measurement date: 10-Sep-2019



Current Image
Date of this assessment: 10 September 2019

PictZar measured Image
Measurement no: 1 of 1

Core measurements Visit number: Visit 1 pre

Initial area (CmSq)	Current area (CmSq)	Percent area change	Length	Width	Depth	Volume
2.231	2.231	.00%	2.81cm	.92cm	0cm	0cc

Detail measurement analysis

Colour	Baseline area	Percent	Tissue type	Current area	Percent	% Change	Non-viable	Depth cm	Colour	Volume	Linear measurements
Yellow	.088	3.9	Granulation-viable	.088	3.9	0	Area cm sq. 2.142	0	Yellow	0	
Blue	2.142	96.0	Slough/fibrinous slough	2.142	96.0	0	Percent 96%	0	Blue	0	Length: 2.81cm
Green	0.00	0	Eschar	0.00	0	0	% Change 0.0	0	Green	0	Width: . 92cm
Red	0.00	0	N/A	0.00	0	0		0	Red	0	Circumference: 7.21cm
Total	**2.231 cm sq**			**2.231 cm sq**			**Aver.**	**0**	**Total volume**	**0**	

Comments:

surface. This non-invasive tool provides accurate surface measurements which may be archived via digital image or printed on paper using regular printers. Digital images were captured at each visit. Thereafter the images were sent electronically to Advanced Planimetric Services LLC, US, which provides blinded, independent wound measurement analysis by experienced wound care specialists, as illustrated in Fig 1. The PictZar Planimetry system provides a method of calibrating digital images without having to know the distance between the camera lens and the subject. A ruler with subject number, date of visit, visit number and information on whether the photograph was taken pre- or post-debridement was placed next to the wound for identification. The ruler acted as the control for proper measurements.

A clinical infection was categorised by the investigator as ongoing if three or more of the five cardinal signs of inflammation (redness, heat, oedema, pain or odour) were present. If two or fewer of the five symptoms were present, no clinical infection was deemed to be ongoing. This is not a specific criterion for quantifying infection but a way to identify clinical infection.

Sample size justification

In order to show that percent complete debridement is significantly greater than 50%, if the actual percentage is 70%, and with a power of 80%, then 52 evaluable subjects are needed. This is identical to the sample size required to demonstrate that the lower two-sided 95% confidence limit for percent complete debridement is significantly greater than 50%, with a probability of 80%, given the actual percentage is 70%. In order to compensate for a 10% drop-out rate, 58 subjects needed to be included in the investigation.

Data analysis

At a group meeting, all decisions on the evaluability of the data from each individual subject for the statistical analysis and final definition of intention-to-treat (ITT), per protocol (PP) and safety populations were made and documented before locking the database. A blinded observer performed the measurements (using the validated tool PictZar, which is compliant with US Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) part 11) of the primary and secondary endpoints based on digital photographs uploaded in the eCRF. Photographs were identified with subject number, visit number, date and pre/post debridement only. When all data from the primary and secondary endpoints had been entered, discrepancies solved and all reconciliation with the serious adverse event (SAE) database was complete, the database was locked, and the data analysed.

Statistical analyses

The main analyses are assessments of changes from baseline to 5 weeks' treatment and description of status after 6 weekly treatments. We also analysed the change

Table 2. Baseline characteristics, medical and surgical history (intention-to-treat (ITT) and per protocol (PP) populations)

Variable	ITT (n=57)	PP (n=52)
Age	71.3 (9.9) 73 (51; 90)	72.2 (9.5) 73.5 (51; 90)
Gender, n (%)		
Male	33 (57.9%)	30 (57.7%)
Female	24 (42.1%)	22 (42.3%)
Smoking	10 (17.5%)	10 (19.2%)
Candidate for cleansing, debridement/ desloughing	57 (100.0%)	52 (100.0%)
Wound size (cm^2)	11.1 (10.5) 7.7 (2.1; 52)	11.1 (10.4) 7.8 (2.1; 52)
Validated wound area at baseline (PictZar) (cm^2)	7.58 (7.18) 5.4 (0.66; 35.18)	7.98 (7.37) 5.49 (0.66; 35.18)
Initial area ≥2cm^2	48/57 (84.2%)	45/52 (86.5%)
Devitalised tissue in percent at baseline (PictZar)	66.1 (28.6) 76.5 (0; 100)	69.2 (25.6) 78 (10.6; 100)
≥50% devitalised tissue at baseline	37/57 (64.9%)	36/52 (69.2%)
Initial area ≥2cm^2 and ≥50% devitalised tissue at baseline	31/57 (54.4%)	30/52 (57.7%)
Location		
Foot	22/57 (38.6%)	19/52 (36.5%)
Leg	35/57 (61.4%)	33/52 (63.5%)

