Topical treatment of chronic venous ulcers with sucralfate: A placebo controlled randomized study

GIOVANNI TUMINO[1], LAURA MASUELLI[2], ROBERTO BEI[3]
LUCILLA SIMONELLI[2], ALBERTO SANTORO[1] and SILVANA FRANCIPANE[4]

Departments of [1]Surgical Sciences, [2]Experimental Medicine, University of Rome 'Sapienza';
[3]Department of Experimental Medicine and Biochemical Sciences, University of Rome
'Tor Vergata'; [4]Accademia di Storia dell'Arte Sanitaria, Rome, Italy

Received December 27, 2007; Accepted February 18, 2008

Abstract. Venous leg ulcers are an important medical issue due to their high incidence in the elderly and the lack of a standard curative approach. Apart from surgical therapy, different medical treatments to effect ulcer wound repair and regeneration are currently being investigated. Sucralfate is a cytoprotective agent employed to prevent or treat several gastrointestinal diseases such as gastroesophageal reflux, gastritis, peptic ulcer, stress ulcer and dyspepsia. In this study we evaluated the efficacy, safety and tolerability of topical sucralfate (SUC-LIS 95) on the healing of chronic venous leg ulcers in 50 patients by a double-blind, placebo-controlled, randomized study. Our results indicated that the daily application of SUC-LIS 95 to non-infected post-phlebitis/vascular ulcers, for a median period of 42.0 days, led to complete healing in 95.6% of patients, against only 10.9% of cases with a matched placebo. A significant improvement was obtained in the SUC-LIS 95-treated patient group with regard to local tissue inflammation as well as pain and burning, and consequently, in ulcer size and the evolution of granulation tissue. Our findings were corroborated for selected patients by the morphological analysis of biopsies obtained before and after treatment. Using ultrastructural analysis we demonstrated that the topical use of SUC-LIS 95 was able to affect neoangiogenesis, increase wound contraction, promote re-epithelialization of the wound area and diminish the inflammatory reaction. Overall, our results indicated that patients with chronic venous ulcers show improvement after the use of topical sucralfate.

Correspondence to: Professor Giovanni Tumino, Department of Surgical Sciences, III Clinica Chirurgica, University of Rome 'Sapienza', Viale Regina Elena 324, I-00161 Rome, Italy
E-mail: giovanni.tumino@uniroma1.it

Key words: sucralfate, chronic venous ulcers, healing process, topical sucralfate

Introduction

Venous leg ulcers are an important medical issue due to their high incidence in the elderly and the lack of a standard curative approach (1,2). Apart from surgical therapy, different medical treatments to effect ulcer wound repair and regeneration are currently being investigated (3,4). Systemic or topical drugs acting in the wound repair and regeneration processes, have been proven to be promising and useful agents for the treatment of chronic venous ulcers (5). Wound repair depends both on neoangiogenesis and the activation of a local immune response, and on the presence of growth factors including epidermal growth factor (EGF), transforming growth factor ß (TGF-ß), and basic fibroblast growth factor (bFGF) (6-9). It has also been demonstrated that the local injection of granulocyte-macrophage colony stimulating factor (GM-CSF) is able to promote and accelerate the wound repair of chronic venous leg ulcers by increasing several cellular functions such as the migration of epithelial cells, local recruitment of inflammatory cells and the proliferation of keratinocytes (10,11). Sucralfate is a cytoprotective agent. It is a safe and well tolerated drug as demonstrated by the complete lack of side effects, and for this reason it is widely employed in clinical practice to prevent or treat several gastrointestinal diseases such as gastroesophageal reflux, gastritis, peptic ulcer, stress ulcer and dyspepsia, and in the treatment of recurrent aphthous stomatitis (12-14). Furthermore, the stimulating effects of sucralfate on vascular factors, including angiogenesis, which play important roles in tissue repair, have been demonstrated (15-17). Recent studies have shown the stimulating effect of sucralfate on EGF expression and on the expression of other factors involved in tissue repair processes (18). The sporadic studies and case reports available in the literature are all consistent, indicating the favorable effect of topical sucralfate in wound repair and in skin protection. Almost all studies indicated the safe and effective behaviour of this compound (19-27).

Therefore, we considered that there were enough supporting data to undertake a study on a new pharmaceutical form of topical sucralfate, specifically dedicated to the local re-epithelializing treatment of non-infected skin lesions. In this study we evaluated the efficacy, safety and tolerability of topical sucralfate on the healing of chronic venous leg ulcers

in 50 patients by a double-blind, placebo-controlled, randomized study. Furthermore we followed the ulcer wound repair and regeneration process in a selected subgroup of patients using morphological and ultrastructural analysis.

