Procedural pain management in the treatment of scleroderma digital ulcers

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Abstract

Objective

Digital ulcers (DU) may develop in half of systemic sclerosis (SSc) patients; they are often resistant to treatments. Deep wound debridement is crucial for DU healing, but very difficult to carry out without adequate procedural pain management. Here, we report the results of our experience on procedural pain management in scleroderma DU.

Methods

The study included 51 DU observed in 32 consecutive SSc patients; procedural pain was treated following a definite schedule: local lidocaine and prilocaine (25 mg of either agent per gram of cream, EMLA 5%) were initially used in all cases, followed by local and oral morphine, according to the severity of pain scored on a 10 cm visual analogue scale (VAS).

Results

At baseline, higher pain VAS was recorded in more severe (p=0.0001) and/or infected DU (p=0.0001). Good compliance to DU debridement was observed in patients with mild pain (VAS ≤4) treated with only EMLA, and in 5 cases with moderate-severe pain (VAS >4) at baseline. While, the majority of DU with moderate-severe pain (34/39) needed a combined therapy with EMLA and local morphine (8/34) or with EMLA, local and oral morphine (26/34). On the whole, pain management during DU debridement required only EMLA application in 33% of cases, EMLA plus local morphine in 16%, while combined EMLA, local and oral morphine were necessary in 51%, generally with more severe and/or infected lesions.

Conclusion

The present study showed valuable control of procedural pain during DU debridement with sequential, combined analgesic treatment.

Key words

scleroderma, systemic sclerosis, digital ulcers, procedural pain, debridement, analgesics

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Introduction

Systemic sclerosis (SSc; scleroderma) is a connective tissue disease characterised by cutaneous and visceral fibrosis and widespread vascular manifestations (1). These latter appear very early in the course of the disease; in particular, typical digital ulcers (DU) represent one of the most frequent and burdensome clinical manifestations in more than 50% of patients. DU are often persistent and recurrent; they may involve many fingers contemporary, inducing severe pain and function limitations (2). The healing of the lesions may lead to scarring and/or digital resorption; most seriously, infected ulcers can be complicated by osteomyelitis and/or gangrene needing amputation (1-6). Although these clinical manifestations occur very frequently, at the moment no validated guidelines for the treatment of skin ulcers are available. Our experience on this topic suggests that a global approach including both systemic and local treatment is always required, including appropriate analgesic therapy. Since DU are extremely painful, patients with skin wounds almost invariably need analgesic treatment for long-lasting, chronic pain, usually defined as background pain, as well as procedural pain management caused by local wound treatment. In the clinical practice, dressing removal is considered to be the time of greatest perceived pain (7). Even in the scleroderma DU local treatment such as removal and replacing dressing and bandages often cause pain. In particular, extensive and in depth debridement of slough and necrotic tissue is an extremely painful procedure (7-8); as a consequence, the patients often ask clinicians to stop local treatment before the debridement is complete because they are unable to tolerate the resulting pain.

Here, we report our recent experience with combined analgesic therapy for procedural pain during the local treatment of scleroderma DU.

Patients and methods

The study evaluated 51 DU in 32 consecutive SSc patients, 6 males and 26 females, mean age 53±14.6SD years, disease duration 10.6±5.2 SD years, 18 patients with limited and 14 with diffuse cutaneous subset), followed at our Rheumatology Unit from January to December 2012. The majority of enrolled patients satisfied the American College of Rheumatology 1980 preliminary criteria for SSc classification (9). However, in all cases the diagnosis of SSc was done by an expert rheumatologist on the basis of a wider panel of clinical, serological, and capillaroscopic parameters, as recently proposed (10). The patients' clinical data were carefully evaluated on the basis of individual clinical records, including demographic and clinico-serological findings, as well as the characteristics of DU. In the absence of validated severity scale for DU, we graded the severity of the lesions according to modified Wagner's scale (11); namely, the scoring of severity included the following parameters: width and depth of DU, presence of necrosis, infection, and/or gangrene. On these basis, DU severity ranged from score 1 for small and superficial lesions to score 5 for large ulcers with extensive gangrene.

