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Healing of Neuropathic Diabetic Foot Ulcers of PEDIS Grade 1-2 at Home Care with Topical Antiseptics: An Observational Follow-Up Investigation

A Korzon-Burakowska[1], M Przezdziak[1], E Orłowska-Kunikowska[1], A Sipponen[2*] and J J Jokinen[3]

[1]*Department of Hypertension and Diabetology, Diabetic Foot Centre, Gdańsk Medical University, Poland*

[2]*Department of Orthopedics and Traumatology, Päijät-Häme Central Hospital, Finland*

[3]*Department of Thoracic and Vascular Surgery, Päijät-Häme Central Hospital, Lahti, Finland*

[*]**Corresponding author:** A Sipponen, Department of Orthopedics and Traumatology, Päijät-Häme Central Hospital, Finland, Tel: +358405813161; E-mail: arno.sipponen@phhyky.fi

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Abstract

Objective: This observational and clinical prospective follow-up study examined the healing of ordinary diabetic foot ulcers at home-care setting with two commercially available topical antiseptics, one in formulation as a solution and the other one as a salve.

Method: The study population consisted of 35 consecutive adult outpatients with diabetic foot ulcers that were classified as grades 1-2 by using the PEDIS (Perfusion, Extent, Depth, Infection and Sensation) classification system. The patients were treated by two commercial antiseptics (Abilar® 10% Resin Salve or Octenidine® solution) and followed-up by a specialized clinic with four follow-up visits during a treatment period of 145 days on average. All patients performed the wound care at home after instructions from the clinic.

Results: At study entry, the mean ulcer area was 221 mm^2 (median 140 mm^2, interquartile range: 73-320 mm^2) in the salve group and 277 mm^2 (median 132 mm^2, interquartile range: 50–365 mm^2) in the solution group. In intent-to-treat (ITT) analysis of the whole study population of 35 patients, the ulcers healed totally in 14 (37%; 95% CI 24-56%), and in 9 of 19 patients (47%; 95% CI: 25%-77%) and in 5 of 16 patients (31%; 95% CI: 9%-54%) in the resin salve and Octenidine solution groups, respectively (P>0.05). The infected ulcer with small median size showed an insignificant trend to heal better than the other ulcers. The number of positive bacterial cultures from ulcers (bacteria of *Staphylococcus* and *Streptococcus* species in great majority of cases), taken on clinical grounds if infection was suspected, was lower in follow-up visits than at study entry. No side effects were observed.

Conclusion: Treatment of diabetic foot ulcers of PEDIS grade 1-2 at home-care with topical antiseptics is an option that results in complete healing of ulcer in more than one third of cases in a 145-day treatment period.

Keywords: Antiseptics; Resin salve; Abilar; Octenidine; Diabetic ulcer; Topical treatment; Home care

Introduction

Topical treatment of diabetic foot ulcer wounds, also with antiseptics, is an option in clinical practice when the ulcer is classified as grade 1-2 using the PEDIS (Perfusion, Extent, Depth, Infection and Sensation) classification system. However, the effectiveness of topical ulcer care agents in treatment of diabetic ulcers is poorly documented, even though such agents are abundantly available for clinical practice [1,2].

Antiseptic octenidine dihydrochloride has been widely used as ulcer care agent worldwide for years [3]. Abilar® 10% Resin Salve is a newer topical antiseptic ulcer agent in formulation of salve, and shows effectiveness in treatment of pressure wounds and complicated surgical wounds [4,5]. Despite different formulation, both are antiseptics, and the microbicidal mechanisms of agents, solution and salve, are likely similar in that they both are thought to work *via* unspecific destruction of the microbial cell wall and cell membrane [6-9]. They may also enhance skin regrowth and regeneration [4,5].