For categorical variables n/N (%) is presented.
For continuous variables mean (standard deviation) / median (minimum; maximum) / n is presented.

Figure 2. Flowchart: disposition of subjects (safety, intention-to-treat (ITT) and per protocol (PP) populations

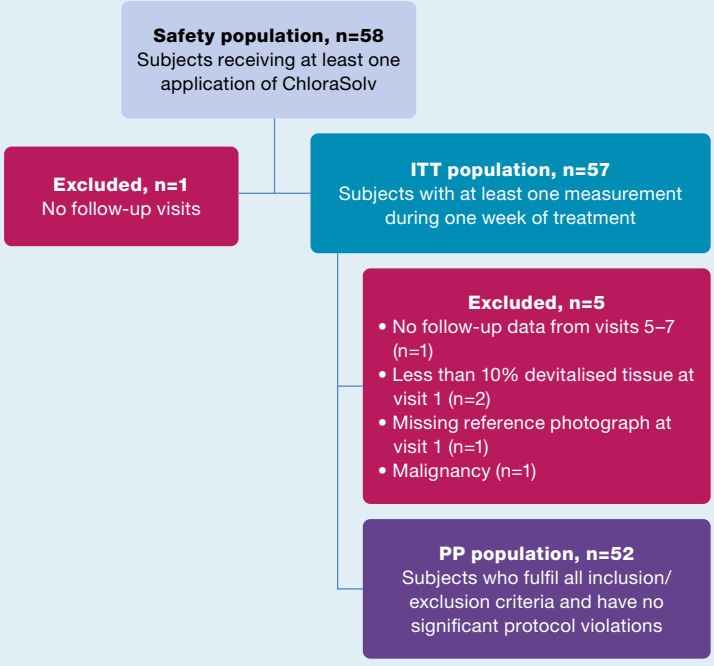


Table 3. Devitalised tissue, wound area and pain at debridement (intention-to-treat (ITT) population)

