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Original research

Effects of a pulsatile electrostatic field on ischemic injury to the diabetic foot: Evaluation of refractory ulcers

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ABSTRACT

Aims: The macro- and microcirculation disease, in patients with type 2 diabetes mellitus (T2DM), induces ischemic wounds of the lower limbs. We have tried to reduce the aggregation of red blood cells and to improve the O_2 supply to the tissues and speed the healing of ulcers in T2DM patients.

Methods: We enrolled 25 obese subjects without glucose intolerance (group A; BMI greater than 30 kg/m^2), 20 obese adults intolerant to glucose (group B) and two subgroups, groups C and D, with T2DM and with leg ulcers. The groups A, B and C were treated with PESF. Body weight, O_2 extraction, the capillary pulse, blood pressure and the surface of the ulcers were monitored.

Results: The technique PESF shows to have positive effects on the metabolism, on the reduction of body weight in the groups A and B, increasing extraction of O_2 in group C and increase the speed of healing of wounds in group C compared to group D. In group A, there was a significant reduction in systolic and diastolic blood pressure.

Conclusions: The technique PESF has affected the metabolic processes and the speed of wound healing ulcer in patients with T2DM.

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1. Introduction

Whilst the incidence of patients with type 2 diabetes mellitus (T2DM) is constantly increasing in countries with a high standard of living [1], there is still no conclusive evidence that primary prevention associated with the administration of antiplatelet drugs confers any significant clinical benefits with a gradual increase in those who develop disabling cardiovascular complications [2]. The aim of available therapies in T2DM patients is to achieve better control of carbohydrates and lipid metabolism. Modification of some risk factors have resulted in an extension of life expectancy by reducing and or delaying complications such as renal, cardiac, vascular disease and hypertension [3,4]. However despite the widespread use of antiplatelet, vasodilators and hemorheological drugs, ischemic ulcers of the lower limbs [5] are frequent in T2DM and do not eliminate the risk from revascularization procedures or interventions that compromise the autonomy of patients. This problem occurs with greater frequency and severity in those with T2DM that have severe renal failure necessitating hemodialysis.

The prevalence of foot ulcers in T2DM patients ranged from 4% to 10% and 85% of these can involve to amputations [6].

The reduced tissue perfusion leads to a decreased O_2 supply to peripheral tissues by the red blood cells. This contributes to ischemic pathology and to endothelial dysfunction characterized by macro- and micro-angiopathy in T2DM. Hemorheologic alterations may be caused by altered plasticity with consequent reduction of the deformability of the red blood cells membrane, and by altered aggregation caused by the inflammatory in T2DM [7–9]. Aggregation of red blood cells, rouleaux formation and alteration of vascular reactivity can be related to an alteration of the electric charge on the surface of the blood cells and the endothelium [7,8,10,11]. This effect is believed to be due to the glycation in diabetes mellitus and carbamylation in uremia.

The aim of the study is to evaluate a non-pharmacological approach to improve the hemorheology of the microcirculation by the O_2 supply to the peripheral tissues and the restoration of vascular reactivity in T2DM patients with and without leg ulcers. We have tried to modify the electrical charges present on the surface of the membrane of the blood cells [7,8,10–12] and to improve the vasomotor performance through the use of an electrostatic pulsating field generator. A secondary objective was to verify whether this procedure had effects on the healing rate of ulcers in T2DM. In some obese patients this technique has been shown to induce improvement in the patho-physiology of the microcirculation as well as on the formation of rouleaux and vasomotor activity [12].

2. Materials and methods

We enrolled 25 obese subjects without glucose intolerance (group A); 20 adults with a concentration of fasting plasma glucose greater than 110 mg% and less than 126 mg% (IFG WHO classification) who were not taking hypoglycemic drugs (group B). We also enrolled 56 patients with T2DM treated with hypoglycemic drugs and with ischemic lesions in the lower limbs that were divided randomly into two subgroups: the first (group C) was composed of 29 patients and the second (group D) with 27 patients. All groups, healthy and diabetics, were matched for age and gender; in our study the patients were included in each group consecutively as they enter: patients with odd numbers were assigned to the group C while those with pair numbers to the group D. We compared groups treated with matching the 95% confidence for age and body mass index (BMI) (see Table 1).

Table 1 – Analysis of variance (ANOVA) of groups A, B, C and D (CI, confidence interval).