In this prospective observational clinical follow-up, our aim was to investigate the effectiveness of topical antiseptics in treatment of PEDIS grade 1-2 diabetic foot ulcers at home-care. We wanted to know by a prospective follow-up trial how often the diabetic foot ulcers will completely heal with strategy that applies topical antiseptics as ulcer treatment agents at a home-care setting. Commercially available Octenidine® solution and Abilar® 10% Resin Salve were selected as antiseptic agents.

Patients and Methods

Study population

The study included 35 patients aged 30-78 years with type 1 or 2 diabetes. All had neuropathic fore-or mid-foot ulceration of grade 1-2 severity according to the PEDIS classification system [10]. The patients were allocated to the solution or salve groups, and carried out the treatment as home-care. The patients were recruited and allocated into the study groups by physicians who were specialized in the treatment of diabetes and its complications. Treatment was initiated and was followed-up at the outpatient clinic of the Diabetic Foot Center, Medical University of Gdańsk, Poland.

The inclusion criteria were as follows: age >18 years; type 1 or 2 diabetes; neuropathic fore-or mid-foot ulceration that was grade 1–2 according to the PEDIS classification of ulcer depth; able and willing to perform at-home wound treatment. The exclusion criteria were as follows: life expectancy less than 6 months; ulceration of ischemic origin; signs of systemic infection; heel ulceration; the presence of osteomyelitis; pregnancy; known hypersensitivity to any of the ingredients in the treatment products; the inability to provide informed consent; advanced malignant disease. Table 1 summarizes the patient demographics and disease information in the two treatment groups.

	Resin salve (n=19)	Octenidine solution(n=16)	P-value
Sex (No, %)			
Male	15 (79)	12 (75)	ns
Female	4 (21)	4 (25)	ns
Age (years)	54 ± 11 [30–78]	59 ± 7 [45–71]	ns
BMI (kg/m2)	30 ± 6 [21–39]	31 ± 5 [25–43]	ns
Type of diabetes (No, %)			
Type 1	4 (21)	3 (19)	
Type 2	15 (79)	13 (81)	ns
Positive family burden	10 (53)	9 (56)	ns
Duration of diabetes (years; mean, SD, range)	17 ± 10 [6–45]	11 ± 5 [1–16]	ns
Diabetic ulcer (days, median, IQR)	529 [105–736]	367 [92–490]	ns
Ulcer size by PEDIS classification			
Depth (mm)	2 [1–2]	1 [1–2]	ns
Area (mm^2; mean and SD)	222 (206)	277 (321)	ns
Area (mm^2, median and IQR)	140 [96–306]	132 [100–400]	-
Previous treatment efforts (No, %)			
Active topical treatment	6 (32)	5 (31)	ns
Debridement or surgical revision	12 (63)	9 (56)	ns
Amputation	2 (11)	4 (25)	ns
Previous revisions (No, %)			
Debridement at baseline	15 (79)	15 (94)	ns
Infected ulcer/ongoing antibiotics	4 (21)	4 (25)	ns
Impaired mobility	-	2 (12)	ns
Use of offloading shoe	10 (53)	7 (44)	ns
Poor compliance	5 (26)	0 (0)	ns
Complications (No, %)			
Retinopathy	7 (37)	7 (44)	ns
Neuropathy	19 (100)	16 (100)	-
Microangiopathy	1 (5)	0 (0)	ns
^{Ne}phropathy	5 (26)	3 (19)	ns
Medication (No, %)			
Long-acting insulin	16 (84)	12 (75)	ns
Short-acting insulin	12 (63)	9 (56)	ns
Metformin	9 (47)	9 (56)	ns
Daily dose (mg)	1867 ± 710	2069 ± 1181	ns
Other oral medication	1 (5)	1 (6)	ns
Concomitant medical Conditions (No, %)			
Hypertension	7 (37)	6 (38)	ns
Hyperlipidemia	3 (16)	1 (6)	ns
PVD or CAD or stroke	3 (16)	1 (6)	ns
Smoking	9 (47)	1 (6)	0.007
Creatinine (µmol/l)	110 ± 58	95 ± 26	ns
GFR (ml/min/1.73 m^2)	73 ± 29	76 ± 24	ns
HbA1c (%)	8.4 ± 2.1	8.8 ± 2.2	ns
Hemoglobin (g/l)	139 ± 10	142 ± 14	ns
Leucocytes (10^9/l)	8.2 ± 3.5	8.5 ± 3.2	ns
C-reactive protein (mg/l)	9 ± 8	8 ± 7	ns
ESR (mm/h)	18 ± 12	21 ± 17	ns