Variable	Visit 1 (post) (n=57)	Visit 2 (day 7) (n=57)	Visit 3 (day 14) (n=57)	Visit 4 (day 21) (n=57)	Visit 5 (day 28) (n=56)	Visit 6 (day 35) (n=56)	Visit 7 (day 84) (n=53)
Devitalised tissue in absolute figures* (PictZar)	4.46 (5.71) 2.59 (0.00; 34.25) n=57	3.63 (4.58) 2.24 (0.00; 23.79) n=56**	3.35 (4.58) 1.32 (0.00; 21.73) n=57	2.82 (4.01) 1.08 (0.00; 18.15) n=57	2.85 (4.78) 0.66 (0.00; 22.85) n=56	2.40 (3.85) 0.68 (0.00; 18.38) n=56	2.35 (5.26) 0.35 (0.00; 30.38) n=51***
Relative change of devitalised tissue from baseline to post values in percent	-18.4 (39.2) -8.7 (-100.0; 104.3) n=57 p≤0.0001	-31.5 (44.7) -28.9 (-100.0; 163.0) n=56** p≤0.0001	-40.0 (46.7) -46.0 (-100.0; 112.1) n=57 p≤0.0001	-49.8 (46.2) -58.8 (-100.0; 113.9) n=57 p≤0.0001	-54.3 (50.3) -68.0 (-100.0; 126.2) n=56 p≤0.0001	-53.2 (68.2) -72.7 (-100.0; 305.2) n=56 p≤0.0001	-54.4 (77.2) -84.4 (-100.0; 337.5) n=51*** p≤0.0001
Validated wound area in absolute figures* (PictZar)	7.54 (7.14) 5.39 (0.75; 35.62) n=57	7.18 (6.83) 4.67 (0.57; 31.01) n=56**	6.72 (6.14) 4.50 (0.54; 27.30) n=57	6.42 (6.19) 4.47 (0.45; 29.56) n=57	6.10 (6.32) 4.05 (0.26; 31.67) n=56	5.68 (6.53) 3.25 (0.08; 34.44) n=56	4.09 (6.79) 1.27 (0.00; 31.58) n=51***
Validated wound area reduction from baseline to post values in percent	0.286 (3.938) -0.140 (-6.260; 16.620) n=57 p=0.42	-5.86 (21.29) -4.29 (-50.79; 107.13) n=56** p=0.0003	-11.1 (26.3) -13.2 (-70.7; 103.0) n=57 p≤0.0001	-16.6 (31.3) -18.0 (-78.9; 102.5) n=57 p≤0.0001	-22.6 (35.1) -21.6 (-87.8; 124.3) n=56 p≤0.0001	-29.4 (39.1) -30.9 (-96.2; 106.8) n=56 p≤0.0001	-48.3 (72.5) -68.2 (-100.0; 319.1) n=51*** p≤0.0001
Pain at debridement (visual analogue scale (VAS))	33.9 (33.1) 30.0 (0.0; 100.0) n=57	28.5 (28.4) 18.0 (0.0; 90.0) n=57	25.7 (29.8) 10.0 (0.0; 90.0) n=57	25.4 (31.4) 10.0 (0.0; 100.0) n=57	22.4 (27.1) 10.0 (0.0; 100.0) n=55**	21.5 (29.1) 5.0 (0.0; 100.0) n=51****	

For categorical variables n (%) is presented.
For continuous variables mean (standard deviation) / median (minimum; maximum) / n is presented.

For comparison over time, the Wilcoxon signed rank test was used for continuous variables.
* Imputation of the visit 1 post-value was used where baseline value was missing and imputation of the pre-value was used where post-value was missing (i.e. at visit 6).
** Missing value for one subject.
*** Missing value for two subjects.
**** Missing value for five subjects.

from baseline and status after 12 weeks. The main analyses were performed according to the ITT principle but we also analysed the PP population. The ITT population includes all subjects with at least one measurement during one week of treatment. Any included subject who deviated from the investigational plan or by error did not meet inclusion/exclusion criteria, was included in the ITT population. The PP population included all subjects who fulfilled all inclusion/exclusion criteria and had no significant protocol violations. Subjects where the approximated area with devitalised tissue at baseline proved to be under 10%, confirmed by PictZar, were not included in the PP population, but in the ITT population.

The distribution of continuous variables is given as mean, standard deviation (SD), median, minimum and maximum and with number and percentages for categorical variables. A binomial test was used to investigate whether percent complete debridement was more than 50% after six weekly treatments. All statistical analysis regarding change over time were paired. Changes over time were analysed with the Wilcoxon signed rank test for continuous variables and with the Sign test for ordered categorical and dichotomous variables. All statistical tests were two-sided and conducted at the 5% significance level. All analyses have been performed by using SAS v9.4 or a later version (SAS Institute Inc., US).

Results

Clinical characteristics

The main results are presented for the ITT as well as the PP populations. Out of 59 recruited patients, 57 remained for ITT analyses (Fig 2 and Table 2) and 53 individuals completed the whole study. One subject was incorrectly enrolled and one subject prematurely discontinued the study after the baseline visit. The compliance in the investigation was high, with only five out of 58 subjects withdrawing from the study prematurely. The remaining 53 subjects (91.4%) completed the investigation and attended all seven visits. Three subjects terminated the investigation prematurely between visits 6 and 7, one subject terminated after visit 4 and one subject terminated after the first visit (Fig 2).

Subject demographics and baseline characteristics are shown in Table 2. The median age in the ITT population (33 males, 24 females) was 73 years. Ten individuals (17.5%) were smokers. Substantial comorbidities were seen, with corresponding medication in the study population. The most frequent comorbidities reported were previously known diabetes (49.1%), venous insufficiency (45.6%), cardiovascular disease (57.9%) and/or other relevant diseases (43.9%) (renal and urinary disorders, musculoskeletal and connective tissue disorders, blood and lymphatic systemic disorders and others).