All patients were treated with standard systemic therapies for scleroderma vasculopathy at the time of DU presentation, using one or more vasoactive drugs; namely, 32 patients underwent long-term calcium-channel blockers, prostanoids in 28, and/or anti-ET-1 in 20. After giving informed consent, each patient underwent to local therapy for DU according to the wound bed preparation model, mainly based on the extensive and in depth debridement of skin lesions (12). Local treatment sessions were carried out in day hospital; the schedule of treatment (from 1 to 3 sessions/week) was tailored on the single patient according to the severity of the DU and its possible complications, mainly local infection. Moreover, after each session, patients remained precautionary for 2 hours in day hospital, in no cases the patient's autonomy was impaired by the analgesics used during local treatment of DU.

Besides the accurate evaluation of DU characteristics (dimension, depth, presence of exudates, smell and /or other signs of infection), a clinical assessment of subjective symptoms due to local management of DU was performed

at the baseline and during the therapeutical procedures.

In particular, before the dressing procedure local pain in the area of wound and surrounding tissue, plus any new regional pain that may have developed were recorded, including events responsible for increased or reduced pain. The intensity of pain was rated before, during, and after the intervention according to standardised timing; namely at baseline, after 30 minutes of first analgesic application, when necessary after 15 minutes of the second application, and at the end of the debridement procedure (Fig. 1). The pain severity was scored using a 10 cm visual analogue scale (VAS), graduated from 0 ("no pain') to 10 ("worst imaginable pain"). All patients were carefully instructed about the localisation and intensity of pain with regards its different origin; therefore, their compliance in evaluating the pain VAS related to DU resulted widely reproducible. According to the previously suggested cut-off , persistent VAS scores ≤4 were regarded as the expression of tolerable discomfort, which may allow the prosecution of the local treatments, while scores >4 were considered to indicate moderate-severe pain (13-14).

Patients with moderate-severe pain were basically treated with analgesics for background pain due to skin lesions (oxycodone, from 5mg bid to 20mg bid).

The eutectic mixture of the two local anesthetic lidocaine and prilocaine (25 mg of either agent per gram of cream, EMLA 5%) was applied in all DU (13). The dose of EMLA was enough to fill the whole ulcer cavity. After 30 minutes application under occlusion with plastic transparent film (3M transparent dressing, Tegaderm), sharp debridement of DU was performed in those patients with stable pain, namely with VAS ≤4 (Fig. 1).

On the contrary, if pain VAS remained high (>4) or abnormally increased during debridement, the cleaning of the skin lesions stopped, local morphine (solution of morphine sulphate in purified water in occlusion with Tegaderm) was added, and after 15 minutes, if VAS ≤4, the debridement was started over according the wound bed preparation guidelines (12). Finally, if though topical morphine was ineffective and patients referred persistent severe pain (VAS >4), oral morphine was administered to patient (morphine sulphate 5mg sublingual, Oramorph); after 15 minutes from the sublingual morphine administration, the cleaning of the DU was carried out in those patients with a significant reduction of pain, *i.e.* VAS ≤4 (Fig. 1).

