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The Role of Carbon Dioxide Therapy in the Treatment of Chronic Wounds

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Abstract. *A wound is defined as chronic when it does not heal according to the normal repair times and mechanisms. This particular condition may be principally due to local hypoxia. Carbon dioxide (CO_2) therapy refers to the transcutaneous or subcutaneous administration of CO_2 for therapeutical effects on both microcirculation and tissue oxygenation. In this study, we report the clinical and instrumental results of the application of CO_2 in the therapy of chronic wounds. The study included 70 patients affected by chronic ulcers. The patients were selected by aetiology and wound extension and equally divided into two homogeneous groups. In group A, CO_2 therapy was used in addition to the routine methods of treatment for such lesions (surgical and/or chemical debridement, advanced dressings according to the features of each lesion). In group B, patients were treated using routine methods alone. Both groups underwent to instrumental (laser doppler flow, measurement of $TcPO_2$), clinical and photographic evaluation. In the group that underwent subcutaneous treatment with CO_2 therapy, the results highlighted a significant increase in tissue oxygenation values, which was confirmed by greater progress of the lesions in terms of both healing and reduction of the injured area. Considering the safety, efficacy and reliability of this method, even if further studies are necessary, we believe that it is useful to include subcutaneous carbon dioxide therapy in the treatment of wounds involving hypoxia-related damage.*

The term chronic wound is used to refer to wounds that both medical and surgical treatments fail to heal according to the normal repair times and mechanisms. Such wounds typically present in patients with compromised local and systemic conditions, which contribute to inhibition of tissue repair. This definition includes non-healing post-traumatic and amputation wounds, and those associated with diabetes, peripheral arthropathies, chronic venous insufficiency and radio and chemotherapy (1). In 1962, the studies of Winter and Scales laid the foundations for the appropriate treatment of such lesions, thus prompting a more effective approach to therapy for chronic wounds (2). The study of the mechanisms behind the healing of wounds led to the production of numerous treatments that work by actively modulating the lesion environment to promote healing. The presence of tissue hypoxia in such wounds is common. Hypoxic damage inhibits healing as it decreases the proliferation of fibroblasts, the production of collagen, neoangiogenesis, re-epithelialization and the activity of leucocytes. Several methods have been proposed to increase the availability of oxygen to tissues and many authors have demonstrated that a transcutaneous partial pressure of oxygen (TcPO2) of over 30-40 mmHg is mandatory for wound healing (3-5). In clinical practice, hyperbaric oxygen therapy (HBOT) is commonly used for this purpose, although various studies have restricted its indications to the treatment of chronic wounds in tissues subjected to radiation therapy, and the prevention and/or treatment of infections caused by anaerobic bacteria (6).One of the main difficulties of HBOT is that it is not uniformly available everywhere and it can therefore be difficult for patients to reach centres where the treatment is provided. Carbon dioxide (CO_2) therapy has been used, initially in spas, since 1932. The method involves the therapeutic use of CO_2 (percutaneously or subcutaneously) to treat patients with vascular impairment. Since the late 1990s, when the Italian Ministry of Health first certified CO_2 therapy devices, the method has been available as an outpatient treatment. Clinical studies have demonstrated the efficacy of carbon dioxide therapy in improving both clinical and instrumental parameters of microcirculation without toxicity or side effects (7-10).

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Table I. *Anatomical site of lesions.*

Site of lesions	No. of cases
Proximal third of tibia	9
Middle third of tibia	27
Distal third of tibia	19
Foot	15

Table II. *Associated pathologies.*

Associated pathology	No. of cases
Peripheral arteriopathy	43
Chronic venous insufficiency	37
Type 1 diabetes	18
Type 2 diabetes	29

These studies highlighted how CO_2 therapy acts by increasing local circulation parameters and tissue perfusion, with a positive action on femoral blood flow, blood pressure of the lower limb and treadmill test parameters (11-13). A statistically significant increase in $TcPO_2$ values has also been reported in tissues treated with subcutaneous CO_2. This phenomenon is related to the increased flow induced by hypercapnia and greater local oxygen availability due to the increased release of oxygen from haemoglobin related to the reduction in pH (Bohr effect) (8).