Patients included in the study had a lower extremity ulcer of various site and origin. This was a leg ulcer in 35 subjects (61.4%) and a foot ulcer in the remaining 22 subjects (38.6%). Four categories of wounds were registered: 22 VLUs, 21 in the ITT population; 12 DFUs; 11 mixed ulcers (combination of venous and arterial origin); and 13 classified as miscellaneous (neurofibromatosis (n=1), abscess (n=1), herpes zoster (n=1), trauma (n=5), unknown (n=3), pressure ulcer (n=1), unhealed partial skin graft (n=1)). Of 33 subjects with a leg ulcer, 25 (75.8%) had a wound registered as a VLU or mixed ulcer. Among all four groups (DFUs, VLUs, mixed and miscellaneous), 21 subjects (36.8%) had a previously diagnosed peripheral vascular disease.

Wound size

The wound size at baseline estimated by the site staff had a mean value of 11.1cm^2 and a median value of 7.7cm^2 compared to 7.58cm^2 and 5.4cm^2, respectively, when validated by PictZar as shown in Table 2. The estimated smallest wound was 2.1cm^2 when validated by the investigators at inclusion.

Devitalised tissue

The median value of devitalised tissue according to PictZar was 76.5%, with the largest value 100% (Table 2). According to PictZar, 37 subjects (64.9%) fulfilled the criterion of having a wound covered with ≥50% devitalised tissue at baseline. In total, 31 subjects (54.4%) fulfilled both criteria of wound size ≥2cm^2 and wound covered with devitalised tissue ≥50%. However, inclusion of subjects was based on visual judgement by the site personnel, and subjects not fulfilling the above criteria were still seen as eligible subjects. Two subjects with less than 10% devitalised tissue at baseline were excluded from the PP population in accordance with the clinical investigation plan. A subgroup with the 31 subjects fulfilling both the criteria of wound size ≥2cm^2 and wound covered with devitalised tissue ≥50% was analysed separately.

Reduction of devitalised tissue

Complete debridement at visit 6 was achieved in 23.2% of the wounds in the ITT population (95% confidence interval (CI): 13.0–36.4%). The figures in the PP population did not differ significantly, with 21.2% completely debrided wounds after six weekly treatments. The median value showed a decrease of 72.7% devitalised tissue, with a decrease from visit 1 to visit 6. The changes in devitalised tissue from visit 1 (baseline) to visits 2, 3, 4, 5 and 6 were all statistically significant (p<0.0001). At the follow-up visit after 12 weeks from baseline, there was a significant decrease (p<0.0001) from baseline in devitalised tissue (median 84.4%; range –100–337.5%) (Table 3). The decrease in devitalised tissue was greater during the weekly treatment period but also continued during the follow-up period. These results were similar in the PP population.

Figure 3. Box plot of wound area reduction by change of devitalised tissue: visit 6 (intention to treat population)
CI—confidence interval

