Vitamin E gel reduces time of healing of digital ulcers in systemic sclerosis

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ABSTRACT

Background. *In systemic sclerosis (SSc), digital ulcers (DU) are painful, difficult to heal and frequently infected, thus greatly affecting quality of life and increasing SSc-related disability. Vitamin E has been previously used in cutaneous lesions for its antioxidant and anti-inflammatory effects.*

Objectives. *To study the healing effect of D-alpha-tocopheryl acetate (acetic ester of alpha-tocopherol) (VE) gel on DU of SSc patients.*

Methods: *27 SSc patients with a total of 86 DU were enrolled in an open pilot study. The patients were randomly assigned to two groups: 15 patients were treated until DU healing with the local standard ulcer care protocol with the application of vitamin E gel (experimental group), while 12 patients were treated with standard ulcer care protocol only (control group). In both groups, DU were treated twice a week and pain was scored by a NRS (numeric rating scale). In both groups the cost of medications was analysed.*

Results. *VE induced a faster healing of DU in respect to controls (13.22±2.72 weeks, versus 20.94±3.65; p<0.0001) with a lower number of medications (26.18±5.63 vs. 41.88±7.31; p<0.0001). Resolution of pain was faster in experimental (17.82±4,59 medications) than in controls (26.26±19.16 medications) (p=0.0022). In the experimental group, the cost of medications was significantly lower (6,919.15 euros/patient) than in the control group (11,056.32 euros/patient).*

Conclusion. *The application of VE reduces time of healing and has a faster resolution of pain, with a significant reduction of costs. Topical VE may improve the management of DU in SSc.*

Introduction

Systemic sclerosis (SSc) is characterised by progressive thickening of skin and fibrosis of internal organs, widespread microvascular damage, and production of autoantibodies (1).

In SSc, digital ulcers (DU) occur in up to 50% of patients, either with limited (lSSc) or diffuse SSc (dSSc) (2). Usually, DU are painful, difficult to heal, frequently infected and heavily affect quality of life and increase SSc-related disability (3-6).

Cutaneous fibrosis and vascular alterations (7) are the main factors involved in the genesis of SSc ulcers, while altered immune reactivity, thinning and loss of skin elasticity, and peripheral neurological damage (8) may contribute to their pathogenesis and severity.

In SSc, ulcers can arise in any part of the body, but usually they start at the extremities of the limbs, where the ischemic insult is more intense and traumas and micro-traumas are more frequent (2).

In SSc, DU may respond to prostanoids, endothelin receptor antagonists and phosphodiesterase-5 inhibitors (9) but also to topical medications (10) that are, however, often expensive and of uncertain efficacy.

Vitamin E (VE) is an ubiquitous, naturally occurring agent derived from plants. The term vitamin E includes all tocopherols and tocotrienols with the biological activity of the isomer RRR-α-tocopherol. Chemically, tocopherol is a 6-chromanol derivative that consists in a chromane ring bearing a phenolic OH group at position 6 and a branched side chain with chiral C atoms at position 2', 4' and 8'. There are four tocopherol stereoisomer (α, β, γ, δ) dependent on different substituent at the position 5 and 7 of the chromane ring.

RRR-α-tocopherol predominates in the natural VE determining its biological activity (11). The activity of VE is usually referred to D-α-tocopheryl acetate, considered today as the standard (12). VE is believed to be the most important naturally occurring non-enzymatic, lipid-soluble antioxidative agent in human tissue (13). Reactive oxygen radicals are generated in numerous physiological and pathological processes like inflammation and vascular disease (14). VE is considered the most important biological supplement of the (water-soluble) enzymatic antioxidant systems (superoxide dismutase, glutathione peroxydase and catalase) and the major membrane-linked radical scavenger in lipid environment (15).

Moreover, VE has complex interactions with the eicosanoid system resulting in an inhibition of prostaglandin synthesis and an antinflammatory effect (16). VE depresses the biosynthesis of PGE_2, probably by preventing the release of arachidonic acid by phopholipase A_2 (17), and the lipo-oxygenase function in thrombocyte and the generation of thromboxane A_2 and B_2 (18). In contrast, lipo-oxygenase function in granulocytes, and the biosynthesis of prostaciclins are enhanced by VE (18). Deficiency of VE impairs membrane stabilisation, producing lipid peroxidation and rupture of the cell membrane, with leakage of proteolytic enzymes denaturing proteins that may trigger an auto-immune response (19).