Groups	Age		BMI	
	Male	Female	Male	Female
A				
95% CI upper	67,989	61,045	28,665	30,517
95% CI lower	49,211	53,455	23,715	26,133
B				
95% CI upper	75,339	75,040	35,812	34,946
95% CI lower	64,376	51,817	30,878	26,597
C				
95% CI upper	75,842	79,540	31,009	35,112
95% CI lower	63,682	66,793	27,372	29,132
D				
95% CI upper	81,500	76,977	31,810	33,777
95% CI lower	69,000	64,148	26,607	27,198

Groups A and B were selected in our nephrology clinic on "World Kidney Day 2011" dedicated to obesity management. T2DM patients (groups C and D) with ulcers were selected from our specialized clinic dedicated to the care of the diabetic foot.

The ulcers were located in the pre-tibial region of the heel or in the foot arch and some patients with T2DM had more than one ischemic injury.

The groups A, B and C were designated for a treatment cycle with Pulsating Electrostatic Field (PESF) generated from a medical device (NewHealth 9000, Akern srl, Pontassieve, Italy). Group D served as a control for group C. PESF permeate the body and stimulate the metabolism.

NewHealth 9000 is able to generate PESF inducing a negative charge with an intensity varying from 2000 to 9000 V at extremely low current levels and is proven to be safe with a pulsatile frequency of 50 Hz. PESF generated is applied by means of a mat consisting of plastic material capable of conducting current (conductivity equal to 200 Ω/cm) and covered with a double layer insulating PVC of 0.5 mm of thickness on which the subject can sit (see Fig. 1), or lie. The patient and ionizing mat must be adequately insulated from ground. Before and during the session, the patients were monitored for body weight, heart rate, blood pressure and hemoglobin saturation (% SpO_2). Fig. 1 illustrates the insulated subject and the theoretical electrical ionic field.

The device is safe, simple, not invasive and is supported by clinically valid documentation and has been granted a European safety certificate (CE).

None of participants had altered the medical or surgical treatment program during PESF. Before the PESF cycle all study participants were informed of the aims and procedures of the study and gave their consent.

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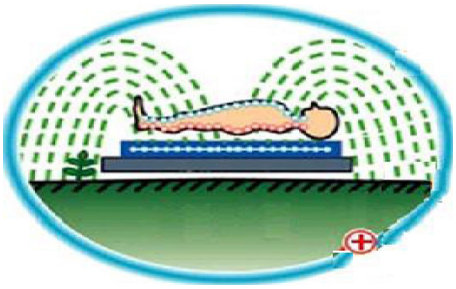

Fig. 1 – Illustrates the insulated subject and the theoretical electrical ionic field.

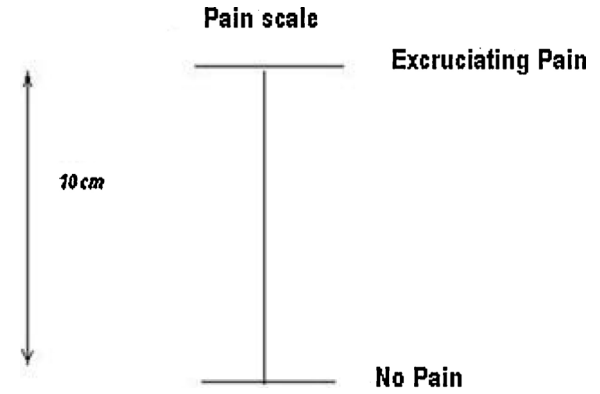

Fig. 2 – To monitor and classify the pain, a simple scale from 0 to 10 has been used in which patients with ischemic ulcer expressing the intensity of pain (0 "no pain" and 10 "unbearable pain").

Groups A, B and C were exposed to a cycle of 13 sessions PESF thrice-weekly on alternate days with exposure of 40 min per session.

The intensity of the treatment was established based on each patient's body cell mass index [13] that was estimated using with bioelectrical impedance analysis (BIA 101 Akern/RJL Systems).

During treatment, the patients remained either seated or lying on the bed, dressed and free to engage in any activity deemed safe and compatible with the position such as reading, listening to music or even sleeping (Fig. 1).

We used a sensor to detect saturation of Hb for O_2 (Type SpO_2 – 512F for adults) that was connected to an oximeter (type PM-60). The measurements were carried out before, during and after exposure to PESF. The sensor was applied to a toe proximal to the skin lesion, and another on a finger of the contralateral hand that was observed to be well perfused.