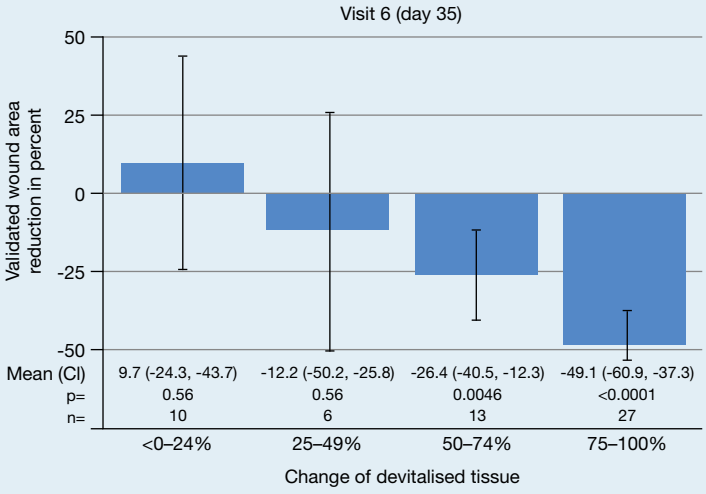
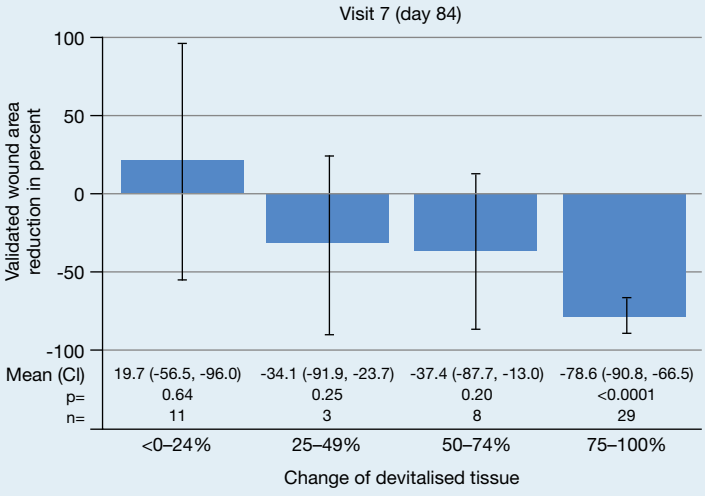


Figure 4. Box plot of wound area reduction by change of devitalised tissue: visit 7 (intention to treat population)
CI—confidence interval



At visit 6, 27 subjects (48.2%) showed a decrease in devitalised tissue with 75–100% having a wound area reduction of around 50% (Fig 3). A greater than 50% decrease in devitalised tissue was seen in 40 subjects (71.4%) (Fig 3). At the follow-up visit after 12 weeks, 29 subjects (56.9%) had a decrease in devitalised tissue, with 75–100% with a wound area reduction of >75% (Fig 4). At 12 weeks' follow-up, correlation between reduction in devitalised tissue and reduction in wound area was R^2=0.72 (data not shown).

Antimicrobial treatment and signs of wound-related infection

At inclusion, eight subjects had a clinical infection in the study wound. At visit 6 the corresponding number

was three. Five subjects (8.8%) were treated with antibiotics at inclusion in the investigation and 21 subjects (36.8%) were treated with antibiotics at some time during the investigation. Of the 21 subjects treated with antibiotics during the investigation, six received antibiotics due to infection in another wound (not the study wound), erysipelas or *Clostridium difficile* infection. The remaining 15 subjects received antibiotics due to infection in the study wound or in another wound (not always stated in the eCRF).

Adverse events

In total, 58 adverse events (AEs) from 31 individuals (53.4%) were reported during the investigation. Of these, 51 were reported as non-serious and seven events from seven subjects reported as serious; however, none of these seven events were reported as related to the investigational device. Forty AEs reported from 23 subjects were reported as not related to the investigational device, five AEs as unlikely related, 12 AEs from eight subjects as possibly or probably related to the investigational device and one AE was reported to have a causal relationship with the investigational device.

Two AEs led to discontinuation from the investigation. One was reported as a foot infection leading to amputation of lower extremity. The other was reported as wound-related pain and due to the progression of intercurrent disease (malignancy) the patient died between visits 6 and 7.

Pain and debridement

Wound-related pain was reported by ten subjects, resulting in 17 AEs; and one subject reported skin-related pain. Some subjects received analgesics locally and/or orally to decrease pain or as pain prevention. However, results indicate that the group receiving analgesics and/or local anaesthetics at some point during the investigation experienced more pain at debridement compared to the whole ITT population. Six subjects reported wound infection resulting in eight AEs; one subject reported foot infection resulting in one AE; and one subject reported skin infection resulting in one AE. Moreover, three subjects reported erysipelas, but it is not clear whether the infection was related to the target wound treated in the investigation or related to another wound.

At baseline, 40 subjects (70.2%) had previously used sharp debridement. During the study seven patients received sharp debridement by the investigating physician as an adjunct to the gel to soften and dissolve/remove necrotic tissue. Wound-related pain during debridement was measured with a traditional Visual Analogue Scale (VAS) ruler (0–100mm) and decreased over time as presented in Table 3. The median value at baseline was 30.0mm compared to 5.0mm at visit 6 ($p \leq 0.02$). Eight subjects (14%) received an oral analgesic agent prior to inclusion and 13 subjects (22.8%) received analgesic during the investigation due to pain or as premedication prior to the debridement. Sixteen subjects (28.1%) received a local anaesthetic during the investigation. Six out of the 16 subjects received both analgesics and anaesthetics during the investigation.

