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Spinal Cord Stimulation: Predictive Parameters of Outcome in Patients Suffering From Critical Lower Limb Ischemia. A Preliminary Study

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Introduction: The aim of our study is to identify the assessment of metabolic and dynamic capillaroscopy parameters that may be predictive of the outcome of spinal cord stimulation in patients affected with non-revascularisable chronic critical limb ischemia.

Materials and Methods: Forty patients, 16 female and 24 male, average age 69 ± 8, underwent microcirculatory screening with transcutaneous oximetry and dynamic capillaroscopy. Microcirculatory assessment was performed before temporary implantation of the spinal cord stimulation stimulator and after one month. The following metabolic parameters were considered: TcPO2-TcPCO2 and with dependent limb, difference between dependent limb and supine values (Δ TcPO2, Δ TcPCO2), change in TcPO2-TcPCO2 after stimulation. Dynamic capillaroscopy parameters were recorded. Follow-up visits were scheduled at three, six, and twelve months after implantation. The procedure was performed placing an Octrode (St. Jude Medical, St. Paul, MN, USA) on the dorsal columns of the spinal cord.

Results: Two groups were identified on the basis of transcutaneous oximetry measurements: group A (22 patients) and group B (18 patients), responding differently to the postural test. After one month of home testing period, there was an improvement in metabolic parameters, differing from one group to the other. The morphofunctional data provided by capillaroscopy highlighted the percentage of open capillaries poststimulation as being a significant parameter, although not mentioned in previous studies.

Conclusions: Spinal neuromodulation is an effective therapy option in the management of patients affected by non-reconstructable chronic critical limb ischemia.

Keywords: Ischemic pain, neurostimulation, patient selection, peripheral vascular disease, SCS

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

The issues concerning pain experienced by patients suffering from chronic critical lower limb ischemia are still extremely complex and much debated. The difficulty is associated with the many nociceptive mechanisms underlying the pain symptoms, identifying which are the main components, and thus the primary target of pain relief treatment. There are still conflicting views as to what time scales and methods should be adopted in a multidisciplinary approach to the treatment of ischemic pain. The task of the pain therapist, when able to contribute to a treatment/pain relief plan for a patient with peripheral arterial disease, is to demonstrate and/or predict the clinical response, synergistically enhancing the treatments applied by other specialists involved in the care of such a patient.

Spinal cord stimulation (SCS) has been proven effective both in controlling the ischemic pain syndrome and in limb salvage. One of the major retrospective studies by Horsch et al. documents pain relief of greater than 75% in 62% of patients treated with SCS over three years (1). The Horsch study is confirmed in findings published by Broseta and Broggi (2,3). The mechanism by which SCS operates in vascular diseases is still not completely clear (4,5). There are numerous theories on the mechanisms of action involved. Among these are:

1. Antidromic stimulation of small-diameter afferent fibers;
2. Influence on cerebral vaso-regulation;
3. Action on the spinal sympathetic nervous system;
4. Release of calcitonin gene-related peptide;
5. Reduction of hyperexcitability in wide dynamic range neurons of the dorsal horns;
6. Activation of supraspinal mechanisms involving the inhibitory descending pathways;
7. Gate control action; and
8. Increase of inhibitory neurotransmitters.

The cascade of events connected with spinal electrical stimulation is an area requiring further verification. Experimental and clinical