Table 1: Baseline patient demographics and disease characteristics at study entry (intent-to-treat-population). Data represent the number (percentage) of patients, or the mean standard deviation [range], or the median and [interquartile range]. 1: GFR<60 ml/min/1.73 m^2 by the MDRD equation; 2: glimepiride and glibenclamide. BMI=Body Mass Index; CAD=Coronary Artery Disease; ESR=Erythrocyte Sedimentation Rate; HbA1c=Glycated Hemoglobin; MDRD=Modification of Diet in Renal Disease; PVD=Peripheral Vascular Disease; ns=Difference Nonsignificant.

Study design

All clinically relevant medical and follow-up data were collected into a Clinical Report Form (CRF) by participating physicians from every patient at the beginning (entry) of the study and at every four visits in Diabetic Foot Center until the study end (145 days in average). The patients were allocated to control at Diabetic Foot Outpatient

Clinic (Diabetic Foot Center, Medical University of Gdańsk, Poland) by follow-up visits with approximately 4-week intervals after the study beginning. The study flow chart is shown in Figure 1.

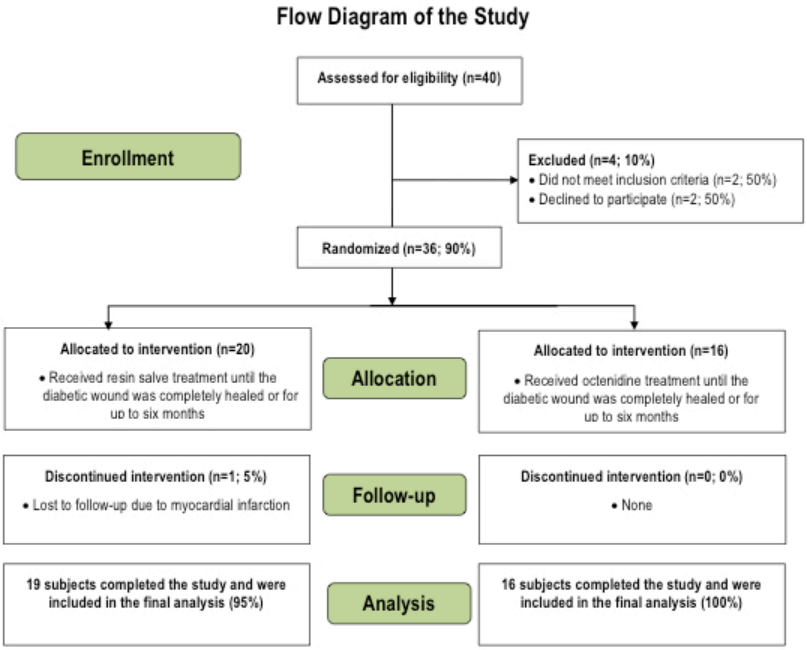

Figure 1: Flow diagram of the study.

Microbiology

Microbial swab-cultures were taken by physicians if considered necessary for clinical reasons. Oral antibiotics were administered if considered clinically necessary and if there was both clinical evidence and laboratory-confirmed evidence of infection (body temperature over 38°C, wound redness or suppuration, and C-reactive protein concentration above 40 mg/l).

Study outcomes and objectives

The primary outcome measure and objective were the frequency and rate of complete healing of the ulcers in the whole study population and separately in the two treatment groups (solution *vs.* salve). Secondary outcomes and objectives were as follows: a healing trend from assessments of ulcer size during the follow-up; frequency of pathogenic bacteria in ulcers during the study period as documented by swab cultures taken on clinical grounds and need; identification of potential contributors to delayed the ulcer healing; frequency of side effects.