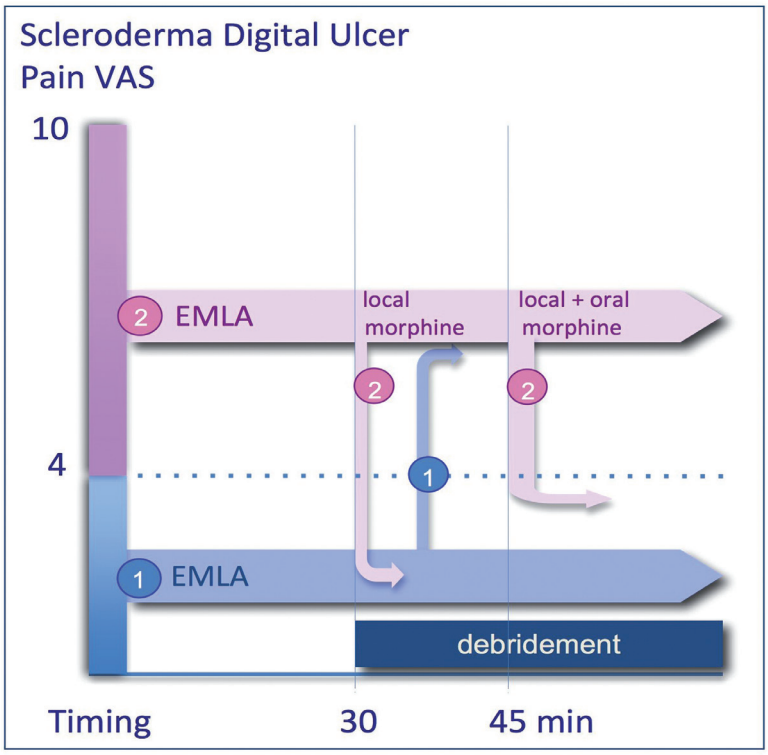

Fig. 1. The figure describes the analgesic treatment strategy during local debridement sessions of digital ulcers (DU). The pain severity was scored using a 10 cm visual analogue scale (VAS) and monitored following a standardised timing; namely at baseline, after 30, 45 and 60 minutes of first analgesic application. VAS scores >4 indicated moderate-severe pain, while scores ≤4 were classified as tolerable discomfort, allowing the prosecution of local treatments. In all cases, two local anesthetics (lidocaine and prilocaine EMLA 5% cream) were applied (see text for details). After 30 minutes a sharp debridement of DU was performed in those patients with stable, tolerable pain (VAS ≤4). When pain VAS remained persistently high (>4) or abnormally increased during debridement, the cleaning was suspended and local morphine was added; after 15 minutes the debridement was started over if pain VAS decreased <4. Finally, if even topical morphine was ineffective (VAS >4), oral morphine was administered to patient; after 15 minutes from the sublingual morphine administration, the cleaning of the DU was completed in patients with tolerable pain (VAS ≤4).

Results

Table I summarises the main clinical characteristics of the 51 SSc DU and the variations of pain VAS during local therapeutical procedures. At the baseline evaluation, medially higher values of pain VAS were recorded in infected DU (p=.0001), as well as in the presence of more severe lesions (p=.0001). According to pain VAS levels, the DU-related pain was classified as 'mild' (VAS ≤4; 12 DU) or 'moderate-severe' (VAS >4; 39 DU). Before local management, all DU were invariably treated with the application of EMLA; a good compliance during the entire session of debridement and dressing was observed in patients with DU characterised by mild pain VAS at the baseline, as well as in few cases (no. 5) with pain VAS of 5–6. While, the majority of DU with moderate-severe pain VAS (34/39) needed a combined therapy with EMLA and local morphine (8/34) or with EMLA, local and oral morphine (26/34) before the debridement. In only one case of particularly severe DU, with infection and gangrene, resistant to analgesic treatments, IV morphine was also administered during the debridement (no. 48, Table I). Pain management during DU debridement re-

Table. I. Pain management during the debridement of SSc digital ulcers (DU).