Patients and methods

The study was conducted in accordance with both the declaration of Helsinki and the ICH's regulations governing good clinical practice. All patients participating in the clinical trial were informed about the study protocol and gave their written consent. The protocol was approved by the local ethics committee of the University of Rome 'Sapienza'. One hundred patients of both sexes, affected by non-infected vascular ulcers, and whose demographic characteristics are described in Table I, were selected for the trial and were randomized into two groups of 50 cases each. Patients with venous stasis or post-phlebitis ulcers were included in the protocol. Patients with known or presumed hypersensitivity to the drug, pregnant women, patients affected by neoplastic or other diseases which rendered them unable to complete the treatment, as well as patients who had previously used a local treatment for the ulcers, were excluded from the study. Four patients did not finish the treatment for unknown reasons that were not, however, related to toxicity of the drug.

Treatment procedure. The sucralfate hydrophilic gel used, SUC-LIS 95, contained as the active principle, precipitated sucralfate (25 g per 100 g gel) in a new physical form, sucralfate humid gel (European patent 0286978-7/11/90), which is endowed with a higher bioadhesivity towards mucosaes. The placebo gel (PBO) lacked the active principle sucralfate. Both gels were manufactured and provided by Lisapharma.

The patients received in double-blind fashion either SUC-LIS 95 gel (50 cases) or matched PBO gel (50 cases) once daily on the whole lesion for a variable duration according to the patient's clinical condition, but in any case for ≥30 and ≤90 days. Before topical application, the ulcers were cleaned with isotonic saline and iodine solution following the surgical removal of debris. The gels were applied daily at the bottom of the ulcers. The ulcers were then covered with sterile dry gauze and in a few cases with an elastic bandage. Before the following day's treatment, the old gel was cleared from the ulcers.

Evaluation criteria of wound repair and regeneration. The following parameters were evaluated at the beginning, after 10 and 20 days, and at the end of the treatment period: lesion size (cm^2), cicatrization time (days), evolution of the granulation tissue, clinical signs including inflammation, exudates and swelling, symptoms including pain and burning, and healing rate. All these parameters were semiquantitatively scored in 4 categories according to their severity (0, absence; 1, light; 2, moderate; 3, heavy).

A semiquantitative evaluation was also applied to the evolution of the granulation tissue (0, absence; 1, scarce; 2, moderate; 3, good). The time of healing was evaluated from the beginning of the treatment in days. Finally, to assess the efficacy of the therapy, each patient was assigned an overall rating (excellent, good, moderate, scarce).

Histopathology and ultrastructural analysis. In order to determine the effects of SUC-LIS 95 or placebo gels on wound repair and regeneration processes, ulcer biopsies were drawn before and after treatments. The specimens were then processed for ultrastuctural evaluation as previously described (28-30).

For light microscopy and ultrastructural analyses, the specimens were fixed in 2.5% glutaraldehyde in PBS pH 7.4 and processed for transmission electron microscopy. For light microscopy, semithin sections were stained with tolouidine blue. Each observation was repeated 2 times. The parameters evaluated encompassed, a) epidermis organization and cellular morphology including cytokeratin expression, cellular junction organization (presence of desmosomes, hemidesmosomes), cellular necrosis, and intraepithelial edema, and b) stroma organization.

Statistical analysis. The endpoints were the evolution of lesion size and the healing rate. The parametric data were statistically analyzed by means of the analysis of variance (ANOVA) and the semiquantitative non-parametric data by the Kruskal-Wallis ANOVA. Distribution data were analyzed by the χ^2 (Chi-square) test. Laboratory data before vs. after treatment were analyzed by the Student's t-test for paired data. The probability level of α=0.05 was chosen to assess the significance of differences.

Analyses were done on the 'intent-to-treat' (ITT) population, i.e. all the patients admitted to the study, and on the 'per-protocol' (PP) population, i.e. the patients who completed the trial following the study protocol.

Safety of the treatment. Systemic safety was assessed by routine hematological and hematochemical laboratory tests at the beginning and at the end of the study. According to the values of these parameters each patient was assigned an overall assessment of the therapy tolerance (excellent, good, moderate, scarce).

Results

In order to test the efficacy and tolerability of the sucralfate hydrophilic gel (SUC-LIS 95) on the treatment of venous ulcers, a total of 100 subjects with non-infected vascular ulcers were recruited. Patients were randomly allocated to receive either SUC-LIS 95, or placebo (PBO) gel devoid of sucralfate. The demographic data are summarized in Table I. Four subjects withdrew during the trial for reasons unrelated to the treatments and five further cases showed major protocol deviations. Fig. 1 shows the flowchart of patients included in both groups. The baseline parameters of the two groups including the initial size of the ulcer as well as the presence of inflammation, exudates and swelling, and symptoms including pain and burning are shown in Table II. The two groups were similar in respect to lesion size and other parameters, except for the presence of granulation tissue.

Results obtained after the topical administration of SUC-LIS 95 or PBO are reported in Table III and Fig. 2A and B. A significant improvement was obtained in the group treated with SUC-LIS 95 vs. PBO with respect to local tissue inflammation and exudates, as well as pain and burning.

