Efficacy of topical pale sulfonated shale oil in the treatment of venous leg ulcers: A randomized, controlled, multicenter study

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Background: Venous leg ulcers are a growing socioeconomic burden. Pale sulfonated shale oils (PSSO) are used for therapy of inflammatory skin diseases and have been shown to enhance wound healing in vitro and in vivo. The aim of this study was to investigate whether PSSO is capable of enhancing venous ulcer healing beyond compression therapy alone.
Methods: One hundred nineteen patients were enrolled in this randomized, multicenter, observer-blind study. In the treatment group, PSSO 10% was applied daily for 20 weeks, and the control group received the vehicle only. Wounds were covered by a nonadherent gauze dressing, and compression therapy with short-stretch elastic bandages was performed in an outpatient setting. The primary study end point was defined as cumulative reduction in wound area; the secondary study end point was treatment success as assessed by both physicians and patients. Additionally, adverse events, including changes with respect to physical examination and vital signs, were documented.
Results: At the end of the study period, ulcer size was significantly more reduced in the PSSO group compared with the vehicle group (15 ± 15.9 to 6.2 ± 12.9 cm^2 vs 11.4 ± 14.5 to 10.8 ± 15.7 cm^2; $P = .0005$). The cumulative relative reduction in ulcer area was significantly higher in the PSSO group (-4391 ± 4748.7 vs -231.9 ± 6283.6 % × days; $P < .0001$). Relative reduction in wound area was significantly greater in the PSSO group as early as 6 weeks after the beginning of treatment (-47.4 ± 28.4 vs $-23.8 \pm 42.2\%$; $P < .001$). PSSO was judged successful both by physicians and patients. There were no significant differences in adverse events (PSSO, 9 [12.2%]; vehicle, 7 [11.1%]. Similarly, tolerability of PSSO was equal to the tolerability of the vehicle.
Conclusion: Pale sulfonated shale oils were capable of favoring venous ulcer healing in addition to compression therapy. PSSO should be considered for future wound care protocols for treatment of venous leg ulcers. (J Vasc Surg 2006;43: 94-100.)

Leg ulcerations are a common problem in the Western world, affecting about 1% of the population at some time of their life.[1-3] Approximately 70% of all lower-extremity leg ulcers are caused by chronic venous insufficiency (CVI).[4] The cornerstones of care consist of the application of gauze dressings and compression therapy.[5-7] However, venous ulcers are often large in size, extremely painful, and have a poor prognosis and high recurrence rates.[8,9] So far, no topical agent is accepted for standard wound care protocols in venous leg ulcers.[8,10]

Sulfonated shale oils (bituminosulfonates) are extracted from sulfur-rich oil shale, a widespread sedimentary rock. Purification by distillation results in two oil fractions: a light-colored, pale sulfonated shale oil (PSSO) is produced from the low-boiling fraction and a dark sulfonated shale oil from the high-boiling fraction. Dark sulfonated shale oil was first introduced for treatment of skin diseases by Unna in 1882.[11] Clinical trials and toxicologic studies have demonstrated that both variants are safe and well tolerated.[12,13]

Pale sulfonated shale oil is already accepted for therapy of inflammatory skin diseases, psoriasis, and seborrhoic eczema.[13-15] The active ingredients of PSSO exhibit antiphlogistic, analgetic, and antibacterial properties.[16,17] PSSO was recently shown to be capable of enhancing proliferation and growth factor expression of keratinocytes in vitro and stimulating wound healing in vivo, measured as epithelization.[18] The aim of this study was to evaluate whether the topical application of PSSO in addition to compression therapy and standard moist wound care favors venous ulcer healing.

PATIENTS AND METHODS

Between October 2002 and June 2004, 119 patients were enrolled in this randomized, multicenter, observer-blinded, controlled trial conducted in 13 outpatient wound clinics in Germany and Slovakia (see Appendix). The study

was performed in compliance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice. Protocol and informed consent procedures were approved by each center's ethics committee.

Patients. Patients aged >18 years with leg ulcers ≥3 cm^2 owing to CVI were eligible for the investigation. Exclusion criteria were defined as ulcerations not due to CVI, severe cardiac, respiratory, gastrointestinal, liver, or renal disease; malignancy, or signs of wound infection. Pregnant women or nursing mothers were excluded.