If ulcer totally "healed" (i.e., the ulcer was fully closed at any time point during the follow-up period), the primary objective was achieved. If unhealed, the ulcer was considered "improved" if the mean ulcer area was decreased by 50%. Ulcer was considered "unchanged" and "unimproved" in the rest.

Photographs were taken at every follow-up visit to the outpatient clinic. Any notable improvement, any deterioration, or any factor that might affect ulcer healing during the follow-up period, e.g. mechanical/surgical ulcer revision, cleansing, or antibiotic treatment, were registered on the CRFs.

Analysis of the ulcer healing by ulcer area

The ulcer healing rate analysis was performed according to the intent-to-treat (ITT) principle. All cases with healed or unhealed ulcers at any time point during the follow-up were included in the analysis regardless of whether the patient did or did not attend all of the follow-up visits before the end of the study. If the ulcer was closed at any follow-up visit, ulcer was considered fully healed. Since there were several unexplained treatment interruptions, particularly in the octenidine group, per protocol (PP) analysis was not used, as it would be misleading.

To estimate the speed of diabetic foot ulcer healing over time, the analysis included only cases that were fully healed. In these analyses,

the mean reduction in area (± SD) of ulcer per treatment day of the wound was calculated.

Treatment agents and wound care in the treatment groups

Octenidine solution: Octenidine dihydrochloride is a cationic surfactant and a bis-(dihydropyridinyl)-decane derivative that is used at concentrations of 0.1%-2.0% in antiseptic solutions. Its mechanism of action is similar to that of quaternary ammonium compounds but has a somewhat broader spectrum in antimicrobial activity. Octenidine is currently used in Europe as a substitute for chlorhexidine), and is formulated as a water or alcohol-based solution. In aqueous formulations, it is often potentiated by the addition of 2-phenoxyethanol [11-13].

Resin salve: Resin salve (Abilar® 10% Resin Salve, Repolar Pharmaceuticals Ltd., Espoo, Finland) is a salve mixture of natural coniferous resin (wood rosin) of Norway spruce (*Picea abies*) as an active ingredient. The salve is commercially available and CE marked as a wound care agent in EU market. The resin originates from trunks of full-grown trees, harvested mechanically, purified, liquefied, and filtered. Salve is a 10% (w/w) mixture of resin ("wood rosin") in a standard salve base. The salve is highly antiseptic (microbicidal) in *in vitro* tests [6-8].

Treatment with Octenidine solution was implemented in similar manner as with resin salve by following instructions of the manufacturers. In Octedine group, the patients were instructed to soak the gauze in octenidine dihydrochloride solution and to set the gauze on the wound. The gauzes recommended for use were those recommended by the manufacturer of Octenedine solution. The resin salve was instructed to be spread directly onto ulcer, after which the ulcer area instructed to be covered with any bandage or gauze that is suitable and applicable for topical wound care by responsible physician or nurse. The bandages or gauzes were ordered to be changed every 1-3 days, depending on the degree of infection and amount of ulcer secretion, and depending the opinion of the responsible nurse.

Diabetes treatment was performed according to standard clinical practices in both groups. Offload shoes were offered to patients and patients were advised to wear them, if appropriate. General instructions for good at-home care were provided to all of the patients at the study entry.

Statistics

Qualitative data are expressed as frequencies and percentages, and differences between groups were compared with the χ^2-test or Fisher's exact test, as appropriate. Normally distributed quantitative data are expressed as means ± standard deviation, and skewed data are presented as medians and middle 50% interquartile range (IQR). All tests were two-sided, and $p<0.05$ was considered statistically significant.

Safety and tolerability

Hypersensitivity or allergy to resin or octenidine treatment was assessed as part of the study plan, and if there were any symptoms or risks of allergic reactions, such as contact dermatitis, patients were instructed to discontinue the treatment.