Table I. Demographic characteristics of the patients receiving SUC-LIS 95 or placebo (PBO).

	SUC-LIS 95	PBO	P
Sex			
Males[a]	23	26	ns
Females[a]	27	24	
Age[b]	64.918±12.076	67.680±6.5479	ns
Ulcer type			
Post-phlebitis	44	49	0.05
Venous stasis	6	1	

[a]number of patients; [b]average years ± SD. ns, not significant.

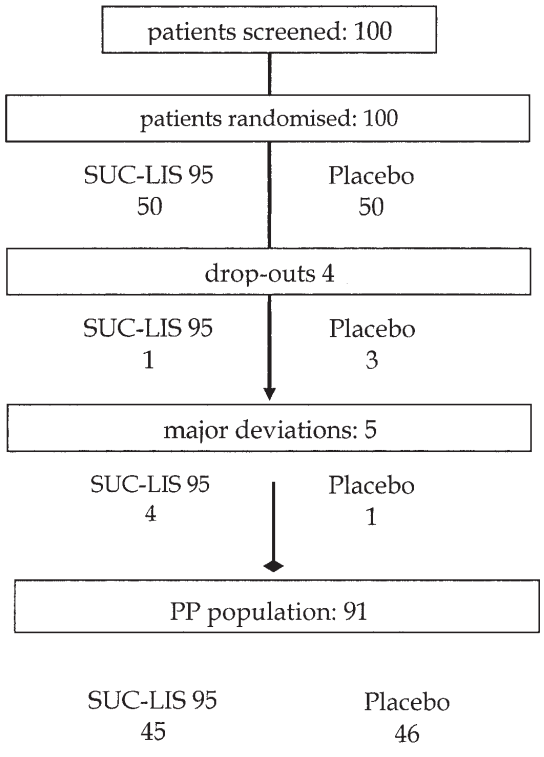


Figure 1. Flowchart of patients enrolled in the study. Patients selected for the trial were randomized into two groups of 50 cases each. Patients with venous stasis or post-phlebitis ulcers were included in the protocol. Four patients did not finish the treatment for unknown reason that were unrelated to toxicity of the drug. PP, per-protocol.

Furthermore, highly significant differences in favor of SUC-LIS 95 gel were observed at all assessment times in the evolution of ulcer size (Fig. 2A) and of the granulation tissue (Fig. 2B).

The healing rate was dramatically different in the two groups. Forty-three out of the 45 (95.6%) SUC-LIS 95 patients healed during the 90-day study period, against only 5 out of 46 (10.9%) of the PBO patients that healed in total (Fig. 3A).

Table II. Baseline parameters of the patients receiving SUC-LIS 95 or PBO (n=50 per group).

	SUC-LIS 95 Mean ± SD	PBO Mean ± SD	P
Inflammation	1.2800±0.4965	1.2600±0.4870	ns
Exudates	0.9800±0.4734	0.9800±0.2466	ns
Swelling	0.9000±0.5051	0.9800±0.3774	ns
Pain	1.0600±0.7669	0.9600±0.6376	ns
Burning	0.7800±0.7637	0.6600±0.6581	ns
Lesion size	6.6250±8.9240	4.6900±9.0840	ns
Granulation tissue	0.3200±0.5127	0.0800±0.2740	0.0045

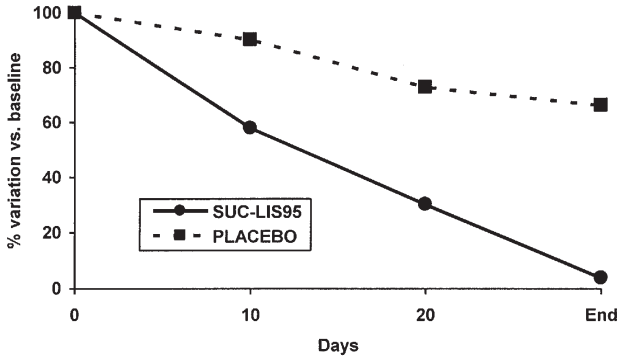
Baseline assessments were done before randomization. ns, not significant.

Table III. Effect of the topical treatment with sucralfate on ulcer status.

	SUC-LIS 95 Mean ± SD (n)	PBO Mean ± SD (n)	P
Inflammation			
Baseline	1.2667±0.4954 (45)	1.2609±0.4915 (46)	ns[a]
End treatment	0.1538±0.3655 (39)	0.7556±0.4346 (45)	<0.00001
Exudates			
Baseline	0.9778±0.4995 (45)	0.9783±0.2573 (46)	ns[a]
End treatment	0.1026±0.5024 (39)	0.2667±0.4472 (45)	0.0102
Swelling			
Baseline	0.8889±0.4872 (45)	0.9565±0.3625 (46)	ns[a]
End treatment	0.0256±0.1601 (39)	0.2220±0.1491 (45)	ns[a]
Pain			
Baseline	1.0667±0.8090 (45)	0.9348±0.6464 (46)	ns[a]
End treatment	0.2821±0.5104 (39)	0.6000±0.4954 (45)	0.0023
Burning			
Baseline	0.7778±0.7946 (45)	0.6087±0.6490 (46)	ns[a]
End treatment	0.1282±0.3387 (39)	0.3111±0.4682 (45)	0.0463

[a]ns, not significant; analyses were done on the 'pre-protocol' (PP) population, i.e., the patients who completed the trial following the study protocol.