Venous status was assessed by a duplex ultrasound scan that showed valvular incompetence or reflux in the superficial or deep veins. Arterial occlusive disease was excluded by measuring the ankle-brachial pressure index (ABI), with an ABI >0.8 defined as inclusion criteria. During the study period, no venous surgery was performed on any patient.

Before randomization, patient eligibility for the study was assessed through a 2-week screening period in which demographic data, medical history, and baseline information were recorded. During this time, ulcers were treated with standard care and compression therapy. After the screening period, patients were randomized to one of the treatment groups by using a centralized computer system with block randomization (1:1) (RanCode, IDV, Gauting, Germany). Investigators were blinded to the randomization process to eliminate bias.

During follow-up visits, which were performed in biweekly intervals, the following parameters were measured and recorded:

- ulcer pain was assessed by patients on a 10-cm visual analogue scale from 0 (no pain) to 10 (maximum pain);
- the extent of fibrinous discharge, defined as yellow eschar, was classified as "none, medium, or complete"; and
- the presence or absence of necrotic tissue was documented.

Additionally, treatment success and tolerability were judged by physicians and patients on a five-point qualitative scale with categories of "very good, good, medium, moderate, and bad." Treatment success was defined by the subjective assessment of response to treatment relative to the baseline. *Tolerability* was defined as local wound discomfort relative to the baseline, including itching, erythema, burning, dryness, or swelling. Adverse events included changes with respect to physical examination and vital signs.

Relative reduction in wound area (R_i) was calculated as $R_i = 100 \times (A_i - A_{baseline})/A_{baseline}$ where A equals wound area and i equals number of visits. Cumulative relative reduction in ulcer area was calculated as area under baseline (AUB) = Σ visit interval $_{i + 1} \times (R_i + R_{i + 1})/2$.

It was determined in advance that a 120-patient study was of sufficient size to provide the required information. Based on the assumption that approximately 95% of the subjects in the treatment group would show complete granulation of the wound by the end of the 20-week treatment period compared with 75% of the subjects in the vehicle group, a sample size of 65 patients per group would provide 90% power to detect a significant difference in primary study end points at a 5% significance level.

Local treatment. Patients were randomized into two groups treated either with 10% Leukichtan, a PSSO gel, (Ichthyol-Gesellschaft, Hamburg, Germany) (PSSO group) or the vehicle. The vehicle consisted of a nonionic polyoxyethylene-polyoxypropylene block copolymer with the general formula $HO(C_2H_4O)a(-C_3H_6O)b(C_2H_4O)aH$ providing the gel component of Leukichtan. PSSO 10% or the vehicle was administered directly onto the wound surface daily as a 2- to 2.5-mm-thick gel layer. Wounds were covered by Jelonet, a nonadherent gauze dressing (Smith & Nephew Medical, Lohfelden, Germany), and compression therapy was performed throughout the entire study in both groups by using short-stretch elastic bandages (Pütter-Bandages, Hartmann, Germany). Prescription footwear was used for pressure relief if necessary.

Clinical parameters, ulcer measurement and ulcer size stratification. Baseline wound size was calculated before randomization by measuring the maximum length and breadth and multiplying them. Patients were examined every 2 weeks. At every visit, ulcer area was assessed by photoplanimetry. The ulcer outline was traced on Opsite transparent paper (Smith & Nephew Medical), and area was calculated in a blinded manner using a standardized computer system.[19]

Study end points. The primary end points of the study were (1) cumulated relative reduction in ulcer area and (2) complete granulation and epithelization of the wound by the end of the 20-week treatment period. Complete healing of the wound was defined as complete epithelization. Secondary end points were time courses for (1) pain, (2) necrotic wound tissue, (3) fibrinous discharge, (4) treatment success, and (5) tolerability.