Ethics, registration, and approval

All patients were given information about the study orally, and written informed consent was obtained from all participants. The study protocol was approved by the Ethics Committee of Gdańsk Medical University (Clinical Trial Number NKBB/75/2014) and was registered in the ClinicalTrials.gov database (ClinicalTrials.gov identifier: NCT02169167). At planning phase, it was considered that the trial has to be an observational follow-up. For ethical reasons, control group without any treatment or placebo, was excluded from the study plan.

Results

Wound healing

Table 2 shows the results regarding the healing rate of ulcers in the whole study population with consideration of the PEDIS parameters. Table 3 shows the conclusions of success of the treatment in all patients, and separately in patients treated with either solution or salve, and gives the ulcer size (area) in all patients at different follow-up time points (follow-up visits).

Grade	Cases at study entry	Fully healed	Unhealed
Perfusion (number of cases)			
I	34	14	20
II	1	0	1
Extent (mm^2; mean and SD)	246 (261)	215 (259)	255 (261)
Extent (mm^2; median and interquartile (middle 50%) range)	140 (72-400)	80 (45-300)	147 (108-325)
Depth (number of cases)			
I	25	10	15

II	10	4	6
Infection (number of cases)			
I	30	11	19
II	5	3	2
Sensation (number of cases)			
I	0	0	0
II	35	14	21
Final outcome (number of cases)			
Fully healed	14		
Improved	6		
Unchanged	15		
Total	35		

Table 2: Outcomes at follow-up and the grades of ulcer parameters according to PEDIS classification at study entry. The analysis was performed using intent-to-treat principles.

In ITT analysis that included all 35 patients, the ulcer was healed in 14 (37%; 95% CI 24-56%), and more specifically, in 9 of 19 patients (47%; 95% CI: 25%-77%) in the resin salve group and in 5 of 16 patients (31%; 95% CI: 9%–54%) in the octenidine solution group ($p>0.05$). Figure 2 shows examples of ulcers that were considered to be fully healed, improved or unchanged by specialized physicians.