A



B

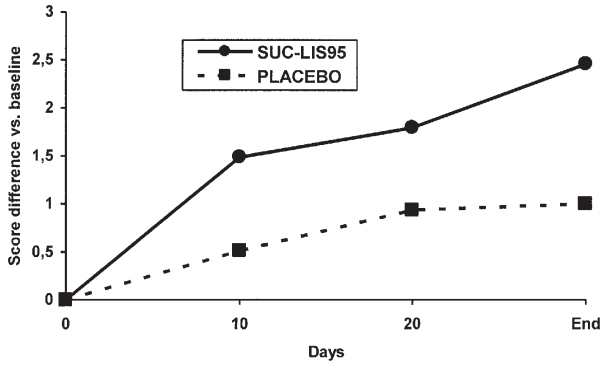


Figure 2. Variation of ulcer size and granulation tissue after topical treatment with SUC-LIS 95. (A) Variation of the ulcer size is represented as percent of the baseline values. (B) Score of the granulation tissue after treatment vs. the baseline value.

On the whole, the efficacy of treatment was judged to be good/excellent in 42 out of the 45 (93.3%) SUC-LIS 95 patients, against only 4 out of the 46 (8.7%) PBO patients (Fig. 3B). These differences were significant between the two differentially treated groups (χ^2=68.89, p<0.00001). A representative example of the healing is shown in Fig. 3C.

No local or systemic unwanted effects were recorded with SUC-LIS 95 at any time during the study.

The morphological study on bioptic specimens taken from the lesions of four patients from each group showed a good re-epithelialization process in 100% of the patients treated with SUC-LIS 95, in comparison with 25% of PBO cases (Table IV, Fig. 4). Fig. 4 shows the representative features of an ulcer treated with SUC-LIS 95 compared with a PBO-treated ulcer: a well organized stratified epithelium and many neoangiogenetic vessels in the connective tissue were present in the SUC-LIS 95 group while re-epithelialization is completely absent in the PBO group. No noticeable areas of necrosis could be detected after treatment with SUC-LIS 95 compared to the PBO group (Table IV, Fig. 4). Ultrastructural analysis of the wound area of patients treated with SUC-LIS 95, showed the presence of a well organized epithelium composed of healthy epithelial cells as indicated by the presence of abundant cytokeratin filaments and well structured epithelial junctions (Fig. 5D). No evident areas of necrosis could be detected in the wound of SUC-LIS 95 compared to the PBO group (Fig. 5A-F). Furthermore, the stratified epithelium from wound areas treated with SUC-LIS 95 was connected with the interstitium by a well arranged basement membrane (Fig. 5D). It is noteworthy that within the stroma of the SUC-LIS 95 group, an incipient neoangiogenesis (100% SUC-LIS 95 vs. 25% PBO) took place, as demonstrated by the abundant presence of an intense network of vasa, mostly deficient of basement membrane (Fig. 5E). Besides, the presence in the stroma of activated myofibroblasts (100 vs. 25%), characterized by abundant cytoskeletal components and rough endoplasmic reticulum, was specific to the wound area of topically treated SUC-LIS 95 ulcers (Fig. 5F, Table IV). Improved stroma organization, characterized by the occurrence of well organized banded type I and III collagens, and amelioration of the inflammation status were also observed in the SUC-LIS 95 group compared to the PBO group (Fig. 5B and F, Table IV).

Table IV. Ultrastructural findings on wound area after topical treatment with sucralfate or placebo gels.

Parameters	Baseline	End treatment	
		PBO	SUC-LIS 95
Necrosis	8/8 (100%)	4/4 (100%)	0/4 (0%)
Inflammatory infiltrate	8/8 (100%)	4/4 (100%)	2/4 (50%)
Neoangiogenesis	1/8 (12%)	1/4 (25%)	4/4 (100%)
Organization of the extracellular matrix	0/8 (0%)	1/4 (25%)	4/4 (100%)
Myofibroblasts	0/8 (0%)	1/4 (25%)	4/4 (100%)
Re-epithelialization	1/8 (12%)	1/4 (25%)	4/4 (100%)