Overall estimation by patient and investigating staff

Of the subjects in the study, 47 out of 53 (88.7%) rated the investigational device as good or very good with regard to pain. The overall experience was rated good or very good by 100% of the responders. The investigational device was rated good or very good by 90% of the subjects with regard to pain during debridement. Compared to previous debridement treatments, it was considered equal (40%) or better (58%). One subject rated the device as worse compared to previous debridement treatments.

At the 12-week follow-up visit, the investigator or nurse was asked to fill in an overall evaluation in the eCRF regarding the use of the investigational device. Of 53 investigators or nurses, 52 (98%) rated the investigational device as easy or very easy to handle and 94% rated the investigational device as easy or very easy to apply. Compared to experience from previous debridement treatments, 70% of the investigators and nurses considered that the investigational device made the debridement easier and 26% considered it to be the same.

Discussion

This open, single-armed pilot study on hard-to-heal lower extremity wounds with devitalised tissue suggests that an amino acid-buffered hypochlorite-based treatment can be efficacious as a debridement agent. There was a 73% reduction of devitalised tissue over 5 weeks, and 71% of the subjects had a decrease in devitalised tissue of ≥50% in 5 weeks, indicating a clinically relevant effect in patients with hard-to-heal lower extremity ulcers with various aetiologies (e.g., DFU, VLU mixed ulcers).[4]

Amino acid-buffered hypochlorite has multiple effects that could be beneficial in wound care. In odontology, amino acid-buffered hypochlorite facilitates effective chemo-mechanical cleansing and debridement while preserving healthy tissue.[17–20] During the treatment, the alkaline environment created when the device is applied in the wound will start to diminish and the environment is neutralised as the debridement progresses and the necrotic tissue, slough, fibrin, eschar and debris are softened. The debridement process is fast. Based on published data, as well as the experience from a clinical investigation, the treatment time with ChloraSolv has been 2×2 minutes for DFUs.[11] With the inclusion of leg ulcers in this clinical study, with potentially larger wound area, the treatment time was prolonged to 2–5 minutes, which was repeated once.

In a previous clinical study during the development phase of the amino acid-buffered hypochlorite gel in patients with DFU, it was observed that the device made it easier and faster to remove devitalised tissue.[11] This

explorative open randomised controlled trial showed that the amino acid-buffered hypochlorite gel could safely be used in the treatment of infected foot ulcers in diabetes. It was suggested that the gel could prove to be a valuable addition in the treatment arsenal, providing non-surgical debridement. The ulcers also appeared more easily debrided without damaging the underlying tissue. However, quantitative data on removal of devitalised tissue was not obtained. Based on the observations from that study, the present study was designed with regard to size, power estimation and study duration to explore the potential value to remove devitalised tissue in hard-to-heal leg ulcers.

In our study, we saw a good correlation (R^2=0.72) between the reduction of devitalised tissue and the reduction in the wound area, providing indirect support for the notion that debridement and cleansing of an ulcer is a prerequisite for the wounds to heal.[6,21] Comparisons between studies are difficult because there is no standard to evaluate the clinical value of a debridement agent in the treatment of hard-to-heal ulcers. Most studies performed have been focused on intact skin as an endpoint for the evaluation, even on those strategies where debridement capacity has been the aim.[4,6] As a consequence, there is a very limited number of studies performed with debridement capacity as a primary endpoint and therefore, comparisons between studies, particularly with regard to debridement, are difficult due to differences in design, setting, patient selection, definitions, endpoints, follow-up time and other confounding factors.[4,6,10]

The present study illustrates the challenges in wound studies to evaluate changes in wound conditions, particularly resolutions of devitalised tissue, and the lack of standardised methods to evaluate the effectiveness of debridement of ulcers in need of cleansing and debridement/desloughing.[4,6] The diversity of wound dressings and their applications, and the absence of standard tests to measure the efficacy of their debridement capacity, as products and not simply the active components, contribute to the challenges. There is an urgent need for test protocols and reporting to ensure claim validity and optimise evaluation of strategies regarding debridement, particularly when a comparative study is needed and blinding of treatments is difficult.

