Digital Ulcers Associated with Systemic Sclerosis Successfully Treated with Botulinum Toxin A in Nine Patients

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Abstract: *Background*: Digital ulcers (DUs) associated to systemic sclerosis is a frequent complication and causes morbidity, decreased quality of life and risk of surgical interventions.

Treatment is multi disciplinary but involves sufficient wound care and medical therapies.

We here report a case series of 9 patients with systemic sclerosis with painful DUs who either did not respond sufficient on conventional therapy or had contraindications for medication due to side effects or co morbidity before surgery intervention.

Method: A combination therapy with blockade of local analgesics and following botulinum toxin A (BTA) or only BTA around the nerves and vessels in the hands and feets where the DU was present was administered in aseptic technique. The effect was rated due to the patient's report of pain on a visual analogue score and by the physician observing signs of healing and documented by photos.

Results: We only observed transient side effects but the treatment was well tolerated and with a good outcome on the healing the DUs, preventing amputations and markedly decreases in pain.

Conclusion: Though further studies are needed we suggest the treatment with a combination of local analgesics and BTA may be offered to systemic sclerosis patients with severe DUs, when conventional therapy with vasodilators are insufficient and if there is a risk of auto or doctor initiated amputation.

Keywords: Raynaud, botulinum toxin A, vasculopathy, local analgesics, connective tissue disease.

INTRODUCTION

Systemic sclerosis (SSc) is a complex multi organ disease characterized by small vessel vasculopathy and fibroblast dysfunction [1, 2]. The small vasculopathy results in digital ulcers (DUs) in 30-60 % of SSc patients and is accompanied by pain, infection and risk of tissue loss and function [3]

The aetiology of DUs is complex but it may be associated to micro traumas, sclerodactyly, dry skin and poor healing. In the study of Steen *et al*., the disability was significantly greater measured by the Scleroderma HAQ among patients with persistent DUs [1, 4].

The aim of DU treatment is to accelerate healing and to prevent auto amputation and surgical interventions including amputations due to necrosis, pain and recurrent infections.

Treatment is two sided with non-pharmacological treatment and pharmacological with calcium channel blockers, phosphodiesterase inhibitors and prostacyclin analogues and endothelin receptor antagonists [5, 6].

In the literature there are reports of beneficial effects on severe raynauds phenomenon without regard to the underlying cause when treated with injection with botulinum toxin A (BTA) [7-9]. Jenkins *et al*. reported 8 patients with severe raynaud complicated with digital ulcers, with failure of standard therapy that were treated with BTA with an increase in the temperature immediately of the hands due to improved vascularisation [7]. Fregene *et al*. treated 26 patients with intractable pain, ulcers or necrosis due to severe raynaud [8]. Treatment resulted in pain relief, improved oxygen saturation and healing of ulcers. 11out of 23 ulcers healed. Neumeister reported of 33 patients with raynaud treated successfully with BTA injection due to improved vascularisation and pain relief [9]. In the mentioned studies there were no description of the causes of severe raynaud with no severe side effects were reported in any of the studies.

BTA inhibits the release of acetylcholine from the pre synaptic membrane in the nerves [10]. This results in a chemical sympathectomy when the smooth muscle cell contraction is prevented and causes a vasodilatation with an increased perfusion which may accelerate the healing of DU.

We here report a case series of 9 SSc patients with severe ischemic DUs treated with BTA and local analgesics with convincing effect on healing and pain.

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METHODS

From January 2010 to February 2014 we identified 11 patients with disabling DUs. They were all diagnosed with SSc complicated with painful, disabling necrotic DUs, where other treatments have been either contraindicated or ineffective. We offered these patients experimental treatment with BTA before surgical amputation. Nine patients were treated, five men mean age 60 year (52-72 year) and four women mean age 62 (51-68 year). The remaining 2 patients had great widespread wounds on the feet and lower legs and the risk of complications e.g. infections was estimated to high and the experimental treatment was therefore not offered. Thus, 9 of 11 SSc patients consecutively were offered and agreed to try the experimental BTA treatment.