Discussion

The care of venous ulcers often relies on palliative and often unsuccessful therapies (2). It is clear that wound healing is dependent on angiogenesis, cell proliferation, extracellular matrix remodeling, tissue inflammation and good re-epithelialization (6-9). Thus the ideal drug for the treatment of venous ulcers should possess properties that improve all these biological parameters. Sucralfate is a basic aluminium complex of sucrose sulfate, structurally related to heparin but without anticoagulant activity. Although structurally related to sucrose, sucralfate is not utilized as a sugar *in vivo* in humans. One of the oldest materials to be used in wound management is honey, the use of which was described by the Egyptians as early as 1600 BC. In recent years there has been an increasing interest in the use of sucrose as a wound dressing. Sugar, either in the form of granulated sugar or pastes composed of caster and icing sugar has been used successfully in the treatment of a variety of wounds, including bedsores and diabetic ulcers (31,32). Recent studies have

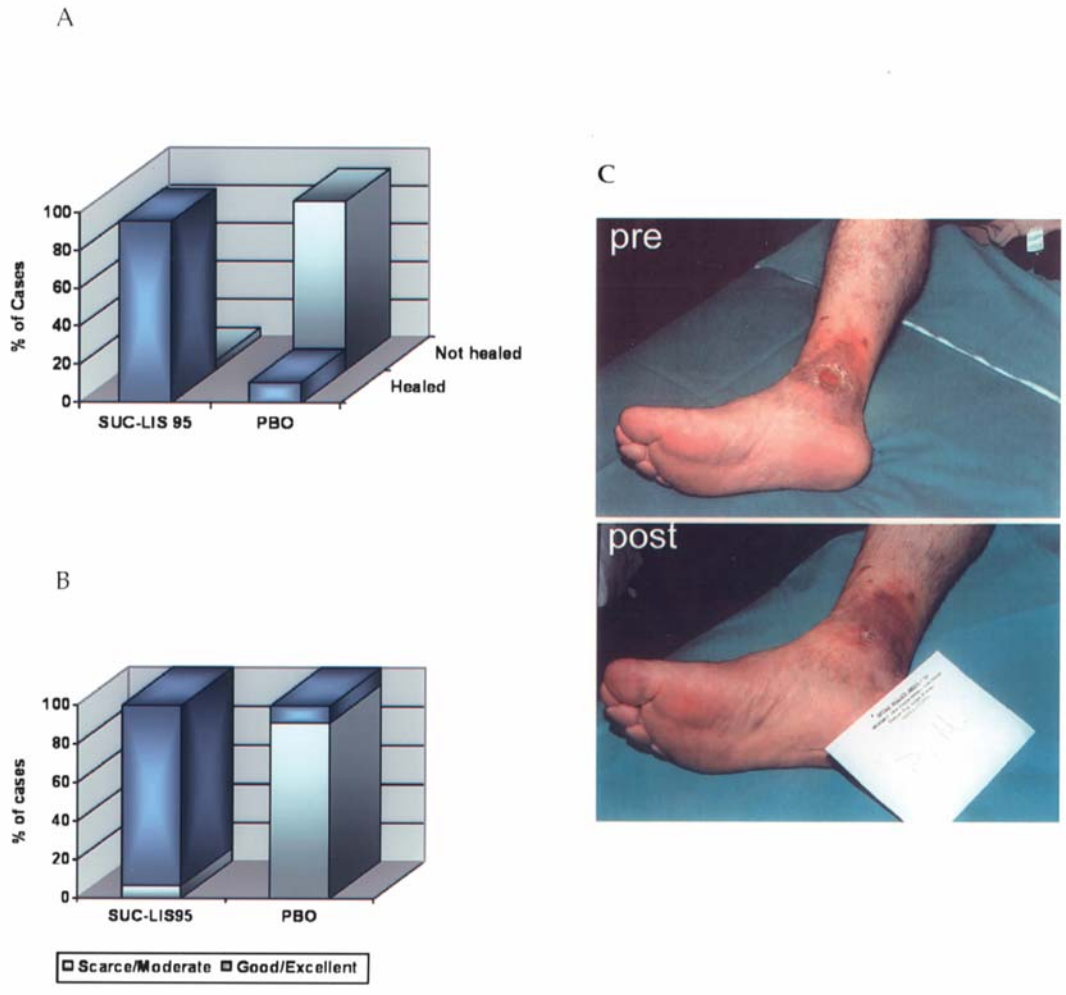


Figure 3. (A) Effect of SUC-LIS 95 treatment on the healing rate of patients. Bars represent the percentage of patients of each group healed (dark blue) or not healed (light blue) at the end of the trial. χ^2=65.45, $p<10^{-5}$. (B) Distribution of the clinical assessment of efficacy. Bars represent the percentage of patients with scarce/moderate and good/excellent clinical ratings. (C) Wound healing of a representative patient before and after topical SUC-LIS 95 treatment.