Since the 1940s, VE has been used on cutaneous lesions of the limbs (20), SSc and morphea (21)**,** discoid lupus erythematosus (22), dermatomyositis (23), Porphyria cutanea tarda (24) and vasculitides (25, 26).

The aim of our work was to evaluate the effect of topical application of D-α-tocopheryl acetate (acetic ester of alpha-tocopherol) (VE) gel on SSc DU evaluating time to healing, number and costs of medications, and reduction of DU pain.

Patients and methods

Twenty-seven SSc patients with at least one DU, attending the Division of Rheumatology of the University of Florence, were consecutively enrolled. Patients gave their written informed consent. All patients were on weekly intravenous infusions of alprostadil-α-ciclodextran (60 mcg) and proton pump inhibitors. At the moment of the study, none was on iloprost, steroids, cyclophosphamide, azathioprine, D-penicillamine, methotrexate or other disease-modifying drugs. Each patient was evaluated for disease duration (onset of the first non Raynaud's symptom), subset [diffuse SSc (dSSc) and limited SSc (lSSc)] (27) and assessed according to international guidelines (28, 29) for skin [modified Rodnan skin score (30)] and lung interstitial [forced vital capacity (FVC), diffusing lung capacity for carbon monoxide (Dlco), high resolution computed tomography (HRCT) and vascular involvement (31)].

DU-related pain was scored on a numeric rating scale (NRS 0-10: 0 ="no pain" and 10 ="worst pain"). For each DU treated, a specific chart (to assess morphological characteristics of the ulcers, schedules of the medications, local or systemic side effects) was filled during every medication.

Mann-Whitney, Kolmogorov-Smirnoff and ANOVA statistical tests were performed with SPSS-15® software. Significance was set at $p<0.05$

Vitamin E gel

The compound was prepared by two pharmacists skilled in galenic preparations. (MA and GR) with D-α-tocopheryl acetate (96.0 %) and micronized silica 4.0 %.

Medication procedure

All lesions were evaluated by the same operator (FG) and medicated by two health professionals of the "Scleroderma Ulcer Care Unit" of our Division (AL, BF).

Patients were randomly assigned to two groups: 15 patients were treated with the standard DU care protocol used in our Department for SSc DU plus the application of VE gel (experimental group, EG) and 12 patients were treated only with the standard DU care protocol (control group, CG).

Twice a week, the standard DU care protocol was applied to both groups as follows:

1) cleansing, irrigation by physiological solution with a syringe of 10 with an 18g calibre needle using the "vortex" technique.
2) disinfection, by Sodium Hypochlorite (chlorine) 5% left to interact for few seconds, followed by immediate rinsing with physiologic solution;
3) curettage with scalpel, if an eschar was present;
4) application of VE gel on the lesion, in experimental group only;
5) application of "hydrogel" tube and/or gauze and covering with a paraffin gauze;
6) closing of the medication.

Costs of medications

The cost of a session of medication was quantified at the cost, assessed by the regional health committee for treatment (including human labour, all the throw-away or re-usable materials and devices), of 264 euros.

The cost of a 40 gr tube of VE gel was quantified at 10.30 euros and the cost of each single application of 0.4 gr, needed to treat an ulcer, was quantified at 0.103 euro/ulcer/medication.

The cost of medications were evaluated as follow:

Control group: (cost of a session of medications x mean number of medications needed for healing).

Experimental group: {[cost of a session of medications + (cost of a single application of VE gel x mean number of ulcers/patient)] x mean number of medications needed for healing}

Results

Patients were classified in 19 limited (lSSc) (70.4%) and 8 diffuse SSc (dSSc) (26.9%) equally distributed in both groups (EG: 10 lSSc (66.67%) and 5 dSSc (33.33%); CG: 9 lSSc (75%) and 3 in dSSc (25%)]. Clinical and laboratory features of SSc patients are presented in Table I. The patients of the 2 groups were not different, at baseline, in any characteristics.