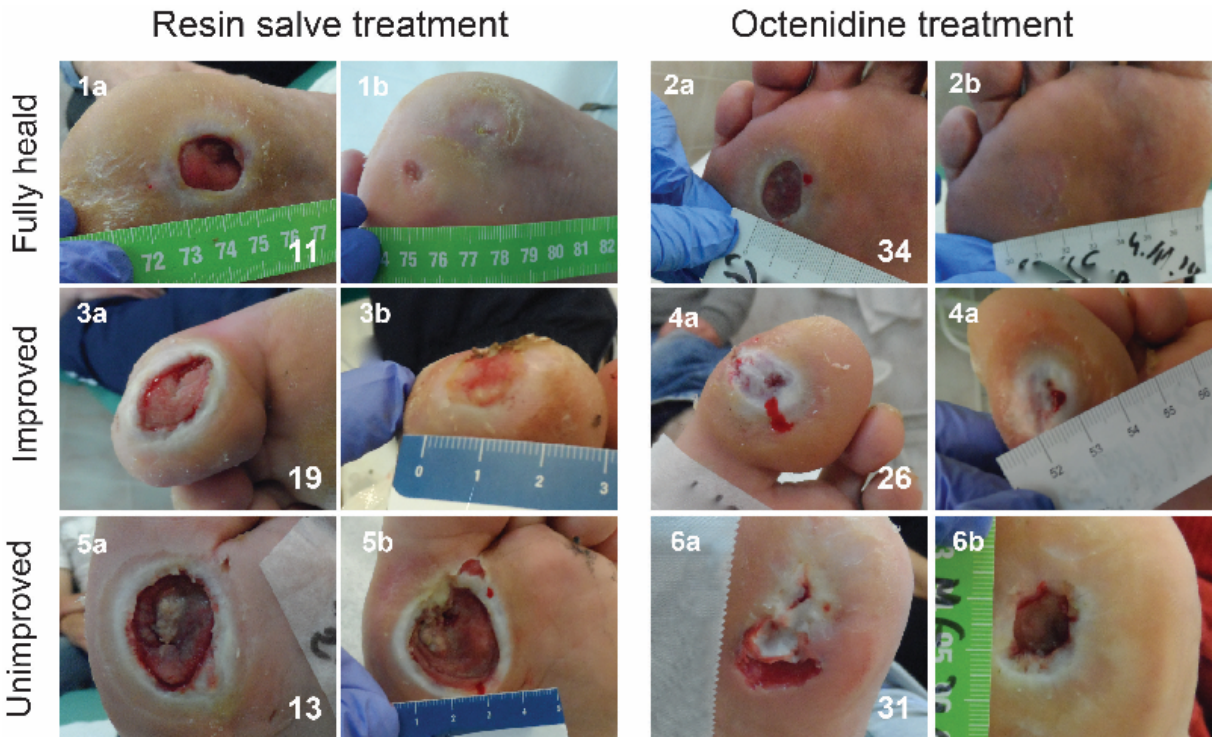

Figure 2: Photographs of representative diabetic ulcers in investigator-blinded settings for objective assessment of the resin salve and octenidine solution treatment arms of the study. Wounds are shown that are (a) fully healed, (b) improved, and (c) unchanged. The photographs were taken at baseline (left panels) and at the end of the follow-up (right panels). The number in the right lower corner of the panels is the patient number (Table 3).

From collected data, we did not find any demographic, ulcer-related or a treatment-associated parameter, not even ulcer depth that could reliably explain why some ulcers healed and others did not. However, the clinically infected ulcers with small median size at study entry tended to heal better than the other ulcers but this difference was insignificant in the present study population (Table 2).

Treatment group	No.	PEDIS classification	Wound history (days)	Wound area (mm^2) at follow-up time points						Outcome conclusion
				ENTRY	FUP1	FUP2	FUP3	FUP4	END	
A	1	1/30/1/1/2	88	30	24	15	12	0	0	Healed
A	2	1/10/1/1/2	ND	10	6	25	9	ND	9	Unchanged
A	3	1/72/1/1/2	63	72	25	16	6	4	0	Healed
A	4	1/306/1/1/2	73	500	300	ND	ND	ND	300	Unchanged
A	5	1/500/1/1/2	11	306	260	270	360	460	460	Unchanged
A	6	1/45/2/1/2	2136	45	9	4	8	0	0	Healed
A	7	1/836/1/1/2	733	836	600	440	90	0	0	Healed
A	8	1/120/1/1/2	5337	120	80	156	180	575	105	Unchanged
A	9	1/420/2/1/2	568	420	405	440	660	540	540	Unchanged
A	10	1/280/1/1/2	2404	280	120	100	66	0	0	Healed
A	11	1/300/2/1/2	547	300	300	300	270	300	0	Healed
A	12	1/56/2/1/2	506	56	16	12	8	20	0	Healed
A	13	1/320/2/1/2	1311	320	300	234	300	360	980	Unchanged
A	14	1/120/2/1/2	736	120	91	66	24	0	0	Healed
A	15	1/140/1/1/2	396	140	80	300	64	48	180	Unchanged
A	16	1/96/1/2/2	444	96	77	48	56	50	8	Improved
A	17	1/80/1/1/2	105	80	48	65	30	0	0	Healed
A	18	1/150/2/1/2	511	150	150	180	240	104	180	Unchanged
A	19	1/325/1/1/2	953	325	253	220	253	325	200	Unchanged
B	20	1/60/1/1/2	101	60	25	15	ND	ND	15	Improved
B	21	1/42/1/1/2	317	42	56	ND	ND	ND	56	Unchanged
B	22	1/100/1/1/2	ND	100	25	4	ND	ND	4	Improved
B	23	1/1250/1/1/2	367	1250	560	500	198	ND	198	Improved
B	24	1/460/1/1/2	365	460	460	216	56	ND	56	Improved
B	25	1/108/1/1/2	2529	108	56	ND	ND	ND	56	Unchanged
B	26	1/110/1/1/2	18	110	100	80	6	12	4	Improved
B	27	1/200/1/1/2	455	200	143	144	ND	ND	144	Unchanged
B	28	1/120/1/2/2	11	120	48	48	30	0	0	Healed
B	29	2/468/2/1/2	1129	468	455	390	ND	ND	390	Unchanged
B	30	1/40/1/1/2	14	40	32	48	15	6	0	Healed
B	31	1/143/1/1/2	490	143	81	120	130	216	216	Unchanged