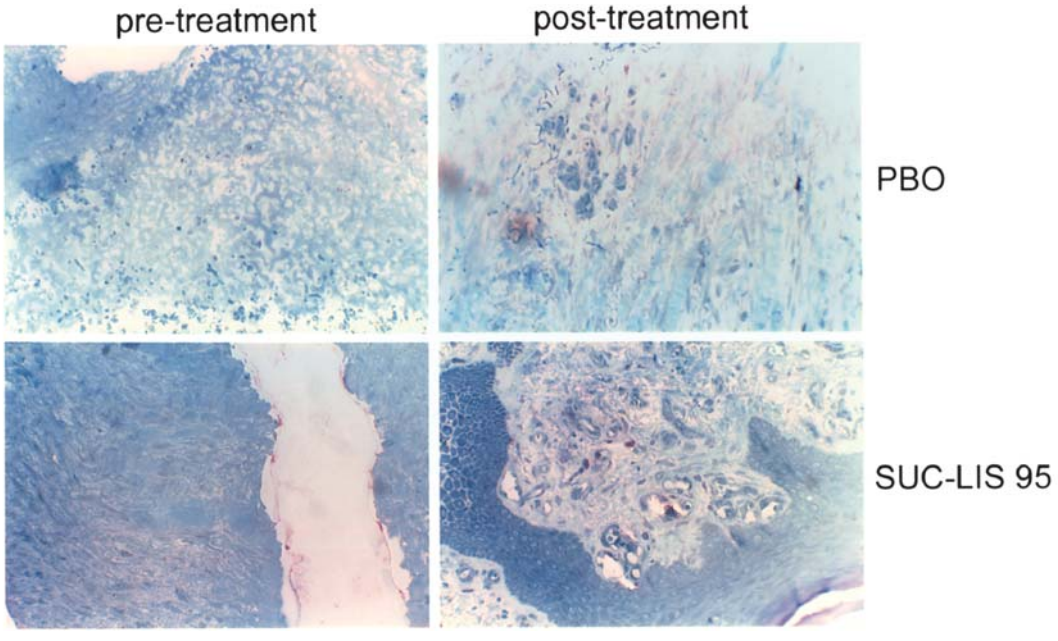


Figure 4. Morphological analysis of two representative patients after topical treatment with placebo or SUC-LIS 95. Histological observation of specimens from patients before and after treatment with PBO, and before and after treatment with SUC-LIS 95. A complete re-epithelialization is visible in SUC-LIS 95-treated patient. Toluidine blue staining, original magnification x200.