Statistics. Block randomization (1:1) was chosen and calculated with the validated program RanCode. Data represent mean ± standard deviation (SD). Comparison of baseline variables was performed by using analysis of variance (ANOVA) and χ^2 test. Differences in end point variables between treatment groups were calculated using ANOVA (relative reduction in ulcer area) and the log-rank test (time to complete granulation and epithelization). Analysis of secondary end point parameters was performed with ANOVA, the χ^2 test (dichotomous data), and the Mantel-Haenszel test (assessment of treatment success). $P < 0.05$ was considered significant.

RESULTS

Baseline data. One hundred thirty-seven patients were assessed for eligibility. Ultimately, 119 patients were enrolled in the study; 62 were randomized to PSSO 10% and 57 to vehicle treatment. Eighteen (15%) of the 119 patients—nine each in the in the PSSO 10% and vehicle groups—did not complete the study for other reasons than ulcer healing. These patients were included in data analysis with their assigned group (Fig 1).
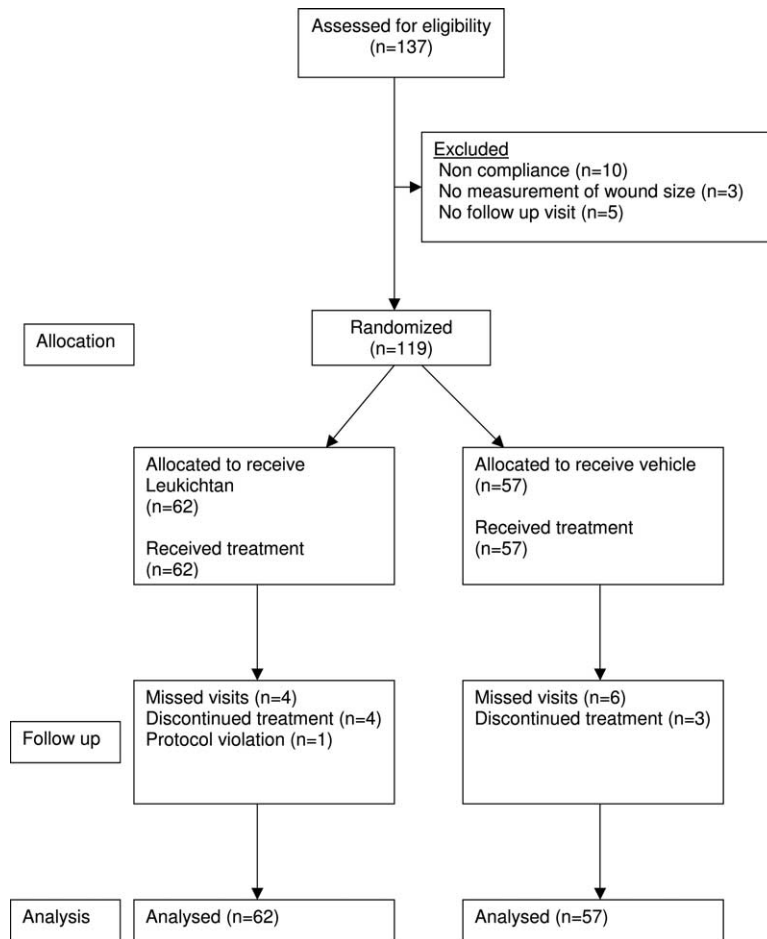
Fig 1. Patient flow through the study.

Groups were comparable for age, sex, height, wound duration, wound size, pain score, and wound stratification; however, patients in the PSSO group had a significantly increased weight. Both groups had comparable superficial or deep venous insufficiency and insufficiency of perforating veins. Significantly more patients were suffering from post-thrombotic changes in the PSSO group compared with the vehicle group (Table I). Additionally, wounds were comparable for granulation, epithelization, and the amount of fibrinous discharge or necrotic tissue (Table II).

