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Frequency-modulated electromagnetic neural stimulation enhances cutaneous microvascular flow in patients with diabetic neuropathy

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Abstract

Aim: The aim of this study was to investigate the effects of frequency modulated electromagnetic neural stimulation (FREMS), a recently developed safe and effective treatment of painful diabetic neuropathy, on cutaneous microvascular function. **Methods:** Thirty-one patients with painful neuropathy were enrolled in a randomised, double-blind, crossover FREMS vs. placebo study; each received two series of 10 treatments of either FREMS or placebo in random sequence within no more than 3 weeks. Patients were studied at baseline, end of FREMS and placebo series, and after 4 months of follow-up. Cutaneous blood flow was measured by laser doppler flowmetry and partial tissue tension of oxygen ($TcPO_2$) and carbonic anhydride ($TcPCO_2$) by oxymetry at the lower extremities in basal resting conditions and as incremental response after thermal stimulation. **Results:** Crossover analysis showed no consistent differences between FREMS and placebo. After 4-month follow-up, a 52% increase of cutaneous blood flow was observed in resting conditions (P=.0086 vs. baseline), while no differences were observed as incremental flow after warming; compared with baseline, no significant differences were observed for $TcPO_2$ and $TcPCO_2$, both in resting conditions and as incremental response to warm. **Conclusion:** These results indicate that 10 treatments with FREMS may induce an enhancement of microvascular blood flow measurable at 4 months of follow-up. The findings of this study will need to be confirmed in a larger, adequately powered study (ClinicalTrial.gov Id: NCT00337324).

1. Introduction

Classic treatment of diabetic neuropathy is largely based on pharmaceutical agents that have variable effects on pain relief but are substantially ineffective in reverting established alterations of nerve function (Boulton et al., 2005). We have recently shown in a placebo-controlled trial that frequency modulated electromagnetic neural stimulation (FREMS), as a nonpharmacological treatment, is a safe and effective therapy for pain in diabetic neuropathy, leading to the amelioration of symptoms and improvement of peripheral nerve function (Bosi et al., 2005). As FREMS is applied transcutaneously, we also hypothesized that this treatment might affect microvascular circulation, with beneficial effects on skin blood flow. We report here, as an ancillary measure of that study, the changes induced by FREMS on skin blood flow measured by laser Doppler flowmetry and on partial tissue tension of oxygen ($TcPO_2$) and carbonic anhydride ($TcPCO_2$) measured by oxymetry.

2. Patients and methods

2.1. Patients and study design

The design and methods of the study have been previously reported (Bosi et al., 2005). Briefly, a two-center, randomized, double-blind, placebo-controlled, crossover

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clinical trial was conducted in 31 patients with painful diabetic neuropathy. Inclusion criteria were diagnosis of either Type 1 or Type 2 diabetes according to American Diabetes Association criteria, between ages 18 and 70 years, painful diabetic neuropathy with reduced sensory, and/or motor nerve conduction velocity below 40 m/s in at least one nerve trunk of lower limbs and vibration perception at big toe above 25 V. Exclusion criteria were the presence of any other severe disease, pregnancy, renal disease with serum creatinine above 2.0 mg/dl, history or actual presence of foot ulcers, or lower limb vascular disease as indicated by an ankle-brachial index below 0.9. Patients have been enrolled in two centers, Milan and Perugia. The study protocol was approved by the ethics committees of San Raffaele University Hospital and Perugia University Hospital, and a written informed consent was obtained by all patients prior to enrolment. Patients' characteristics at baseline were age 63.1±3.1 years; 21 males; 8 participants had type 1, whereas 23 Type 2 diabetes; disease duration was 15.9±3.0 years; 13 participants were on insulin, 17 on oral agents, and 1 on diet alone; and mean HbA1c was 8.3±0.4%. The treatment regimen consisted of two series, in random sequence, of 10 sessions of placebo, followed by 10 sessions of FREMS, or vice versa, separated by a 1-week washout. Treatment sessions were administered at intervals of at least 24 h, and each series of 10 sessions lasted no more than 3 weeks. Electrotherapy and placebo were administered by Physioflog ETS 501 (Lorenz Therapy System, Medolla, MO, Italy) via four transcutaneous electrodes applied to both lower limb extremities. Neural stimulation by FREMS had the following characteristics: sequences of monophase-compensated negative potential electric pulses, characterised by a sharp spike and asymmetrical shape; peak amplitude variable from 0 to 255 V; pulse frequency variable in the range 1–50 Hz; pulse duration variable in the range 10–40 μs. Placebo consisted of no electric current transmission.