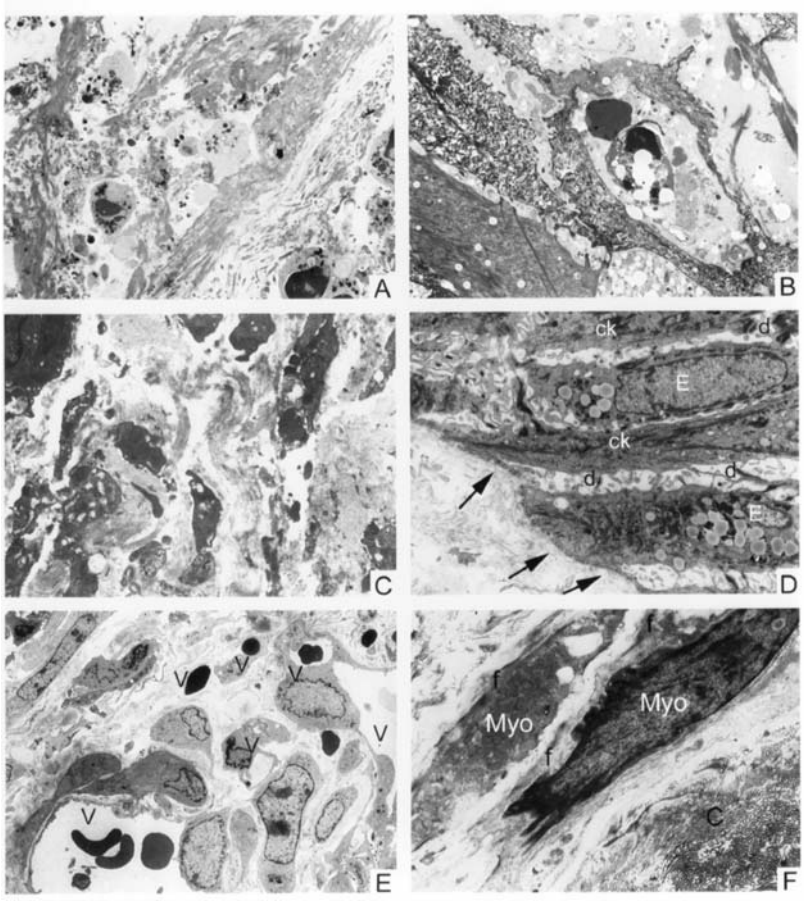


Figure 5. Ultrastructural analysis of tissue samples from patients before and after topical SUC-LIS 95 (C-F) and PBO (A and B) treatments. Presence of tissutal disorganization and necrosis before (A) and after (B) treatment with PBO. Ultrastructural observation of patients ulcer before (C) and after (D, E and F) treatment with SUC-LIS 95. (C) Tissutal disorganization and necrosis before treatment. (D) The presence of a well organized stratified epithelium characterized by epithelial cells rich in cytokeratin filaments (ck), jointed by well organized desmosomes (d), with a well defined basal membrane (arrows) is evident in SUC-LIS 95-treated ulcer patients. Presence in the stroma of SUC-LIS 95-treated ulcer patients of a conspicous neoangiogenesis, characterized by many small vessels (v) (E), and of numerous myofibroblasts (Myo), characterized by the presence of cytoplasmatic filaments (f) (F). Original magnifications: A and B, x2450; C, x1950; D, x2900; E, x2100; F, x4900.

shown the stimulating effect of sucralfate on EGF expression and on the expression of other factors involved in tissue repair processes (18). Furthermore, the stimulating effects of sucralfate on the vascular factors, including angiogenesis, which play important roles in tissue repair, have been demonstrated (16,17). The sporadic studies and case reports available in the literature were all coherent indicating the favorable effect of topical sucralfate in wound repair and in skin protection. Topical sucralfate has been successfully studied in peristomal and perineal dermatoses, in moist desquamation during radiotherapy, in erosion and ulceration of the perineal area, in vaginal ulceration, in dystrophic epidermolysis bullosa, in second and third degree burns, and in a pilot trial with non-healing, full-thickness venous stasis ulcers refractory to 8 weeks of conventional therapy (19-27). The main objective of this study was to determine the effectiveness, safety and tolerability of the local treatment of chronic wounds with a sucralfate gel (SUC-LIS 95). Our results indicated that the daily application of SUC-LIS 95 to non-infected post-phlebitis/vascular ulcers, for a median period of 42.0 days (range 19-86 days), led to complete healing in 95.6% of patients (43 out of 45), against only 10.9% of cases with matched placebo. A pilot study using sucralfate to treat 10 patients with chronic venous stasis ulcers was previously undertaken (27). Our study extends the observations to a larger group of patients. Furthermore, our findings were corroborated both by clinical evidence and by the morphological analysis of the biopsies drawn from selected patients. It has been previously suggested that sucralfate can bind basic fibroblast growth factor, thus protecting its degradation and allowing it to act as an angiogenetic molecule (33). Furthermore, sucralfate is able to stimulate the synthesis and release of epidermal growth factor which in turn stimulates healing and affects prostaglandin synthesis (18). It has also been indicated that sucralfate induces the proliferation of dermal fibroblasts and keratinocytes *in vitro*, and inhibits the release of interleukin-2 and interferon-γ from damaged skin cells (34) In this respect we demonstrated by ultrastructural analysis, that the topical use of SUC-LIS 95 was able to affect neoangiogenesis, increase wound contraction and re-epithelialization of the wound area, and diminish the inflammatory reaction. Overall, our results indicate that patients with chronic venous ulcers can benefit from the use of topical sucralfate.