Therefore, the possibility for a safe and feasible outpatient treatment, which has been shown to be effective in the treatment of tissue hypoxia, prompted us to verify the use of CO_2 therapy as part of a therapeutic strategy for cutaneous lesions in which the hypoxic mechanism is particularly involved.

Patients and Methods

From January 2005 to December 2007, a total cohort of 70 patients (45 men and 25 women, age: 45-75 y, average: 66 years) with chronic lower limb lesions (Table I) were enrolled in the study at the Plastic Surgery Unit of the Universitary Hospital in Siena. The cutaneous lesions, some of which were caused by trauma, had persisted for an average of 12 months (range 4-24 months) and were variably associated with diseases of the arterial trunks, chronic venous insufficiency and alterations of glucose metabolism (Table II). The general and/or local conditions of all patients initially contraindicated reconstructive procedures. The patients were selected by aetiology and wound extension and randomly divided into two homogeneous groups of 35 (A and B). Group A was treated using advanced dressings and CO_2 therapy, while group B was treated using advanced dressings alone.

All the cutaneous lesions were treated with the routine methods, involving surgical and/or chemical debridement culture analysis for targeted antibiotic therapy, and the use of dressings according to the features of each lesion (hydrogels, hydrocolliods, alginates, activated characoal). Neither vacuum therapy nor other treatments (such as growth factors), which have been shown to directly influence microcirculation, were used in any case (14-15). Ulcers were considered as healed when re-epithelialisation occurred and, in the other cases, the study was conducted (using dressings only in both groups) for a period of 60 days, at the end of which the percentage variation in the size of the lesion was measured and recorded using a transparent millimetre grid.

In group A, subcutaneous administration of CO_2 was performed, with the patient awake and without any kind of anesthesia, twice a week for six weeks, beginning on the first day of treatment (12 treatments in total), using a Carbomed CDT Evolution device produced by L.E.D. (Latina, Italy), with 30G/13 mm needles according to the following method:

Treatment of the vascular axes: the machine was set at a speed of 80 cc/min for the first 3 treatments and subsequently at 100 cc/min; programme 13 was used; the quantity of gas administered subcutaneously was 50 cc per area. In all cases the injection sites were bilateral, in the lower limbs (even when the lesion only affected one limb) at the: femoral triangle (proximal terminal perforating veins), middle third of thigh, adductor canal (lower third of the thigh), Boyd perforator; popliteal fossa and middle third of leg (Figure 1).

Treatment of the lesion: Flow was set at a speed of 30 cc/min, programme 14 was used; the quantity of gas per sector was 5 cc. Injections were made in the healthy area around the wound, at least 2 cm from the damaged skin (Figure 2). If cicatrization was achieved during treatment, CO_2 was continued therapy according to the methods described, as scheduled.

On the first day of treatment and one week after the last session (or after 60 days in the non-healed cases), the microcirculation in

Table III. *Values before and after twelve CO_2 treatments in group A patients. Comparison by Student's t-test for paired data.*

Group A	Mean	Standard deviation (SD)	Standard Error (SE)	*p*-Value
PU				
Before	11.21	6.35	1.70	$p=0.003$
After	26.09	13.08	3.49	
$TcPO_2$				
Before	21.55	10.64	2.84	$p<0.001$
After	41.18	16.70	4.46	

PU: perfusion unit; $TcPO_2$: transcutaneous oxygen tension.

Table IV. *Results.*

	Group A	Group B
Mean percentage healing (%)	71	51
Mean healing time (days)	25	37
Mean percentage reduction (%)	85	60

