Potential therapeutic role of pharmacological sympathectomy in Martorell ulcer

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Martorell ulcer (MU) is a rare complication of arterial hypertension. It was first described in 1945 by the Spanish cardiologist Fernando Martorell, who reported 4 clinical cases [1]. A few cases of MU have been treated with pharmacological sympathectomy [2]. Here we report another small group of cases of MU treated in this manner.

Sixteen patients with MU, aged 69 to 92 years, were selected. A precise diagnosis of MU was made by checking the Martorell diagnostic inclusion criteria: anterolateral site in the lower third of the leg, diastolic hypertension in the lower third of the leg, hyperpulsation of the arteries of the leg, absence of arterial calcification and other causes of the ulcer, possible presence of symmetrical lesions and stronger pain in the horizontal position [1].

The patients had a long history of arterial hypertension that was occasionally not well controlled by medical therapy. The ulcers were extremely painful, located in the external perimalleolar distal third of the leg, often bilateral and with small satellite lesions. The patients (one male and 16 females) had a history of chronic leg ulcers. Nine had type II diabetes mellitus.

Prior to our first clinical evaluation, all patients had been treated with the classic medical therapies (antihypertensive therapy, systemic analgesics and topical conservative therapy). At the first clinical examination, all patients had one or more superficial, extremely painful ulcers on the lower limbs, characterized by central necrosis in the deep dermis surrounded by an erythematous margin more intense towards the centre.

The symptoms of each patient were scored by the visual analogue scale (VAS) at the beginning, during and at the end of observation (0 = no symptoms, 10 = severe signs/symptoms). This subjective pain scale can be used to evaluate pain attenuation and overall percentage improvement of daily activities.

At the first clinical evaluation, anti-hypertensive, topical and analgesic therapy was approved or optimized. Analgesics were oral, transdermal or intravenous non-steroid anti-inflammatory drugs (NSAIDs) and/or paracetamol for moderate pain; combined transdermal or oral opiates (buprenorphine, tramadol, morphine) for severe pain. Tolerability and compliance were assessed by direct interviews of patients.

One month after the first clinical evaluation, pharmacological sympathectomy was suggested to a group of 6 patients whose pain did not improve without heavy side effects. Sympathectomy involves spinal or intrathecal administration of local anaesthetic, an initial dose of bupivacaine hydrochloride (Marcaine 0.5%, AstraZeneca SpA), then infusion of morphine (morphine hydrochloride, Molteni SpA) starting with a minimum dose of 0.5 mg/day, using opiate conversion tables, for at least 4 days. The patients to whom this strategy was proposed were given comprehensive information regarding treatment, its consequences and possible side effects. All signed written informed consent.

Our 16 cases were patients of the General Medicine and General Surgery divisions of S. Orsola Fatebenefratelli/Poliambulanza hospital in Brescia. They sought care for severe pain and had been misdiagnosed, resulting in long periods of inadequate therapy and disability.

One month after standard topical ulcer treatment, 11/16 MU patients achieved satisfactory pain relief. The other five patients continued to have pain despite high doses of anti-inflammatory drugs and opiates. Lumbar pharmacological sympathectomy (bupivacaine and mor-

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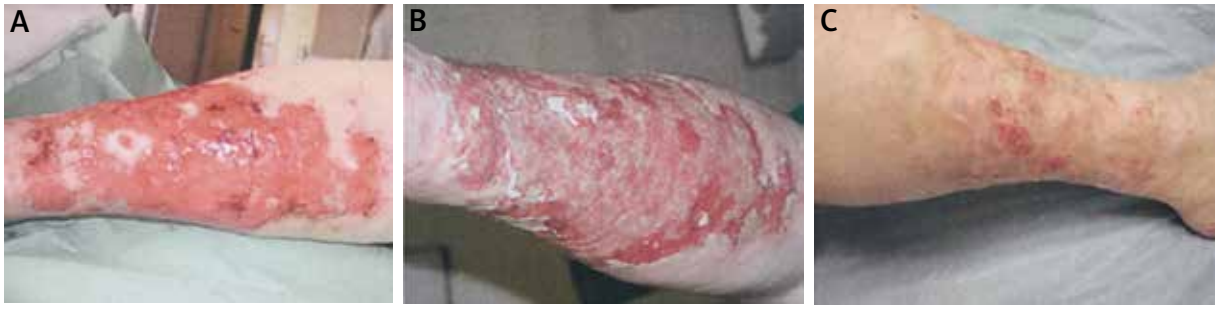