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studies have demonstrated the effect of spinal neuromodulation on the microcirculation region by increasing capillary perfusion, reducing ischemic pain, and stimulating the process by which trophic lesions are healed (6). In the three randomized controlled studies available (7–9), where SCS applied to non-revascularisation chronic limb ischemia in conjunction with conservative treatment was compared to stand-alone conservative treatment, including prostanoids, the authors report an evident pain-relieving effect and a lower amputation rate in the SCS group, albeit not significant, at 12 months (15–53% in the SCS group vs. 20–65% in patients undergoing conservative treatment). Hence the problem of selection: identifying patients who could "potentially" be responders to a treatment acknowledged as costly and invasive. Certain microcirculatory parameters have been proposed as selection criteria: in the Dutch randomized study (10), baseline TcPO2 (cut-off value 10 mmHg); in the European study Spinal Cord Stimulation in the Treatment of Non-reconstructable Stable Critical Leg Ischaemia: Results of the European Peripheral Vascular Disease Outcome Study (SCS-EPOS) (11), the increase in TcPO2 following the trial period (Δ TcPO2 15 mmHg). This prospective observational study that took place over three years takes into account the metabolic parameters and capillaroscopy. The aim of our study is to identify the assessment of metabolic and dynamic capillaroscopy parameters that may be predictive of the outcome of SCS in patients affected with non-revascularizable chronic critical limb ischemia.

MATERIALS AND METHODS

Forty patients, 16 female and 24 male, average age 69 ± 8, underwent microcirculatory screening with transcutaneous oximetry (Kontron Microgas 7640 [Kontron Medical AG, Germany] with Combi Sensor [Kontron Medical AG] at 44°C) and dynamic capillaroscopy (Capiflow; computerized system of CapiFlow AB, Sweden), on the big toe nailfold; all patients were affected by chronic critical ischemia from atherosclerotic arterial disease, defined on the basis of the TransAtlantic Inter-Society Consensus criteria, and identified as non-revascularizable from the type and location of the lesions or the condition of the patient, or had previously undergone surgery and/or percutaneous transluminal angioplasty without success, whereby further surgery was not indicated. Conservative treatment had proved to be of little or no effect. Anamnesis revealed nicotinism in 62% of patients, hypertension in 45%, and diabetes in 30%. Patients had no contraindications to implantation of the SCS (i.e., coagulation diseases, sepsis, spinal disorders, etc.). SCS procedures were carried out on patients in a prone position under fluoroscopic guidance. Particular attention was paid to the induction of paresthesia covering the pain area in its entirety.

Microcirculatory assessment was performed before temporary implantation of the SCS stimulator and after one month. The following metabolic parameters were considered: TcPO2-TcPCO2 on dorsum of foot in supine posture and with dependent limb, difference between dependent limb and supine values (Δ TcPO2, Δ TcPCO2), and change in TcPO2-TcPCO2 after stimulation. The following dynamic capillaroscopy parameters were recorded: erythrocyte flow velocity through capillaries (rCBV), number of capillaries per square millimeter (capillary density, CD), and perfused or "open" capillaries (OC) currently active and their percentage relative to CD (%OC).

Ischemic pain was assessed before and after the trial, employing a visual analog scale and the Brief Pain Inventory. Prior to the stimulation procedure and during the treatment, patients underwent a psychological assessment employing Italian Pain Questionnaire (QUID), Short-Form 36 items Health Survey (SF-36), and Millon Clinical Multiaxial Inventory tests. In the case of patients who had reported a reduction of greater than 50% in pain symptoms during the trial period, the procedure was completed with the deployment of an implantable pulse generator. Follow-up visits were scheduled at three, six, and twelve months after implantation. The procedure was performed placing an Octrode (St. Jude Medical, St. Paul, MN, USA) on the dorsal columns of the spinal cord with the tip at T8-T9. The stimulation parameters were set up in order to obtain a complete paresthesic coverage of the painful area.

RESULTS

Two groups were identified on the basis of transcutaneous oximetry measurements: group A (22 patients) and group B (18 patients), responding differently to the postural test. In baseline conditions, before temporary SCS implantation, the following values (mmHg) were recorded for group A: supine TcPO2 19 ± 4, TcPCO2 52 ± 5, dependent limb TcPO2 37 ± 5, TcPCO2 38 ± 4. Dependent limb posture measurements showed an average increase of 18 mmHg in TcPO2 (Δ TcPO2), and an average reduction of 14 mmHg in TcPCO2 (Δ TcPCO2).