In the two groups with T2DM lesions the effect on the foot ulcers was evaluated by measuring the surface area of the lesion expressed in cm^2. This was calculated electronically by evaluating the total number of megapixels from a photograph. The wounds were photographed before, during and at the end of the cycle. Before the photos were taken, an area of skin next to the injury was marked with a measured grid for comparative purposes.

To monitor and to classify the pain a simple VAS analog scale was used. Patients with ischemic ulcer were asked to express the intensity of the pain on a scale of 0–10; 0 indicating "no pain" and 10 "unbearable pain" (Fig. 2).

In groups B, C and D glycated hemoglobin (HbA1c) was only measured at the beginning of the first exposure cycle.

The statistical significance between means was assessed by Student's *t*-test for matched pairs.

3. Results

The levels of glycated hemoglobin (HbA1c) were for group B: 6.45% ± 0.50; group C: 7.54% ± 1.09 and for group D: 7.57% ± 0.89 (Group D–C, p = NS).

Table 2 – Statistical results of body weight (kg), % SpO_2, systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and heart rate (bpm) in groups A, B, C and D (pre and post treatment).

GROUPS	A	B	C	D
Body weight (kg)				
PRE	77.03 ± 20.72	83.55 ± 13.36	76.71 ± 13.50	76.90 ± 13.96
POST	76.30 ± 20.51	82.45 ± 13.80	76.21 ± 14.31	76.65 ± 14.02
p	0.007	0.019	NS	NS
% SpO_2				
PRE	95.53 ± 8.68	95.10 ± 4.66	94.78 ± 4.94	93.56 ± 8.62
POST	96.32 ± 3.96	96.97 ± 2.51	20.22 ± 7.71	94.56 ± 6.23
p	NS	0.020	0.015	NS
Systolic blood pressure (mmHg)				
PRE	134.56 ± 19.72	134.50 ± 22.93	130.63 ± 19.39	126.19 ± 19.89
POST	125.03 ± 19.66	133.32 ± 23.58	133.19 ± 25.30	131.13 ± 22.90
p	0.004	NS	NS	NS
Diastolic blood pressure (mmHg)				
PRE	79.94 ± 8.91	75.00 ± 11.70	75.05 ± 14.91	74.25 ± 8.99
POST	75.52 ± 9.47	74.50 ± 12.34	67.72 ± 14.56	74.44 ± 10.73
p	0.002	NS	0.005	NS
Heart rate (bpm)				
PRE	72.44 ± 10.76	74.24 ± 10.98	73.11 ± 10.85	69.35 ± 9.69
POST	75.63 ± 11.02	75.03 ± 11.96	69.50 ± 6.47	68.59 ± 12.61
p	NS	NS	0.04	NS

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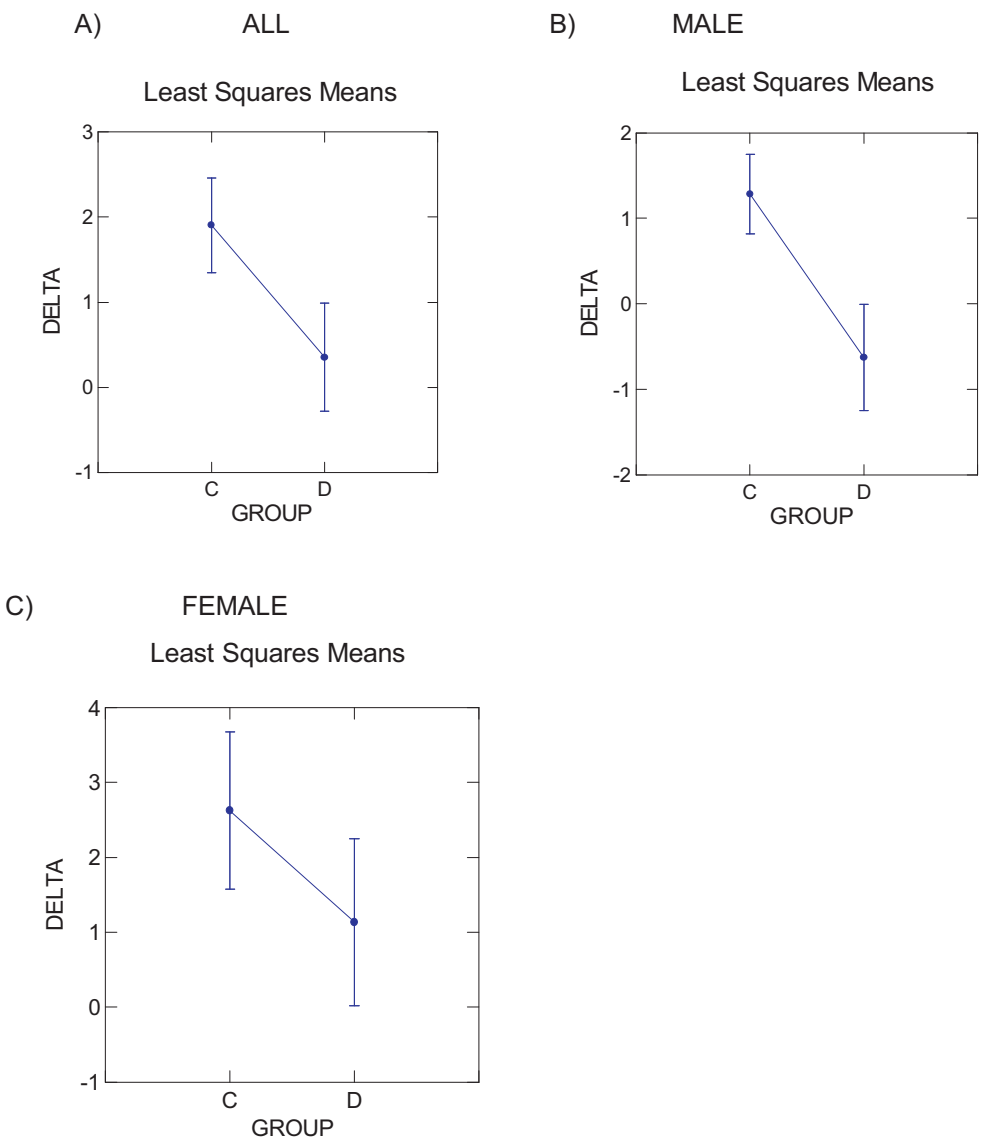