Study end points. At the end of the study period, ulcer size was significantly more reduced in the PSSO group compared with the vehicle group (15 ± 15.9 to 6.2 ± 12.9 cm² vs 11.4 ± 14.5 to 10.8 ± 15.7 cm²; $P = .0005$) (Table III). Cumulative relative reduction in ulcer area was significantly greater in the PSSO group compared with the vehicle group (-4391 ± 4748.7 vs -231.9 ± 6283.6 % × days; $P < .0001$). Relative reduction in wound area assessed at every visit showed that as early as 6 weeks after the beginning of treatment, the reduction in wound area was significantly increased in the PSSO group compared with the vehicle group (-47.4 ± 28.4 vs -23.8 ± 42.2%; $P < .001$)

(Fig 2). There was no difference in groups regarding complete epithelization or granulation. After 20 weeks of treatment, 33 patients (53.2%) in the PSSO group showed complete granulation, and 21 patients (33.9%) had complete epithelization. In the vehicle group, 21 patients (36.8%) developed complete granulation ($P = .161$), and 13 patients (22.8%) had complete epithelization ($P = .177$).

Throughout the entire observation period there was no significant difference in pain score between the groups (baseline, 4.6 ± 2.9 vs 5.3 ± 3.2; study end point, 1.8 ± 2.3 vs 2.6 ± 2.4). Additionally, wounds in both groups did not show a significant difference in the presence of fibrinous discharge or necrotic tissue.

Treatment success of PSSO 10% compared with vehicle was assessed at every visit both by physicians and patients (Table IV). After 20 weeks of treatment, physicians and patients thought PSSO 10% to be significantly more effective than therapy with vehicle alone ($P = .001$; $P = .001$).

There were no significant differences in adverse events between groups (PSSO, 9 [12.2%]; vehicle, 7 [11.1%]). At the end of the investigation, tolerability of PSSO 10% was

Table I. Main demographic and clinical characteristics at baseline*

	10% PSSO (n = 62)	Vehicle (n = 57)	P
Sex			1.0
Male	20 (32.3)	19 (33.3)	
Female	42 (67.7)	38 (66.7)	
Age (years)	66.8 ± 13.7	70.6 ± 11.1	.1
Weight (kg)	88.7 ± 19.2	79.4 ± 14.6	.004
Height (cm)	169.5 ± 8.7	167.8 ± 7.7	.26
Wound duration (months)	24.9 ± 51.2	17.8 ± 18.4	.32
Wound size (cm^2)	26.2 ± 49.0	17.2 ± 21.0	.26
Wound stratification			.36
<20 cm^2	48 (77.4)	50 (87.7)	
≥20 but <35 cm^2	7 (11.3)	3 (5.3)	
≥35 cm^2	7 (11.3)	4 (7)	
Venous disease			
Superficial reflux	17 (27.4)	25 (43.9)	.110
Deep reflux	1 (1.6)	2 (3.5)	1.00
Perforator vein insufficiency	9 (14.5)	8 (14.0)	1.00
Post-thrombotic syndrome	35 (56.5)	22 (38.6)	.037
CEAP class			
C6	62 (100)	57 (100)	
Pain score	4.6 ± 2.9	5.3 ± 3.2	.22

PSSO, Pale sulfonated shale oil.
*Data are expressed as mean ± SD and n (%); *P* < .05 was considered significant.

Table II. Wound characteristics at baseline*

	10% PSSO (n = 62)	Vehicle (n = 57)
Signs of granulation in the wound bed		
Yes	32 (51.6)	29 (50.9)
No	30 (48.4)	28 (49.1)
Signs of epithelization at the wound margins		
Yes	7 (11.3)	7 (12.3)
No	55 (88.7)	50 (87.7)
Fibrinous tissue		
Yes	45 (72.6)	35 (61.4)
No	17 (27.4)	22 (38.6)
Necrotic tissue		
Yes	7 (11.3)	3 (5.3)
No	55 (88.7)	54 (94.7)

PSSO, Pale sulfonated shale oil.
*Data are given as n (%); *P* was not significant for all data.

Table III. Ulcer area assessed by photoplanimetry before treatment and at the end of the study and relative change in ulcer area*

	10% PSSO (n = 62)	Vehicle (n = 57)	P
Initial ulcer area before treatment (cm^2)	15.0 ± 15.9	11.4 ± 14.5	.20
Final ulcer area (cm^2)	6.2 ± 12.9	10.8 ± 15.7	.0005
Relative change in ulcer area (%)	−72.0 ± 37.2	−18.7 ± 68.1	<.0001

PSSO, Pale sulfonated shale oil.
*Data are given as mean ± SD. *P* < .05 was considered significant.

assessed equal to tolerability of the vehicle alone both by physicians and by patients (Table V).