References

1. Valencia IC, Falabella A, Kirsner R and Eaglstein WH: Chronic venous insufficiency and venous leg ulceration. J Am Acad Dermatol 44: 401-421, 2001.
2. Mekkes JR, Loots MAM, Van Der Wal AC and Bos JD: Causes, investigation and treatment of leg ulceration. Br J Dermatol 148: 388-401, 2003.
3. Choucair MM and Fivenson DP: Leg ulcer diagnosis and treatment. Dermatol Clin 19: 659-678, 2001.
4. Palfreyman S, King B and Walsh B: A review of the treatment for venous leg ulcers. Br J Nurs 16: S6-S14, 2007.
5. Bello YM and Phillips TJ: Management of venous ulcers. J Cutan Med Surg 3 (Supp 1): 6-12, 1998.
6. Eming SA, Krieg T and Davidson JM: Inflammation in wound repair: molecular and cellular mechanisms. J Invest Dermatol 127: 514-525, 2007.
7. Werner S and Grose R: Regulation of wound healing by growth factors and cytokines. Physiol Rev 83: 835-870, 2003.
8. Roy H, Bhardwaj S and Yla-Herttuala S: Biology of vascular endothelial growth factors. FEBS Lett 580: 2879-2887, 2006.
9. Neal MS: Angiogenesis: is it the key to controlling the healing process? J Wound Care 10: 281-287, 2001.
10. Bianchi L, Ginebri A, Hagman JH, Francesconi F, Carboni I and Chime S: Local treatment of chronic cutaneous leg ulcers with recombinant human granulocyte-macrophage colony-stimulating factor. J Eur Dermatol Venereol 16: 595-598, 2002.
11. Marques Da Costa R, Jesus FM, Aniceto C and Mendes M: Double blind randomized placebo-controlled trial of the use of granulocyte-macrophage colony-stimulating factor in chronic leg ulcers. Am J Surg 173: 165-168, 1997.
12. Marques Da Costa R, Jesus FM, Aniceto C and Mendes M: Double blind randomized dose-ranging of granulocyte-macrophage colony-stimulating factor in patients with chronic venous leg ulcers. Wound Rep Reg 7: 17-25, 1999.
13. McCarthy DM: Sucralfate. N Engl J Med 325: 1017-1025, 1991.
14. Sweetman SC (ed): Sucralfate. In: Martindale: The Complete Drug Reference. 33rd edition, The Pharmaceutical Press, London, pp1250-1251, 2002.
15. Rattan J, Schneider M, Arber N, Gorsky M and Dayan D: Sucralfate suspension as a treatment of recurrent aphthous stomatitis. J Intern Med 236: 341-343, 1994.
16. Folkmann J, Szabo S and Stovroff M: Duodenal ulcer: discovery of a new mechanism and development of angiogenic therapy that accelerates healing. Ann Surg 214: 414-426, 1991.
17. Szabo S, Vattay P, Scarbrough E and Folkman J: Role of vascular factors, including angiogenesis, in the mechanisms of action of sucralfate. Am J Med 91: 158-160, 1991.
18. Konturek SJ, Konturek JE, Brzozowski T, *et al*: Effect of sucralfate on growth factor availability. In: Sucralfate: From Basic Science to the Bedside. Hollander D and Tytgat GNJ (eds). Plenum Medical Book Co., New York, pp175-189, 1993.
19. Hayashi AH, Lau HY and Gillis DA: Topical sucralfate: effective therapy for the management of resistant peristomal and perineal excoriation. J Pediatr Surg 26: 1279-1281, 1991.
20. Lyon CC, Stapleton M, Smith AJ, Griffiths CE and Beck MH: Topical sucralfate in the management of peristomal skin disease: an open study. Clin Exp Dermatol 25: 584-588, 2000.
21. Delaney G, Fisher R, Hook C and Barton M: Sucralfate cream in the management of moist desquamation during radiotherapy. Australas Radiol 41: 270-275, 1997.
22. Maiche A, Isokangas OP and Grohn P: Skin protection by sucralfate cream during electron beam therapy. Acta Oncol 33: 201-203, 1994.
23. Markham T, Kennedy F and Collins P: Topical sucralfate for erosive irritant diaper dermatitis. Arch Dermatol 136: 1199-1200, 2000.
24. Lentz SS, Barrett RJ and Homesley HD: Topical sucralfate in the treatment of vaginal ulceration. Obstet Gynecol 81: 869-871, 1993.
25. Marini I and Vecchiet F: Sucralfate: a help during oral management in patients with epidermolysis bullosa. J Periodontol 72: 691-695, 2001.
26. Banati A, Chowdhury SR and Mazumder S: Topical use of Sucralfate Cream in second and third degree burns. Burns 27: 465-469, 2001.
27. Tsakayannis D, Li WW, Razvi S and Spirito N: Sucralfate and chronic venous stasis ulcers. Lancet 343: 424-425, 1994.
28. Masuelli L, Bei R, Sacchetti P, Scappaticci I, Francalanci P, Albonici L, Coletti A, Palumbo C, *et al*: Beta-catenin accumulates in intercalated disks of hypertrophic cardiomyopathic hearts. Cardiovascular Res 60: 376-387, 2003.
29. Bei R, Mentuccia D, Trono P, Masuelli L, Cereda V, Palumbo C, Marzocchella L, *et al*: Immunity to extracellular matrix antigens is associated with ultrastructural alteration of the stroma and stratified epithelium basement membrane in the skin of Hashimotos thyroiditis patients. Int J Immunopathol Pharmacol 19: 661-674, 2006.
30. Masuelli L, Focaccetti C, Cereda V, Lista F, Vitolo D, Trono P, Gallo P, *et al*: Gene-specific inhibition of breast carcinoma in BALB-neuT mice by active immunization with rat Neu or human ErbB receptors. Int J Oncol 30: 381-392, 2007.
31. Sweetman SC (ed): Sucrose. In: Martindale: The Complete Drug Reference. 33rd edition, The Pharmaceutical Press, London, pp1380-1381, 2002.
32. Thomas S: Polysaccharide pastes, granules and beads. In: Wound Management and Dressing. The Pharmaceutical Press, London, pp64-68, 1990.
33. Volkin DB, Verticelli AM, Marfia KE, Burke CJ, Mach H and Middaugh CR: Sucralfate and soluble sucrose octasulfate bind and stabilize acidic fibroblast growth factor. Biochim Biophys Acta 1203: 18-26, 1993.
34. Burch RM and McMillan BA: Sucralfate induces proliferation of dermal fibroblasts and keratinocytes in culture and granulation tissue formation in full-thickness skin wounds. Agents Actions 34: 229-231, 1991.