B	32	1/660/1/2/2	375	660	0	ND	ND	ND	0	Healed
B	33	1/400/2/1/2	772	400	400	440	620	495	495	Unchanged
B	34	1/260/1/2/2	92	260	280	216	33	0	0	Healed
B	35	1/12/1/2/2	379	12	10	6	0	ND	0	Healed

Table 3: Outcome conclusions, pre-entry duration of wound by information given by the patients themselves, wound size (area) at study entry and in follow-up visits (FUP) in all patients with resin salve (A) or octenidine solution (B). PEDIS classification indicates the grade of the wound by perfusion, extent (wound area), depth, infection and sensation at study entry in all patients.

Microbiology and side effects

Findings of microbiology of swab cultures, taken by physicians if an infection was suspected on clinical grounds, are presented in Table 4. Number of positive swab-cultures tended to be lower in cultures from follow-up visits than in cultures at the study entry, the *Staphylococcus* and *Streptococcus species* being the microbes that were most frequent in positive cultures in general, and at study entry in particular.

	Entry	FUP1	FUP2	FUP3
Staphylococcus aureus	8	1	3	1
MRSA	1	0	0	0
Pseudomonas aeruginosa	2	1	2	0
Enterobacter sp.	1	0	0	1
Enterococcus fecalis	0	0	1	0
Escherichia coli	1	0	0	0
Betahemolytic streptococcus	3	0	1	0
Streptococcus sp.	7	1	0	1
Klebsiella pneumoniae	1	0	0	0
Hemophilus parainfluenzae	1	0	0	0
Morganella morgagnii	1	0	0	0
Proteus mirabilis	1	1	0	1
Proteus vulgaris	0	0	0	1
Serratia marcescens	0	1	0	0
Pasteurella canis	0	0	1	0
Acinetobacter baumanii	0	0	0	1
Porfyromonas sp.	0	0	0	1
Veillonella sp.	0	0	0	1
Total	27	5	8	8

Table 4: The results of positive bacterial cultures at baseline (study entry) and at follow-up (FUP) visits. The number indicates the number of positive bacterial cultures (strains) obtained and pooled from separate ulcers and patients at the time point of follow-up (MRSA=Methicillin-Resistant *Staphylococcus aureus*).

No allergic reactions or side effects were observed during the study period. During the follow-up visits, there were no observed changes in laboratory parameters other than those related to the ulcers themselves.

Discussion

The observations suggest that topical antiseptics are objectively effective in improving of the healing of PEDIS grade 1–2 diabetic foot ulcers, even if applied in home-care settings. Complete healing was achieved in 37% (95% CI: 24-56%) of ulcers on average in 145 treatment-days. In addition, 6 (29%; 95% C: 9-48%) of 21 ulcers, that did not completely heal, improved in the sense that the ulcer size (area) was reduced at least by 50% during the 145-day study period. It may be concluded that a majority, 57% (95% CI 41-74%) of all ulcers, benefited, i.e., the ulcer healed or clearly improved. The topical antiseptics used in this study were similar in treatment success, regarding all of parameters recorded, suggesting that the formulation of the topical antiseptic is not likely a critical issue that would predict a treatment success. For such comparison, a much larger and more strictly controlled study population would be needed.