Fig. 3 – Analysis of variance (ANOVA) between groups C (conventional treatment + new health) and D (conventional treatment) pre and post (DELTA Δ). (A = all (groups C and D); B = male and C = female).

PESF induces a reduction in body weight in healthy controls group A, in group B but not in groups C and D.

After treatment the variation of % SpO_2 feet is significantly higher in group B, significantly lower in group C but does not change in groups A and D.

Systolic blood pressure is only significantly lower in group A after PESF.

Diastolic blood pressure is significantly lower in groups A and C.

Heart rate is significantly lower only in group C. The results are shown in Table 2.

The percentage of wounds that worsened due to infections was 11.90% in group C and 26.09% in group D.

The percentage of wounds that recovered, before the end of the cycle, was 14.29% in group C and 17.39% in group D.

Ulcers were recovered before the end of the cycle, were excluded from the calculation of the final results of the groups C and D (treated and untreated with PESF) because we have not considered refractory [14].

Group C, before and after the cycle of 13 sessions PESF, showed a significant reduction of surface ulcer areas (cm^2: pre = 2.356 ± 2.6; post = 1.291 ± 1.9; $p = 0.004$) but not in group D (cm^2: pre = 1.714 ± 1.0; post = 1.627 ± 1.2; $p = 0.622$) after a similar period of observation.

This result was associated with a significant reduction of pain as perceived by the patients in groups C (pain scores: pre = 8; post = 3). In Group D, the intensity of the pain was unchanged.

We used analysis of variance (ANOVA) to estimate effects and interactions on surface lesion between group C (conventional treatment + New Health) and D (conventional treatment) pre and post (DELTA Δ) (see Fig. 3).

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4. Discussion

In recent decades the scientific world has turned its attention to the study of electric and electromagnetic fields to demonstrate the effects on physiological changes [9].

In the "Western medicine" current science is reluctant to accept the idea that the disease can be caused by an imbalance of energy flowing in the body.

Western medicine makes usually an extensive use of electric currents for diagnostic and for therapeutic purposes.

The cultural difference between East and West may be due to a lack of knowledge of the effects on sub-cellular biological phenomena produced by electrical currents.

However, the membrane potential is the basis of life for all living beings and in our body is continually producing microscopic electrical currents through both mechanical and chemical mechanisms. These currents follow paths of least resistance creating a kind of electric grid around to the body.

In diabetics, intensive blood glucose and multifactorial control may reduce major cardiovascular and microvascular events, especially in diabetic nephropathy [15,16] but on the contrary it does not improve outcomes resulting from microvascular disorders [17–19].

Diabetic foot ulcers, wherever located (foot or pretibial region) frequently become refractory to medical treatment and pose a high-risk for infection complications requiring urgent action.