Substantial challenges had to be met in the present study. The sample size, the power estimation of the study, as well as the duration of evaluation of debridement, were based on the previous clinical study.[11] The definition of a clinically relevant reduction of area of devitalised tissue was based on previous recommendations.[4,6] A reduction of 50% or more of devitalised tissue is considered clinically relevant when a change in a wound characteristic is measured due to debridement. However, it can also be difficult to estimate necrotic tissue surface coverage in wounds of various aetiologies, partly covered by devitalised tissue. To facilitate these estimations, a digital image analysis technology (PictZar) was chosen for a systematic and independent evaluation of size of ulcer as well as extent of devitalised tissue.

The compliance in the investigation was high, with only five out of 58 subjects withdrawing from the investigation prematurely. In total, 58 AEs from 31 individuals were reported during the investigation. That has to been seen from the perspective of the comorbidity in the study population with extensive necrotic ulcer in the lower extremity. The majority of the subjects had diabetes with related complications, particularly in the lower leg/feet and/or a cardiovascular disease and peripheral vascular disease. Seven SAEs were reported during the investigation, but none of these were considered to be related to the investigational device. These findings further serve to recognise comorbidity as a confounder in studies in patients with lower extremity ulcers.

Sharp debridement had previously been used by 40 out of 57 subjects for their ulcers. During the study seven patients received sharp debridement by the investigating physician as an adjunct to the gel to soften and dissolve/remove necrotic tissue. This finding indicates a decreased need for sharp debridement.[4]

Ten subjects reported wound-related pain throughout the study period. The investigational device was rated by 90% of the individuals in the study as good or very good, with regard to pain. Of the subjects who did experience pain during debridement, a connection to the investigational device could not be verified. All subjects evaluated the treatment as a good or very good overall experience. No patient withdrew or stopped treatment due to pain related to the investigational device. Pain related to debridement decreased during the observation period as well as the need for sharp debridement. The methodological issues regarding pain evaluation are well recognised.[22]

Study limitations

This study is limited by its open design, exploratory nature, small size and lack of comparative data. The concordance in the investigation was high and the number of drop-outs low. The investigation included 57 subjects in the ITT population, which limited the possibility for subgroup analyses. As there were no identical devices to the investigational device an open study design to evaluate its performance was used. Measures to avoid bias, such as randomisation/blinding/masking were not possible. To compensate, an independent assessor (PictZar) was used for evaluation of the wound images. The investigational device has a

Reflective questions

- Is removal of devitalised tissue an essential prerequisite to achieve wound area reduction?
- Is there a standardised method to evaluate the effectiveness of debridement of ulcers?
- How can an amino acid-buffered hypochlorite gel be effective in the treatment of hard-to-heal lower extremity ulcers in need of debridement?

chlorine odour which made blinding unfeasible. In the previous clinical investigation performed on the investigational device, the primary objective was wound area reduction and data on incidence of debridement were not collected.[11] Wound healing as an endpoint in terms of intact skin requires significantly longer observation time compared to reduction of devitalised tissue over time. Comparative studies available in this area are very few as most studies are based on wound healing and not change in wound condition as the endpoint. This limited the calculation of power and duration of the investigation. The known duration of the wounds included in the study was more than one month. The actual duration of the wounds was not recorded as it was not possible to obtain accurate information, with the exception that the wounds had a known duration of at least one month. The present study reflected clinical practice in a variety of different clinical settings (primary care units to specialist wound care centres). To improve wound care research, more control of underlying disease progress and other parameters and biomarkers would be essential.

Conclusion

This clinical study suggests that amino acid-buffered hypochlorite gel can be effective and well tolerated in the treatment of hard-to-heal lower extremity ulcers to dissolve and remove devitalised tissue. The treatment was perceived as positive and easy to handle both from the perspective of care recipients and caregivers. A treatment regimen based on use of amino acid-buffered hypochlorite gel could represent a valuable addition to wound care. **JWC**

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