DISCUSSION

Several topical agents were investigated as adjuvant therapy for venous leg ulcers. However, none of them could be proven effective in clinical practice.[20-22] Apligraf (Graftskin, Orangogenisis, Inc, Canton, Mass), a living skin equivalent, has been shown to accelerate wound closure in hard-to-heal venous leg ulcers, but it is no longer available on the European market.[23] So far, compression therapy and moist wound care are still the gold standard in the treatment of venous leg ulcerations.[6,7,24,25]

With this prospective, multicenter, randomized, and observer-blind study, we describe an enhancement of venous ulcer healing by a topical agent in addition to standard care consisting of compression therapy. The groups had highly comparable baseline and demographic characteristics. It was noticeable that patients in the PSSO group were significantly heavier (*P* = .004); however, there are reports that obesity does not affect venous ulcer healing.[26] The higher weight of the PSSO group even strengthens our results.

Additionally, wound duration and actual healing status were comparable, because there was no significant difference in the presence of fibrinous discharge or necrotic tissue and the percentage of epithelization and granulation were equal. The relative reduction in ulcer area was significantly increased by treatment with PSSO 10% compared with the vehicle. This effect was seen as early as 6 weeks after

the beginning of treatment and was sustained throughout the entire observation period.

There was no significant difference, however, regarding complete epithelization and granulation. Complete healing, defined as complete epithelization, was observed in 33.9% in the PSSO group and in 22.8% in the vehicle group. After 20 weeks of treatment, wounds in the PSSO group were smaller but showed an equal extent of granulation tissue and epithelization. These results are comparable to other studies in the literature, especially where wound duration and initial wound area are concerned. It is well known that large venous ulcers (>12 cm^2) and ulcers with long duration show poor healing.[9,27] Additionally, the high percentage of post-thrombotic changes in both groups might provide another possible explanation for the relatively low rates of complete epithelization reported in our study.

Although healing, defined as complete epithelization, was not different between both groups at the end of the observation period, we believe that the significant reduction in wound size found for the PSSO group has a clinical relevance, as Gelfand et al[28] showed the percentage change in wound area as a valid surrogate marker for complete healing of venous ulcers. The implication is also that epi-
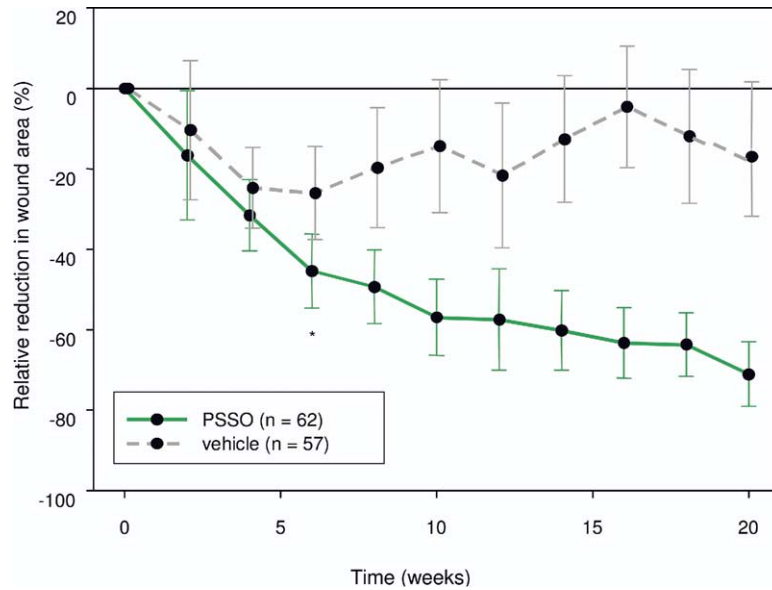
Fig 2. Relative reduction in wound area during treatment. After 6 weeks, relative reduction in wound size is significantly increased in the pale sulfonated shale oil *(PSSO)* group compared with the vehicle group. This difference was sustained throughout the entire observation period. Data shown are ± standard deviation. *$P < .001$ (analysis of variance).