Since 2002 treatments of chronic skin ulcers include nutritional, electro, ultrasound and laser therapy [15,20].

Non-pharmacological treatments, that could be effective in at least 50%, does or not usually used in T2DM. These treatments are complex, invasive, not risk-free, acting locally, more expensive and may not have a permanent effect [21–23]. For these reasons the use of hyperbaric oxygen is reserved for confined to severe cases [24–26].

Recently, a gene that modulates cellular movements following the application of electrical currents has been identified [27].

PESF is a simple, non-invasive system, that has limited affordable costs and is safe and capable of producing documented clinical effects, local and systemic. PESF accelerates the healing of wounds, helps reducing body weight, lowers systolic and diastolic blood pressure and improves perfusion of O_2. The reduction in of the ulcerated surface area demonstrates the efficacy of the PESF treatment. Other researchers have found that the use of PESF can stimulate basal metabolism, reduce body weight in obese women [13] and increase vascular motility [12].

In our case PESF reduces body weight in patients with glucose intolerance without a hypocaloric diet.

Ischemic ulcers are the result of reduced O_2 supply conditioned by metabolic and rheological changes, peripheral neuropathy and macro- and micro-circulation disease [5]. We believe that PESF improved tissue O_2 perfusion, reduced pain and accelerated the healing and probably correlated with lower cellular aggregation and peripheral reduced vascular resistance.

PESF is a non-invasive pain reducing aid in contrast with systems using implant electrodes to treat neuro-ischemic pain with electrical stimulation [28].

In conclusion, in T2DM, PESF accelerates wound healing by reducing the formation of rouleaux [7], increasing vasomotion [12] and metabolic activity [13] and stabilizing autonomic nervous system [11].

Our results, even if preliminary, are encouraging and leading us to study several possible use of PESF.

Conflict of interest

The authors state that they have no conflict of interest.

REFERENCES

[1] C. Nolan, P. Damm, M. Prentki, Type 2 diabetes across generations: from pathophysiology to prevention and management, Lancet 378 (9786) (2011) 169–181.
[2] A.A. Bartolucci, M. Tendera, G. Howard, Meta-analysis of multiple primary prevention trials of cardiovascular event using aspirin, Am. J. Cardiol. 107 (12) (2011) 1796–1801.
[3] C.E. Hogensen, Prevention and management of diabetic nephropathy, in: Therapy in Nephrology and Hypertension, W.B. Saunders Company, 1999, pp. 239–247.
[4] M.E. Cooper, Pathogenesis, prevention and treatment of diabetic nephropathy, Lancet 352 (9123) (1998) 213–219.
[5] G. Landini, G. Panigada, S. Meini, E. Melillo, R. Cappelli, G. Bellandi, Management of critical limb ischemia: proposal for a multidisciplinary operating network in Tuscany, Ital. J. Med. 5 (2011) 135–142.
[6] A. Piaggesi, Gruppo di Studio Interassociativo SID-AMD "Piede Diabetico". Documento di consenso internazionale sul piede diabetico, Mediserve 2, 2006.
[7] T. Shiga, K. Imaizumi, N. Harada, M. Sekiya, Kinetics of rouleaux formation using TV analyzer for human erythrocytes, Am. J. Physiol. 245 (2) (1983) H252–H258.
[8] S.M. Bertoluzzo, A. Bollini, M. Rasia, A. Raynal, Kinetics model for erythrocyte aggregation, Blood Cells Mol. Dis. 25 (5–6) (1999) 339–349.
[9] S. Genet, R. Costalat, J. Burger, The influence of plasma membrane electrostatic properties on the stability of cell ionic composition, Biophys. J. 81 (5) (2001) 2442–2457.
[10] W. Dzwinel, K. Boryczko, D.A. Yuen, A discrete-particle model of blood dynamics in capillary vessels, J. Colloid Interface Sci. 258 (1) (2003) 163–173.
[11] R. Pop-Busui, L. Roberts, S. Pennathur, M. Kretzler, F.C. Brosius, E.L. Feldman, The management of diabetic neuropathy in CKD, Am. J. Kidney Dis. 55 (2) (2010) 365–385.
[12] G. Gargiulo, F. Labanca, D. Lapi, R. Oliviero, E. Quarto, A. Colantuoni, The effects of treatment with pulsating electrostatic fields on cutaneous microvascular flow motion patterns, in: Atti del 5th Conference if the European Study Group on Cardiovascular Oscillation, Parma, 7–9 April, 2008, pp. 5–7.
[13] A. De Lorenzo, R. Martinoli, M.G. Carbonelli, G. Monteleone, N. Di Lorenzo, N. Di Daniele, Resting metabolic rate incremented by pulsating electrostatic field (PESF therapy), Diabetes Nutr. Metab. 17 (5) (2004) 309–312.
[14] L. Collins, S. Seraj, Diagnosis and treatment of venous ulcers, Am. Fam. Physician 81 (8) (2010) 989–996.
[15] Action to Control Cardiovascular Risk in Diabetes Study Group, H.C. Gerstein, M.E. Miller, R.P. Byington, D.C. Goff Jr., J.T. Bigger, J.B. Buse, W.C. Cushman, S. Genuth,