2.2. Assessment of microvascular function

Patients were evaluated at baseline, at the end of each series of treatment with FREMS and/or placebo, and 4 months after completion of the study. Measurements were performed using PeriFlux System 5000 (Perimed, Sweden). On the occasion of each measurement, patients were received in an acclimatized room with stable temperature of 22–24°C and allowed to rest in recumbent position for at least 20 min prior to blood flow measurements and oxymetry measurements. Cutaneous capillary blood flow was measured by laser Doppler on three different areas of the dorsal surface of the foot, and results were expressed as perfusion units. All measurements were performed in resting conditions (with a skin temperature of 37°C) and in a continuous manner as skin temperature was progressively increased up to 44°C by thermal stimulation. $TcPO_2$ and $TcPCO_2$ were continously measured electrochemically on a contiguous skin area by a Clark-type electrode. All measurements were

Table 1
Effects of treatment with FREMS or placebo

	n	Pre-treatment			Post- treatment			Baseline	4 month follow-up	P value
		Placebo	FREMS	P value	Placebo	FREMS	P value			
LD perfusion at rest [Units]	31	13.52±6.53	14.18±6.67	ns	13.57±7.90	13.07±6.81	ns	13.08±5.87	19.88±13.32	.0086
LD perfusion TS/R	31	6.89±5.06	6.22±2.97	ns	7.23±3.61	7.65±5.02	ns	6.82±5.12	6.11±4.53	ns
$TcPO_2$ at rest [mm Hg]	31	56.47±15.37	61.38±11.68	ns	60.78±15.71	53.96±10.41	.0291	59.19±14.07	54.45±14.28	ns
$TcPO_2$ TS/R	31	0.95±0.09	0.96±0.13	ns	0.91±0.18	0.97±0.12	ns	0.93±0.41	0.75±0.43	ns
$TcPCO_2$ at rest [mm Hg]	31	36.95±4.93	37.34±4.90	ns	36.92±4.86	36.76±4.71	ns	37.42±4.53	37.10±6.31	ns
$TcPCO_2$ TS/R	31	1.02±0.05	1.04±0.09	ns	1.01±0.04	1.02±0.06	ns	0.91±0.21	0.87±0.24	ns

LD (Laser Doppler), TS/R thermal stimulation/resting ratio, $TcPO_2$ (Transcutaneous O_2 Tension), $TcPCO_2$ (Transcutaneous CO_2 Tension). Data are presented as mean±SD.

independently performed by two blinded investigators with the same training.

2.3. Statistical analysis

Comparisons of FREMS vs. placebo before and after the treatment were made. A Mann–Whitney *U* test was used for analysing the changes of all variables during FREMS or placebo. A crossover model was used to evaluate both carryover and treatment effects. In addition, the effect of FREMS at 4-month follow-up was analyzed vs. baseline.

3. Results

Patients' characteristics at baseline were not significantly different between the two-sequence assignment groups. Results are summarized in (Table 1). Within the 3-week time frame of treatment, skin cutaneous blood flow did not change after FREMS or placebo, neither in resting conditions nor as response to thermal stimulation; conversely, $TcPO_2$ appeared to be reduced after FREMS when measured in resting conditions (P=.0291 vs. placebo), while no differences were observed as incremental response to warming. No significant changes were observed for $TcPCO_2$. Analysis at 4 months showed a significant increase of cutaneous blood flow in resting conditions (+52% vs. baseline; P–.0086), while flow response to thermal stimulation remained unchanged. No other significant changes were found for the remaining measures compared with baseline.

4. Discussion

These findings indicate that FREMS, a newly developed transcutaneous electrotherapy effective in the treatment of painful diabetic neuropathy, induces measurable changes in skin microvascular blood flow. While within a short-term time frame no differences were observed between FREMS and placebo, a significant enhancement of cutaneous blood flow was observed 4 months after completion of 10 treatments with FREMS; in comparison with baseline, microvascular blood flow measured on the dorsal surface of the foot by laser doppler was found to be increased in resting conditions by 52%. This remarkable finding may suggest that, upon treatment with FREMS, the skin of individuals with diabetes generates a response at the microvascular level.

The decrease of $TcPO_2$ observed during FREMS in comparison with placebo over the short term of 3 weeks of treatment is difficult to explain: although statistically significant, this finding might in fact represent a regression towards the mean due to discrepancy in pretreatment measurements; $TcPO_2$ could have been by chance slightly lower before placebo treatment followed by an increasing trend and conversely somewhat higher before active treatment, with a subsequent trend to decrease.

In conclusion, this is the first observation of an in vivo vasoactive effect induced by an electrotherapy in humans and is consistent with a number of experimental observations suggesting that electrical and/or electromagnetic stimulations might have potential proangiogenic effects (Hang, Kong, Gu, & Adair, 1995; Tepper et al., 2004; Zhao, Bai, Wang, Forrester, & McCaig, 2004). Interestingly, the enhancement of microvascular circulation observed at 4 months of follow-up parallels that of peripheral nerve function (Bosi et al., 2005). An intriguing hypothesis would be that the improvement in cutaneous blood flow might be mirrored by a similar effect at the endoneural level, thus suggesting that an increment in nerve blood flow might be a mechanism through which FREMS induces amelioration of peripheral nerve function. In fact, a number of recent observations have demonstrated that blood vessels and nerves use similar signals and principles to differentiate, grow, and navigate towards their targets (Carmeliet, 2003), and, therefore, could also show synergistic responses to a common stimulus such as that induced by FREMS. Clearly, additional clinical, biochemical, and instrumental measures and a larger adequately powered study are needed to confirm these findings.

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