Table IV. Assessment of treatment success at the end of the study (20 weeks)*

	10% PSSO (n = 62)	Vehicle (n = 57)	P
Physician			.001
Missing	16 (25.81)	21 (36.84)	
Very good	25 (40.32)	9 (15.79)	
Good	11 (17.74)	5 (8.77)	
Medium	5 (8.06)	11 (19.3)	
Moderate	3 (4.84)	7 (12.28)	
Bad	2 (3.23)	4 (7.02)	
Patient			.001
Missing	16 (25.81)	21 (36.84)	
Very good	26 (41.94)	7 (12.28)	
Good	11 (17.74)	10 (17.54)	
Medium	6 (9.68)	10 (17.54)	
Moderate	1 (1.61)	6 (10.53)	
Bad	2 (3.23)	3 (5.26)	

PSSO, Pale sulfonated shale oil.
*Data are given as n (%). Differences between groups were calculated by the Mantel-Haenszel test, with $P < .05$ considered significant.

Table V. Assessment of tolerability at the end of the study (20 weeks)*

	10% PSSO (n = 74)	Vehicle (n = 63)	P
Physician			.077
Missing	27 (36.49)	27 (42.86)	
Very good	29 (39.19)	17 (26.98)	
Good	16 (21.62)	14 (22.22)	
Medium	2 (2.70)	4 (6.35)	
Moderate	0 (0)	1 (1.59)	
Bad	0 (0)	0 (0)	
Patient			.154
Missing	27 (36.49)	27 (42.86)	
Very good	25 (33.78)	15 (23.81)	
Good	19 (25.68)	16 (25.40)	
Medium	2 (2.70)	3 (4.76)	
Moderate	1 (1.35)	1 (1.59)	
Bad	0 (0)	1 (1.59)	

PSSO, Pale sulfonated shale oil.
*Data are given as n (%). Differences between groups were calculated by the Mantel-Haenszel test, with $P < .05$ considered significant.

thelization might have been significantly different between both groups if our study had been prolonged to a longer observation period.

When sulfonated shale oils were first introduced by Unna in 1882, they were mainly used for the treatment of inflammatory skin diseases.[11] Venous ulcers are also characterized by a chronic inflammatory state with long-standing inflammatory cellular infiltrates and elevated levels of proinflammatory cytokines in their wound fluid.[29] In addition, the cellular environment becomes less inflammatory as the wound heals.[30] PSSO

exhibits a markedly anti-inflammatory action comparable with 0.5% hydrocortisone.[16] In vitro, PSSO has been shown to inhibit cytokine production of leukocytes and leukocyte migration.[31,32] Similarly, bituminosulfonates have been proven antibacterial through in vitro tests.[33] This might be another mechanism of action, because healing slows down in proportion to the bacterial burden of a wound.[34] There is a growing body of evidence that bacteria present in chronic wounds delay healing even in the absence of the typical clinical signs of infection.[34]

These micro-organisms live on the wound surface within a biofilm that provides protection from host defense mechanisms.

Bituminosulfonates were previously demonstrated as safe and well-tolerated agents in the therapy of skin diseases.[12,15] Similarly in this study, there was not a significant greater number of adverse events during treatment with PSSO 10% compared with vehicle. Four patients, two each in the PSSO and vehicle groups (2.7%), had eczema and pruritus. No severe side effects were reported throughout the entire study period. At the end of the study, both physicians and patients assessed PSSO 10% significantly superior to vehicle. Both thought PSSO 10% to be more effective regarding treatment success with equal tolerability compared with vehicle treatment.

CONCLUSION

With this randomized, controlled, observer-blind, multicenter study, we demonstrated pale sulfonated shale oil is capable of favoring venous ulcer healing beyond compression therapy alone. Additionally, the new agent was safe and well tolerated. Pale sulfonated shale oil should be considered for future wound care protocols in the treatment of chronic venous leg ulcers.

AUTHOR CONTRIBUTIONS

Conception and design: SB, JW, HZ, OK, HS, WC, AK, SC
Data collection: SB, HZ, OK, HS, SC
Analysis and interpretation: SB, SC
Writing the article: SB, SC
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