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F. Ismail-Beigi, R.H. Grimm Jr., J.L. Probstfield, D.G. Simons-Morton, W.T. Friedewald, Effects of intensive glucose lowering in type 2 diabetes, N. Engl. J. Med. 358 (24) (2008) 2545–2559.
[16] P. Gaede, P. Vedel, N. Larsen, G.V.H. Jensen, H.H. Parving, O. Pedersen, Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes, N. Engl. J. Med. 248 (2003) 383–393.
[17] M.A. Pellegrino, C. Patrini, E. Pasini, L. Brocca, V. Flati, G. Corsetti, G. D'Antona, Amino acid supplementation counteracts metabolic and functional damage in the diabetic rat heart, Am. J. Cardiol. 101 (11A) (2008) 49E–56E.
[18] ADVANCE Collaborative Group, A. Patel, S. MacMahon, J. Chalmers, B. Neal, L. Billot, M. Woodward, M. Marre, M. Cooper, P. Glasziou, D. Grobbee, P. Hamet, S. Harrap, S. Heller, L. Liu, G. Mancia, C.E. Mogensen, C. Pan, N. Poulter, A. Rodgers, B. Williams, S. Bompoint, B.E. de Galan, R. Joshi, F. Travert, Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes, N. Engl. J. Med. 358 (24) (2008) 2560–2572.
[19] O. Yenice, H. Kazokoğlu, E. Ozcan, M. Yüksel, G. Adigüzel, G. Haklar, D.G. Yavuz, Erythrocyte membrane anionic content and urinary glycosaminoglycan excretion in type 1 diabetes: association with retinopathy, Curr. Eye Res. 31 (11) (2006) 975–981.
[20] P. Palombo, La cura delle ferite sotto vuoto, in: Atti del Secondo Congresso Nazionale Co. R. TE, Roma, 27–29 Febbraio, 2008, pp. 52–53.
[21] A. Di Censo, N. Cullum, D. Ciliska, Implementing evidence based nursing: some misconception, Evid. Based Nurs. 1 (1998) 38–39.
[22] N. Cullum, E.A. Nelson, J. Nixon, Piaghe da decubito, Clin. Evid. 3 (2001) 1051–1057.
[23] R. Saggini, Il bombardamento delle ulcere croniche, in: Atti del Secondo Congresso Nazionale Co. R. TE, Roma, 27–29 Febbraio, 2008, p. 53.
[24] P. Plafki, P. Peters, M. Almeling, W. Welslau, R. Busch, Complications and side effects of hyperbaric oxygen therapy, Aviat. Space Environ. Med. 71 (2) (2000) 119–124.
[25] M. Rocco, L. Ditri, M. Brauzzi, G. Vezzani, L. Cucci, E. Nasole, Linee guida sulle indicazioni all'ossigenoterapia iperbarica, Med. Subacquea Iperbarica 1 (2007) 24–26.
[26] P. Bonadeo, M. Fumagalli, Inquadramento patogenetico dell'ulcera, Med. Subacquea Iperbarica 1 (2007) 8–9.
[27] M. Zhao, B. Song, J. Pu, T. Wada, B. Reid, G. Tai, F. Wang, A. Guo, P. Walczysko, Y. Gu, T. Sasaki, A. Suzuki, J.V. Forrester, H.R. Bourne, P.N. Devreotes, C.D. McCaig, J.M. Penninger, Electrical signals control wound healing through phosphatidylinositol-3-OH kinase-gamma and PTEN, Nature 442 (7101) (2006) 457–460.
[28] A. Cardani, La stimolazione midollare nel trattamento del dolore cronico non maligno. http://www.painomore.net/site/stampa.asp?id_area=3&id_rubrica=22&id_articolo=61

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