Noteworthy observations were that even some large wounds healed during the 145-day treatment period. The mean speed for reduction of the ulcer area was calculated to be 1 mm^2 per day when the estimation was based on cases in which the ulcer fully healed. Thus, the healing process is slow in general and may take weeks in large ulcers. A surprise was also that the likelihood of ulcer to heal totally did not clearly and markedly correlate with ulcer size even though some such trends may exist. There was an insignificant trend of small and infected ulcers to heal with the antiseptic better than other ulcers. In this sense, however, larger patient populations would be needed for reliable conclusions.

One of the inclusion criteria was the preconception that the patient included is able to perform ulcer care at home. However, there may still be biases associated with the home care of diabetic ulcers in terms of treatment consistency and correctness. Specifically, there may have been unknown compliance issues that may have possibly reduced treatment efficacy of self-care at home. Indeed, there were several unexplainable deviations from the study protocol and unexpected study interruptions regarding the arrivals to scheduled control visits (Figure 1 and Table 3).

In present study, based on self-given ulcer history, the patients, in whom the ulcer totally healed in 145 days, had suffered from ulcer for

mean duration of 377 days in median. Since healing or marked improvement was achieved in less than 145 days, it seems reasonable to assume that the healing trends observed in present patients were positively linked with the application of antiseptic treatment rather than were results only of spontaneous ulcer healing.

Even though the present study was not designed to specifically monitor ulcer microbiology, the use of antiseptics seemed to decrease the number of positive swab microbe cultures from ulcers in follow-up visits compared to those at study entry. Positive cultures in swab cultures taken on clinical grounds at follow-up visits were more infrequent than in those taken at study entry. Both treatment agents applied in present study are known to be antiseptics *in vitro* against a broad spectrum of microbes [6-9]. Control of infection is one of the key issues in successful wound care in general [14]. Therefore, the antiseptic may have positively contributed to ulcer healing, in some of the cases at least [15]. However, the topical agents may also have effects on tissue growth factors and repair mechanisms and may, therefore, also enhance ulcer healing in uninfected wounds [16].

This study was designed and limited to investigate whether the antiseptic agents would help wound healing in patients with typical diabetic foot ulcers that were of PEDIS grades 1–2 only. In these patients, the ulcer is not associated with critical limb ischemia (CLI), nor is necrotizing. Specifically, some ulcers penetrated below the dermis into the subepidermal tissue (PEDIS depth of grade 2), but they did not penetrate into subsequent tissue layers. The ulcers showed at most subcutaneous inflammation, and there were losses of protective sensation as well [17].

We cannot explain why some of the patients, 15 cases of 35 (43%, 95% CI 26-59%), did not seem to respond to the treatment at all. It may be that a self-treatment strategy at home for chronic ulcers is not successful in all patients. Complete wound healing in some patients may require treatment over several months, as the case is also in severe pressure ulcers [4]. Resilience may be lacking in some. In addition, like in many other chronic wounds, the development of diabetic foot ulcers may be a result of several dissimilar pathogenetic mechanisms. Thus, all diabetic ulcers may not respond to all treatment options in same way. Gauzes and bandages used in wound care, in addition to antiseptic solution or salve, were those recommended by the manufacturers of the solution and salve, and accepted by responsible physicians and nurses. Unknown is, however, how accurately these instructions were followed by the patients at home-care.

Despite limitations, our results strongly suggest that the treatment of diabetic wounds with topical antiseptic agents, either in formulation of solution or salve, can help in improvement of the healing of typical, non-necrotizing diabetic foot ulcers in remarkable part of patients. There were no cases of allergies or any signs of side effects in the present study, suggesting that the tested wound care agents are also generally safe and well tolerated.

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Declaration of Interest

AS and JJJ are shareholders of Repolar Pharmaceuticals Oy, a Finnish company that develops and markets resin-based products for medical purposes. There are no other conflicts of interests.

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