The total number of DU was 86, at *intermediate* (89.65%) or *deep stage* (10.35%) as described, at international level, for pressure ulcers (32).

The mean number of DU per patient was 3.46±2.35 in the experimental group

Table I. Clinical features of SSc patients.

		SSc patients	Experimental group (EG)	Control group (GC)	*p* (EG v*s*.CG)
Age (years)		52.67 ±11.70	52.00 ± 11.66	48.50 ± 13.85	NS
Sex	F	24 (88.88%)	13 (86.66%)	11 (91.66%)	NS
	M	3 (11.12)	2 (13,34%)	1 (8.34%)	NS
SSC subset	ISSc	19 (70.4%)	9 (75%)	10 (66.67%)	NS
	dSSc	8 (29.6%)	3 (25%)	5 (33.34%)	NS
Disease duration (years)		7.33± 5.02	7.59 ± 5.0	7.17 ± 3.78	NS
Skin score		18.78± 9.17	19.47 ± 9.47	17.25 ± 10.37	NS
Capillaroscopy	Early	6 (22.22%)	3 (20.0%)	3 (25%)	NS
	Active	8 (29.62%)	4 (26.66%)	4 (33.33%)	NS
	Late	13 (48.14%)	8 (53.33%)	5 (41.66%)	NS
Autoantibodies	ANA +	27 (100%)	15 (100%)	12 (100%)	NS
	Scl-70 +	8 (39.6%)	4 (26.6%)	4 (33.33%)	NS
	ACA +	15 (55.6%)	9 (60.0%)	6 (50.0%)	NS

SSc: Systemic sclerosis; ISSC: limied SSc; dSSc: diffuse SSC; ANA: antinuclear antibodies; ACA: anticentromere antibodies; SCI-70: anti SCI70 antibodies.

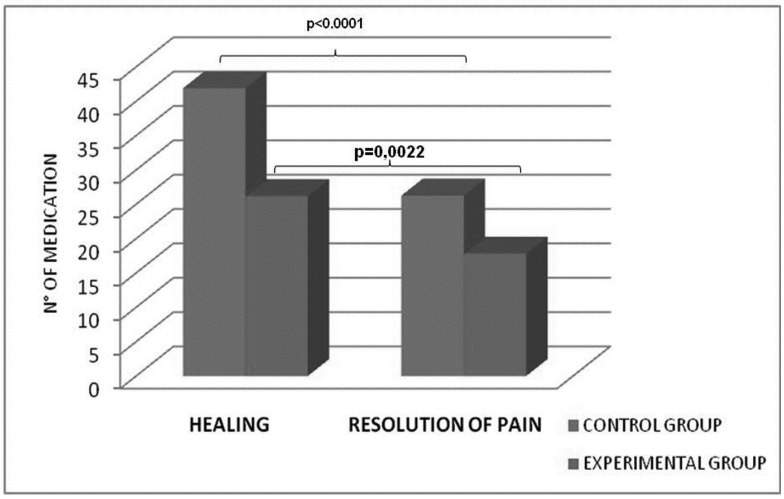

Fig. 1. Difference in the number of medications needed for healing and the number of medications needed for the resolution of pain between the experimental and control group.