We used a combined blockade with local analgesics Marcaine® (bupivacaine) 2,5mg/ml, AstraZenica and Lidocaine® (lidocaine) 10 mg/ml, FarmaPlus 1:1 and Botox® (botulinum type A toxin) 100 IU diluted in 2-3 ml sterile normal saline solution.

With an aseptic technique we injected 10-15 IU BTA in accordance with the description and illustration in Fregene A *et al*. [7] by two trained physicians with years experience in blockade with local analgetics in wrists and hands and familiar with BTA injections.

Before injection ostitis and osteomyelitis and allergies to local analgesics was ruled out.

Primary endpoints of efficacy was healing of DUs and decrease of pain score (visual analogue score, VAS). The patients were evaluated clinically by two experienced physicians after 1 week and after 4 to 6 weeks after the treatment and thereafter every 3rd months routinely. The response of treatment was graduated in no response, partial response and complete response according to healing and reduction in pain VAS score. The patients were instructed to contact us without delay if they suspected complications; new DUs or an increase in the pain VAS. The patients continued already prescribed vasodilating medication and no other new medication was initiated during the experimental BTA treatment. The medication is listed in Table **1**.

RESULTS

Mean SSc disease duration was 13, 5 years. Three patients were ongoing smokers with mean 39.6 pack years and one was ex-smoker with 22 pack-years. None of the smokers discontinued smoking during the experimental BTA treatment despite our recommendation. Six patients were anti-centromere positive (the smokers were in this group) and three were Scl-70 positive (Table **1**).

We observed that 8 out of 9 patients had complete healing of DUs within 17, 3 weeks (range 4 – 52 weeks) after BTA treatment and none of the treated SSc patients had surgical amputations done. Figure **1** illustrates the clinical response of the patient marked with (#) in Table **1**. One patient (marked with (*) in

Table 1: lSSc: Limited systemic sclerosis; dSSc: Diffuse systemic sclerosis; VAS: Visual analogue scale; N: nifidipine; S: Sidenafil; T: Tadalafil; B: Bosentan; (*): Proceeded to treatment with endothelin antagonists; (#): Treatment response illustrated in Figure 1

	Male					**Female**			
	Non-smoker		**Smoker**			**Non-smoker**			**Smoker**
Age/diagnosis	**61/lSSc**	**72/dSSc**	**52/dSSc**	**59/dSSc**	**56/dSSc**	**68/lSSc**	**68/dSSc (*)**	**62/dSSc**	**51/lSSc (#)**
Pack year	-	-	36	43	40	-	-	-	22
Medication during treatments	S	N, T	N, S	N	N	N	T	S	N, T, B
Number of treatments	5	2	3	1	1	6	2	1	2
Outcome									
Time to healing (weeks) (P = partiel, C = complete)	52/C	6/C	4/C	4/C	6/C	52/C	4/P	6/C	8/C
Pain (VAS) (before/after)	9/2	8/1	8/2	9/2	5/3	9/0	9/2	8/1	9/0