Figure 1. A 73-year-old patient treated with pharmacological sympathectomy: **A** – ulcer at the first clinical evaluation; **B** – 1 month after sympathectomy: appearance of the first areas of re-epithelialization; **C** – 2 months later, areas of re-epithelialization extend across the whole surface of the lesion

Table 1. The double table shows the healing progress of patients in the months following treatment with standard therapy or additional sympathectomy. The columns on the right show the VAS scores of subjective pain perception (0 = no symptoms, 10 = very severe symptoms). The average healing time of the two groups was significantly different ($p < 0.05$)

Patient	Gender	Follow-up [months]	Healing time [months]	Age	First VAS	VAS (after 1 month)	VAS (after 2 months)	VAS (after 6 months)	VAS (after 10 months)	Last VAS
Standard medical therapy:										
1	F	8	9	84	10	6	3	3	4	3
2	F	12	8	83	8	5	4	2	2	2
3	F	11	8	78	9	6	3	3	3	2
4	F	4	10	89	7	5	2	3	3	5
5	F	5	6	72	6	4	2	3	7	3
6	F	3	10	77	8	6	2	5	4	2
7	F	7	8	81	10	6	2	4	2	2
8	F	9	8	79	8	5	4	2	5	2
9	M	16	8	86	8	5	4	2	2	2
10	F	15	8	79	8	5	4	2	2	5
11	F	0	10	91	7	4	4	2	6	–
		Average healing time	8.45							
Sympathectomy:										
12	F	4	5	83	7	7	3	2	2	2
13	F	5	3	85	9	8	4	2	2	2
14	F	6	4	76	8	8	4	2	2	2
15	F	13	4	75	9	8	4	3	5	1
16	F	5	4	69	8	7	4	4	4	1
		Average healing time	4							

phine) was proposed as an additional treatment. This approach gave excellent pain control and healing (Figure 1). The progress of these 5 patients suggests that lumbar sympathectomy affects the underlying causes of MU. In fact, once good control of arterial blood pressure was obtained and maintained, sympathectomy patients showed faster pain resolution, faster healing, and lower average opiate and anti-inflammatory requirements. Most importantly, areas of re-epithelialization appeared only 1–2 months after sympathectomy (Figure 1). The difference with respect to the unsympathectomized group was statistically significant ($p < 0.05$).

In the other cases of MU where sympathectomy was not necessary, pain was well controlled but the ulcer re-

mained clinically unchanged for a longer period and re-epithelialization took longer to appear. The average healing time was 8.45 months in the topically-treated group compared to 4 months in the sympathectomy group (Table 1); this difference was statistically significant ($p < 0.05$).

Wound healing depends mostly on tissue perfusion by the microcirculation [3]. It is also known that the sympathetic reflex controls vasoconstriction of capillaries [4] and related activation of some specific adrenergic factors, also resulting in vasoconstriction [5]. Some previous cases of MU treated with lumbar sympathectomy [2, 6] provided better peripheral vasodilation and improved perfusion of the affected limb [7, 8]. Other studies showed that pharmacological sympathectomy can induce the same vasodilatation effects by concentration-dependent activity of anaesthetics, such as bupivacaine [9]. In an *in vivo* study, 2 weeks after lumbar sympathectomy, wound healing accelerated and dopamine β-hydroxylase and norepinephrine expression reduced, confirming local sympathetic denervation [10]. The sympathetic nervous system can also modulate inflammatory processes, suppressing increases in pro-inflammatory cytokines [11] and restoring normal immune homeostasis in rat models of inflammatory pain [12]. Patented wound-healing methods exploit bupivacaine's regenerative properties to accelerate wound healing [13].

In conclusion, our results add some other cases to previous research showing that blocking the sympathetic nerve can reduce hypertension associated with MU, restore normal blood pressure and improve tissue reperfusion and consequently wound healing. These results confirm the antalgic and healing possibilities of sympathetic block.

Conflict of interest

The authors declare no conflict of interest.

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