	DU		DU-related Pain VAS						
no.	Infection	Severity	Baseline	EMLA	Local morphine	Oral morphine	Local treatment duration (mo.)	Systemic treatmen drug combination	DU outcome*
1	0	2	2	0			6	CCBs	H
2	0	2	3	1			6	CCBs, P	I
3	0	2	3	1			2	CCBs	H
4	0	2	3	1			3	CCBs, P	I
5	1	3	3,5	1			7	A; CCBs	H
6	0	1	4	2			3	CCBs, P	H
7	0	2	4	2			7	CCBs, P	H
8	0	1	4	2			2	CCBs, P, B	H
9	0	1	4	1			4	CCBs, P;B	H
10	0	2	4	1,5			6	CCBs; P	H
11	0	2	4	2			4	CCBs, P; B	H
12	0	1	4	3			6	CCBs, P, B	H
13	0	1	5	1			2	CCBs, P	H
14	0	2	5	2			6	A; CCBs	H
15	0	2	5	2			2	CCBs; P	H
16	0	1	5	2			1	CCBs, P, B	H
17	0	1	6	2			2	CCBs; P; B	H
18	0	2	6	4,5	2		3	A; CCBs; P	I
19	1	3	6	6	4		4	A; CCBs; P	I
20	0	2	6	5	2		2	A; CCBs	H
21	0	1	7	5	3		2	CCBs, P; B	H
22	0	2	7	5	2		3	A, CCBs, P;B	H
23	0	2	7	5	2		8	A, CCBs, P;B	I
24	1	3	7	5	2		2	A; CCBs; B	I
25	1	3	7	5	4		1	CCBs, P;B	I
26	0	2	7	5	5	3	1	A, CCBs, P, B	H
27	0	2	7	5	5	4	5	CCBs, P; B	I
28	0	1	7	6	6	2	1	CCBs, P; B	H
29	0	2	7	5.5	5	4	1	CCBs, P; B	H
30	0	2	7	6	5	4	2	CCBs; P; B	H
31	0	2	7	5.5	5	3	1	A; CCBs; P	H
32	1	5	8	6	5	2	6	A; CCBs; P	I
33	0	2	8	6	5	4	3	CCBs; P; B	H
34	0	2	8	7	5	2	1	CCBs, A; P	H
35	1	5	8	8	8	3	3	CCBs, A; P	H
36	0	2	8	7	7	2	2	CCBs, A; P	H
37	1	3	8	7	6	2	1	CCBs, A; P	H
38	0	4	8	5	6	2	4	CCBs, P; B	I
39	0	3	8	6	4.5	3	6	CCBs, P, B	H
40	1	3	9	7	6	2	2	A, CCBs, P;B	I
41	1	3	9	8	7	2	3	A; CCBs; P	I
42	1	3	9	6	5	3	4	A; CCBs; P	I
43	1	3	9	7	7	2	3	A; P;B	H
44	1	3	9	9	8	2	1	A, CCBs, P, B	H
45	1	4	9	5.5	5	0	3	A, CCBs, P;B	I
46	0	2	9	6	5	5	3	CCBs; P; B	I
47	1	4	10	8	8	4	3	A; CCBs; P; B	I
48	1	5	10	9	8	2	6	A; CCBs; P; B	U
49	1	3	10	9	8	3	2	A; CCBs; P; B	I
50	1	5	10	9	8	2	3	A; CCBs; P; B	I
51	1	4	10	6	4.5	2	2	A; CCBs; P; B	H

VAS: 10 cm visual analogue scale at baseline and after analgesic treatments. *H: healed; I: improved (>50% of DU clinical features); U: unchanged (digit amputation); CCBs: calcium-channel blockers; P: prostanoids; B: bosentan; A: antibiotics.

quired only EMLA application in 33% of cases, EMLA plus local morphine in 16%, and EMLA plus local and oral morphine in the remaining 51%. On the whole, Table I shows the correlation between the levels of pain VAS at baseline and the therapeutical escalation of analgesic therapy during DU debridement. Combined treatment with EMLA, local and oral morphine was necessary in the presence of DU with higher pain VAS as evidenced by pain VAS variations (dark grey and light grey bars) during DU debridement'.

In all instances, the use of analgesics,

in particular local and oral morphine, revealed manageable and well tolerated; in no cases sensitisation phenomena were observed. Oxicodone administered for background pain due to skin lesions was generally well tolerated, with the exception of mild constipation. Moreover, all patients showed a good compliance for the entire treatment cycle, without relevant side effects to analgesic treatments.

The variable combinations of systemic treatments (calcium-channel blockers, prostanoids, anti-ET-1, and/or antibiotics) are reported in Table I.

During the study (12 months), the combination of systemic and local treatments leads to the improvement (reduction >50% of DU clinical features: size, depth, perilesional erythema, and signs of infection) or healing of 19 (37%) and 31 skin lesions (61%), respectively. Only one DU (2%) did not improve after 6 months of treatment, needing digit amputation for gangrene and osteomyelitis (case no. 48, Table I).