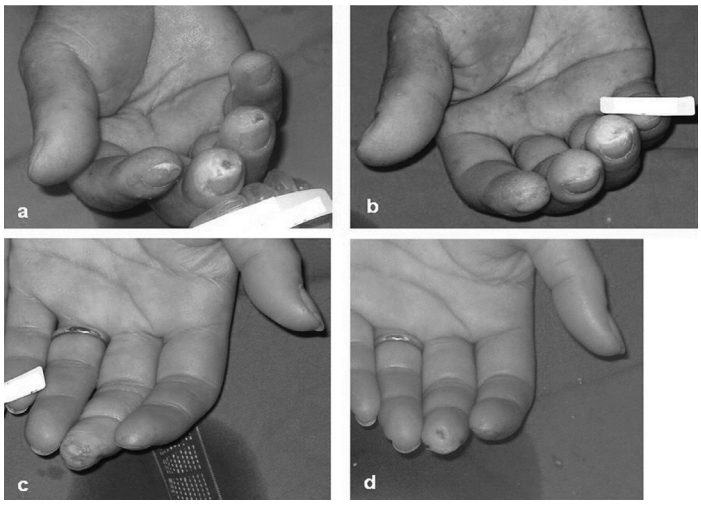

Fig. 2. Fingertip DU on the 3rd and 4th fingers before (a) and after 13 weeks (b)of topical application of VE gel. Fingertip DU on the 3rd finger before the application of VE gel (c) and after only 5 weeks (d).

versus 2.83±2.62 in controls. The mean diameter of DU is similar in both groups (1.1±0.4 in EG *vs*. 0.84±0.6 in CG) as well as the stage (*intermediate*: 90.38% in experimental *vs*. 91.42% in control; *deep*: 9.62% in experimental *vs*. 8.58% in control).

Mean time to healing of DU treated with VE gel was 13.22±2.72 weeks *vs*. 20.94±3.65 weeks of the control group ($p<0.0001$). This result was achieved with a significantly low number of medications (26.18±5.63 *vs*. 41.88±7.31 medications in controls) ($p<0.0001$).

Finally, VE application combined with the standard ulcer care protocol led to a faster resolution of pain ("0" in NRS) after 17.82±4.59 medications *vs*. 26.26±19.16 medications of the control group ($p=0.0022$) (Fig. 1). This result led also to a significant reduction of the costs of medications: 6,919.15 euro/patient in experimental group versus 11,056.32 euro/patient in controls ($p<0.0001$).

Discussion

This is the first study assessing the efficacy of topical VE on DU in SSc and the data obtained clearly show that the application of VE gel leads to a fast resolution of the DU-related pain and achieves healing in almost half time in respect to the standard topical treatment.

VE increases the expression of cytosolic phospholipase A2 and cyclooxygenase increasing, in a dose-dependent mode, the release of prostacyclin (produced by cyclooxygenase), a potent vasodilator that inhibits platelet aggregation, adhesion and degranulation. Due to its antioxidant, antiaggregant and slightly vasodilatating capabilities, VE may both reduce the ischemic damage of reperfusion and stimulate the growth and stabilisation of the granulation tissue, as well as reepithelization. In anecdotic case reports, VE has been of benefit in recovering SSc-related cardiomyopathy (33) and in favouring a successful pregnancy of a SSc patient after repeated spontaneous abortions (34). However, in 2 short duration double blind trials, oral VE supplementation did not result in clinical benefit in SSc patients (35, 36). In a 10-week placebo-controlled double-blind crossover study, the combination of micronutrient antioxidants

(selenium, beta-carotene, vitamin C, vitamin E and methionine) with allopurinol in patients with lSSc did not show any effect on von Willebrand factor levels, on rewarming curve at thermography, and on Raynaud's phenomenon (34). In a double blind randomized controlled 3-month trial, vitamin E (500 and 1000 mg/day) neither decreased the basal rate of lipid peroxidation (evaluated by urinary F2-isoprostanes) nor improved microvascular perfusion following cold exposure (35).

It is also interesting to note that the standard topical care treatment of digital ulcers was able to heal DU and to resolve pain, but with a longer time and with a significant higher number of medications. The reduction of medications and the abatement of medical and nursing activities have led to a significant lowering of costs needed to heal DUs. In addition, a faster control of pain might have a positive impact not only on direct costs of specialist care, but also on indirect costs related to the absence from work and also the consumption of NSAIDs and painkillers. Finally, this study has highlighted the importance of implementing a protocol of care, comprehensive of topical and systemic treatments, which may act synergistically to achieve a rapid healing of digital ulcers, and thus improving the quality of life of scleroderma patients.

For this reason, VE application could be an added value to the topical care of DU which may shorten the time to healing, reduce pain and the number of medications and, overall, of the medication costs. Further studies are needed to determine in RCTs the long term efficacy of VE application.

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