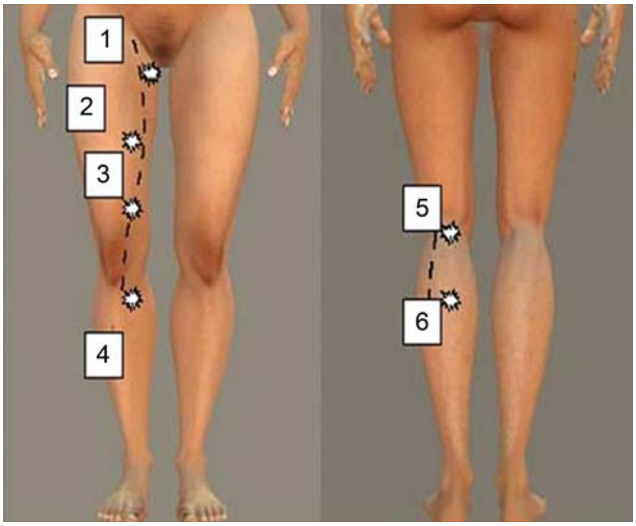

Figure 1. *Treatment at the origin of and along the main vessels. Injection sites: 1) Femoral triangle (proximal terminal perforating veins); 2) middle third of thigh; 3) adductor canal (lower third of the thigh); 4) Boyd perforator; 5) popliteal fossa; 6) middle third of leg.*

Figure 2. *Treatment at the site of the lesion. Injection sites: circumferentially, 2 cm from the area of perilesional inflammation.*

the affected limbs of all patients (groups A and B) was studied using a Doppler laser and Perimed PeriFlux System 5040 (Stockholm, Sweden) to determine $TcPO_2$. Measurements were made at baseline and 30 min after the administration of CO_2, examining patients in a supine position and at a constant environmental temperature (22˚C), for a duration of 30 min per trace. To determine the values of $TcPO_2$ (in mmHg) the probe was set at a temperature of 44˚C and calibration was performed according to the barometric pressure values. The ulcers were considered healed when full and stable (almost 30 days) re-epithelialisation was achieved with or without surgical procedures. In cases in which the lesion failed to heal, wound dressings and clinical observation were continued for a period of 60 days, after which the percentage variation in the size of the lesion was measured and recorded. Photographic documentation was acquired and the data were analyzed using a paired Student's *t*-test: a *p*-value of below 0.05 was considered statistically significant.

Results

Based on the data recorded using the PeriFlux System 5040, the analysis of the $TcPO_2$ in group A showed an increase in mean values from 21.55 mmHg to 41.18 mmHg, with $p<0.001$ (Table III), while in group B, the mean increased from 22.15 mmHg to 32.54 mmHg, not showing statistically significant p-values. Only in group A (treated with CO_2 therapy) changes in the signals observed using the Laser Doppler technique demonstrate a significant increase in the values (expressed in PU) observed after treatment. In this group, the means of the values observed before and after CO_2 treatment were 11.21 (standard error (SE)=1.70) and 26.09 (SE=3.49) respectively ($p=0.003$). This confirmed the result of a previous study in individuals without vascular problems (8) A total of 43 (61%) patients' wounds healed, 25 out of the 35 patients in group A (71%), and 18 in group B (51%), in 16 of these cases, which were evenly distributed between the two groups, reconstructive plastic surgery was performed by skin graft and/or local flaps. Mean healing time of 25 days in group A and 37 days in group B. All patients included in this study continued treatment and screening even after healing in order to stabilize the results and study local reactions of the microcirculation. In patients whose wounds had not healed at the sixtieth day (group A: 10, group B: 17), the mean percentage reduction in wound size was 85% in group A and 60% in group B (Table IV). No general or local adverse events or complications related to subcutaneous CO_2 injection occurred. When the study was finished, the cutaneous lesions which had not healed were continued to treat with the routine methods.

Discussion

It should be pointed out that a positive effect on the ability to walk of the patients treated with CO_2 was observed, as already described in previous studies (7, 11-13). Although we did not carry out specific tests for variations in the treadmill test in this study, the patients treated with CO_2 reported a greater ease in walking and a reduction of pain in the lower limbs even after the first CO_2 therapy. In our opinion, in addition to the increase of the partial pressure of oxygen, which was particularly evident in group A, the better clinical progress of these patients, in comparison to those in group B, contributed significantly to their general and local improvement.

From an analysis of the data obtained in this study, it can be affirmed that CO_2 therapy can be administrated outpatient treatment without important side-effects and is simple to use; it demonstrated a positive action on local circulation from both clinical and instrumental viewpoints, and made a positive contribution to promoting healing of the wounds. Although further confirmations will be useful, we can affirm that CO_2 therapy can be used in therapeutic strategies with the aim of treating wounds related to a condition of tissue hypoxia.

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