Generally, the response to treatments was correlated to the severity of the DU at baseline, as well as the duration of local treatment and the number of dressing/debridement sessions.

Discussion

The present report focuses on one of the challenging therapeutical difficulties observed in patients with scleroderma DU. To our knowledge, this is the first report on the use of combined analgesics, EMLA and morphine, for procedural pain in patients with scleroderma DU. Procedural pain represents a serious limitation to successful local treatment of these severe disease manifestations. In particular, the lesion debridement may be very difficult or totally hampered by procedural pain; indirectly, it may also promote local infections. The prolonged healing process may affect the quality of life of the patients and can lead to therapeutic failure and not rarely to digit amputation.

Our results showed a valuable control of procedural pain during DU debridement with the use of sequential, combined analgesic treatment. In particular, application of EMLA cream was enough to treat DU with mild pain VAS, while the addition of local and oral morphine was necessary to treat the more severe lesions. In our experience, EMLA represents the basic local treatment able to improve the pain severity as reported in previous studies (15-17); maximal improvement of pain relief was observed within the first 30 minutes from cream application, without any signs of sensitisation also after repeated debridement sessions (17). However, the analgesic usefulness of EMLA revealed not sufficient for an adequate debridement session in two third of cases, needing the use of morphine, more often both local and sublingual. By following the proposed schedule of different analgesic administration according to pain VAS it is possible to optimise their entire utilisation during each debridement session. On the whole, good patients' compliance was invariably observed during combined analgesic treatments.

Previous reports focusing on the assessment and management of pain at dressing changes in chronic wounds show that this is a poorly understood area of therapeutical practice. Similarly, no validated guidelines are available for the treatment of SSc-DU; they are often resistant to various systemic treatments mainly because of the presence of advanced microangiopathy. Therefore, heavy local treatment is often decisive for the overall outcome of these lesions. The removal of necrotic and devitalised tissue, slough and fibrin from the ulcer limits the risk of infections, reduces odour and promotes the growth of granulation tissue that is generally recognised to improve the healing process (18).

Even if healing represents the major purpose of treatment, the management of DU-related pain has been identified as a major issue. It may affect the overall patient's quality of life; moreover, management of procedural pain may be decisive for the final treatment outcome. A topical anesthetic drug suitable for use in skin ulcer debridement should have a documented evidence of clinical efficacy, low systemic toxicity and potential for sensitisation, and no adverse effects on healing process. Controlled studies on anesthetics/analgesics and their topical administration revealed the largely prevalent use of lidocaine/prilocaine cream, EMLA (16-17). Only this topical anesthetic shows evidence of analgesic efficacy for ulcer debridement it represents the first choice considering its commercial availability, low cost, and manageability. Given the high number of patients with debridement-related pain resistant to EMLA, the association with other analgesics is often necessary. Opioid drugs, such as morphine, remain the standard course of care in providing analgesia to patients with chronic cutaneous wounds. For years opioid analgesia was believed to originate exclusively via the activation of opioid receptors within the central nervous system. Accumulating evidence over the past decade reveals the analgesic efficacy of peripheral opioids, offering a promising new alternative in the treatment of pain (19). In addition, studies have shown that topical administration of exogenous opioids impairs wound healing by inhibiting the peripheral release of neuropeptides, thereby inhibiting neurogenic inflammation (20).

In about 50% of cases with severe procedural pain sublingual morphine revealed particularly useful and well tolerated. The introduction of combined analgesic treatment could represent the correct approach to obtain a complete adherence to local treatment, particularly the DU debridement; in several cases it revealed decisive for the final outcome of DU often resistant to systemic treatments.

The direct benefit of pain relief on wound healing rates requires further detailed studies on larger SSc series. It is indubitable that a correct approach to the single patient with DU is fundamental for the final result of our therapeutical approach; moreover, personal respect and empathy and care to individual patient is the essence of good health care, and will facilitate the overall outcome of such painful procedures.