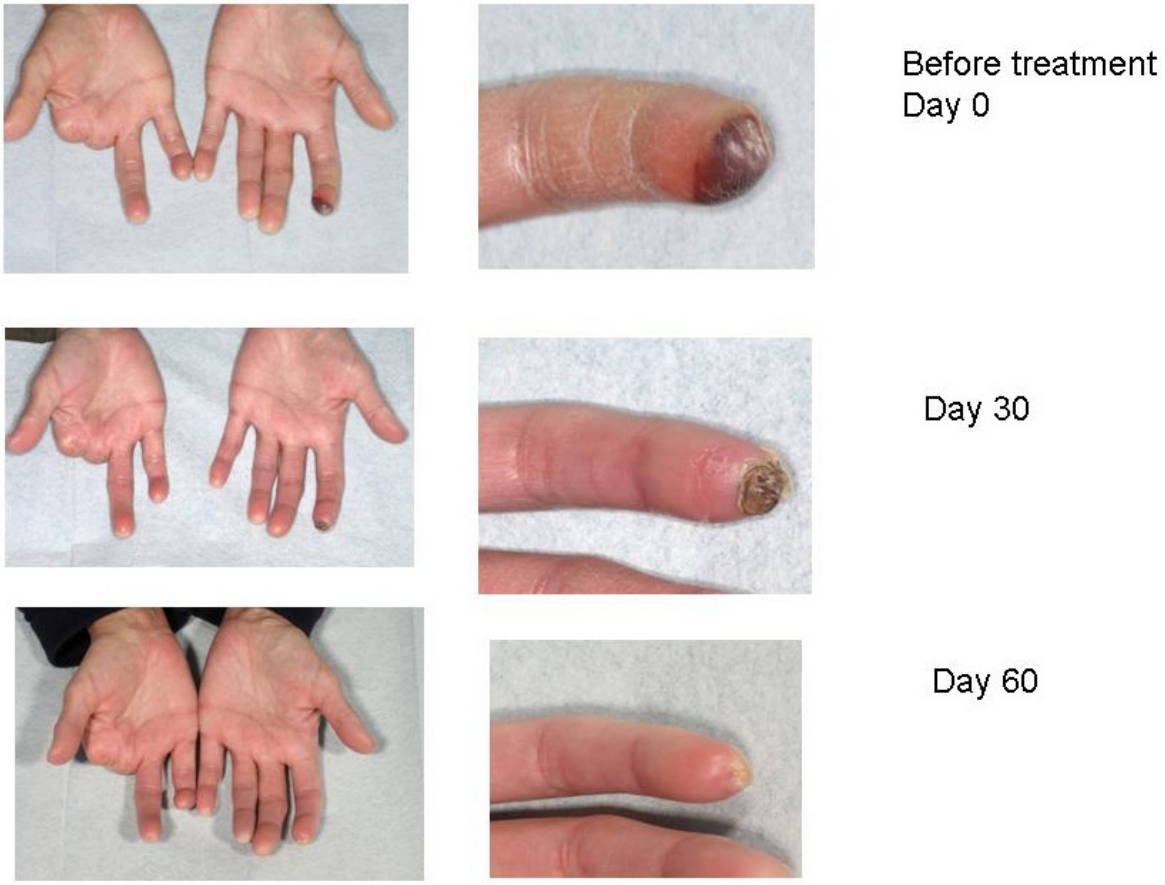

Figure 1:

Table **1** had only partial response after first BTA injection and did not respond to the 2nd BTA injection. Therefore the patient proceeded to treatment with endothelin antagonists and still suffers from DUs especially during the winter season. All patients experienced a reduction in pain VAS in average 7 (range 9 – 2) (Table **1**).

We treated 23 episodes of DUs with a total of 12 injections with BTA alone, 4 injections with local analgesics and 7 combined treatments with both local analgesics and BTA. The combination of local analgesics and BTA was offered patients with severe pain, threatening necrosis of DUs or when 2 or more DUs were present at the same time and BTA alone was primarily used as a maintenance therapy or if the patient refused local analgesics. We only observed transient side effects with pain at the injection sites no longer than 24 hours and transient weakness of the inter digital muscles.

CONCLUSION

In this highly selected case series of DU treatment among SSc patients we observed a significant effect on healing of DUs and a reduction on pain measured by consecutive VAS scores in both ischemic DUs on hands and feet. The expected effect of vasodilatation is caused by a chemical sympatectomy due to BTA combined with local analgesics. To our knowledge, this is the first time the BTA effect has been described in DUs associated to SSc, but it has earlier been described as an useful treatment in severe raynaud disease [7-9].

The BTA treatment was only initiated when other conventional treatments were ineffective, complicated with unacceptable side effects or contraindicated.

Blockade with local analgesics and BTA should be performed by physicians trained in this procedure to ensure the blockade is injected the right place in relation to vessels and nerves [10].

Due to our experience we suggest blockade with local analgesics and BTA as a primary treatment and BTA as maintenance therapy every 10-12 weeks for selected patients with ischemic DUs. We experienced no serious side effects of this treatment strategy but achieved good results.

Though further studies are needed to confirm the convincing results in highly selected patients we suggest that the treatment with a combination of local analgesics and BTA may be offered to SSc patients with severe ischemic DUs, if there is a risk of auto amputation or doctor initiated amputation is under consideration.

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