References

1. FERRI C, VALENTINI G, COZZI F *et al*.: Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine* 2002; 81: 139-53.
2. GUILLEVEIN L, HUNSCHE E, DENTON CP *et al*.: DUO Registry Group. Functional impairment of systemic scleroderma patients with digital ulcerations: results from the Duo Registry. *Clin Exp Rheumatol* 2013; 31: 71-80.

3. FRECH TM, SHANMUGAM VK, SHAH AA *et al*.: Treatment of early diffuse sistemi sclerosis skin disease. *Clin Exp Rheumatol* 2013; 31 (Suppl. 76): 166-71.
4. XU D, LI MT, HOU Y *et al*.: Clinical characteristics of systemic sclerosis patients with digital ulcers in China. *Clin Exp Rheumatol* 2013; 31: 46-9.
5. GIUGGIOLI D, MANFREDI A, COLACI M, LUMETTI F, FERRI C: Scleroderma digital ulcers complicated by infection with fecal pathogens. *Arthritis Care Res* (Hoboken) 2012; 64: 295-7.
6. GIUGGIOLI D, MANFREDI A, COLACI M, LUMETTI F, FERRI C: Osteomyelitis complicating scleroderma digital ulcers. *Clin Rheumatol* 2013; 32: 623-7.
7. MOFFATT CJ, FRANKS PJ, HOLLINWORTH H: Understanding wound pain and trauma: an international perspective. EWMA Position Document: Pain at wound dressing changes 2002.
8. HOLLINWORTH H: Pain and wound care. Wound Care Society Educational Leaflet. Huntingdon, UK: Wound Care Society 2000
9. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23: 581-90.
10. MATUCCI-CERINIC M, ALLANORE Y, CZIRJÁK L *et al*.: The challenge of early systemic sclerosis for the EULAR Scleroderma Trial and Research group (EUSTAR) community. It is time to cut the Gordian knot and develop a prevention or rescue strategy. *Ann Rheum Dis* 2009; 68: 1377-80.
11. WAGNER FW, JR: The dysvascular foot: a system for diagnosis and treatment. *Foot Ankle*1981; 2: 64-122.
12. VANSCHEIDT W, UKAT A, HAUSS F: Systematic management of chronic wounds employing the TIME concept. International Wound Bed Preparation Advisory Board. *MMW Fortschr Med* 2005; 147 (Suppl. 3): 119-26.
13. SCHIEIR O, THOMBS BD, HUDSON M *et al*.: Prevalence, severity, and clinical correlates of pain in patients with systemic sclerosis. *Arthritis Care Res* (Hoboken) 2010; 62: 409-17.
14. PRINCIPLES OF BEST PRACTICE: Minimising pain at wound dressing-related procedures. A consensus document. London: MEP Ltd, 2004.
15. ROSENTHAL D, MURPHY F, GOTTSCHALK R, BAXTER M, LYCKA B, NEVIN K: Using a topical anaesthetic cream to reduce pain during sharp debridement of chronic leg ulcers. *J Wound Care* 2001; 10: 503-5.
16. VANSCHEIDT W, SADJADI Z, LILLIEBORG S: EMLA anaesthetic cream for sharp leg ulcer debridement: a review of the clinical evidence for analgesic efficacy and tolerability. *Eur J Dermatol* 2001; 11: 90-6.
17. LOK C, PAUL C, AMBLARD P *et al*.: EMLA cream as a topical anesthetic for the repeated mechanical debridement of venous leg ulcers: a double-blind, placebo-controlled study. *J Am Acad Dermatol* 1999; 40: 208-13.
18. VOWDEN KR, VOWDEN P: Wound debridement, Part 2: sharp techniques. *J Wound Care* 1999; 8: 291-4.
19. STEIN C: The control of pain in peripheral tissue by opioids. *N Engl J Med* 1995; 332: 1685-90.
20. WOO KY, ABBOTT LK, LIBRACH L: Evidence-based approach to manage persistent wound-related pain. *Curr Opin Support Palliat Care* 2013; 7: 86-94.