In group B, baseline measurements gave lower values for TcPO2 and higher for TcPCO2, compared to group A: supine TcPO2 12 ± 3.5, TcPCO2 58 ± 7.2, dependent limb TcPO2 20 ± 3.5, TcPCO2 51 ± 7. In the postural test, group B likewise showed an increase in TcPO2, albeit distinctly less—well below 50%—than that of group A (Δ TcPO2 8). There was an average reduction of 7 mmHg in TcPCO2, namely half the value measured in the case of group A.

Data on the capillary bed provided by dynamic capillaroscopy was in line with the oximetry findings. Group A: rCBV 0.07 mm/sec, CD 14/mm^2, OC 2, %OC 14.2%. Group B: rCBV 0.05 mm/sec, CD 9/mm^2, OC 1, %OC 11%. After one month of home testing period, there was an improvement in metabolic parameters, differing from one group to the other. In group A patients, TcPO2 in supine posture reached a value of 32.3 ± 6.8, representing a 70% increase over the baseline value ($p < 0.001$); TcPCO2 fell to 44 ± 5, representing a reduction of 15.3%. In group B, TcPO2 reported an increase lower than in group A, reaching a value of 17.3 ± 3 (+44%), and similarly, there was less of a reduction in TcPCO2, which fell to 53 ± 6 (–8.6%). Of particular interest were the dynamic capillaroscopy readings, which indicated a level of capillary recruitment, following SCS implantation, with regard to the improvement in metabolic indicators. Group A patients registered increases in rCBV of up to 0.18 mm/sec ($p < 0.001$), and in mean capillary density up to 20/mm^2, but most notable was the increase in open capillaries to an average value of 14.4/mm^2, corresponding to a %OC of 72% ($p < 0.0001$).

In group B, the improvement in capillaroscopic parameters was self-evidently more modest: rCBV 0.09 mm/sec, CD 11/mm^2, OC 4.4, %OC 40%. Relief from ischemic pain following the trial period, in terms of both duration and of intensity, was greater than 50% in all patients; after six months/one year, pain relief in 80% of group A patients was greater than 75%, with no need for additional painkillers. At one year, the level of pain relief was significant ($p < 0.005$). Healing of trophic lesions also occurred, with the result that the percentage of patients ranking as stage IV after 12 months, in the case of group A, fell from 55% to 27%.

Further amputation became necessary in two patients at six months and in another five at 12 months (total amputations after one year: seven; amputation rate after one year: 17.5%). Three of the

seven patients who underwent amputation suffered from diabetes. All amputees were in group B (38.8%) (12). From analysis of the microcirculatory screening results, it was found that all amputated patients had a baseline postural Δ TcPO2 of less than 15 mmHg, and none reached the absolute TcPO2 value of less than 20 mmHg, whilst the reduction in TcPCO2 was less than 7 mmHg. Following the trial period, moreover, the increase in TcPO2 was less than 5 mmHg. As regards capillaroscopic parameters, analysis showed that all amputees had a %OC of less than or equal to 40% following the trial period.

DISCUSSION

Patients affected by non-reconstructable chronic limb ischemia can benefit from SCS not only in terms of relief from their ischemic pain, but also of wound healing and limb salvage. Pain relief is important in itself, as well as being correlated to limb salvage. As a matter of fact, tissue perfusion can be improved by the consequent reduction of edema by pain-relieving posture, and of reflected sympathetic vaso-constriction, and by greater patient mobility. The positive effect of SCS may be boosted by the selection of patients on the basis of local microcirculatory conditions, bearing in mind that microcirculatory perfusion deficit is the last cause of tissue loss. It is especially important to evaluate the microcirculatory reserve capacity healing potential is associated to, which can be elicited by SCS.

Most references in the literature indicate successful predictive parameters of the procedure as being: a baseline TcPO2 cut-off value of less than or equal to 10 mmHg in the supine position, an increase in TcPO2 of greater than 15 mmHg in a sitting position (mentioned by few authors), and finally, the increase, following the stimulation test, of 4–15 mmHg (13–16). This study highlights the importance of transcutaneous oximetry with postural testing, a good outcome being indicated by a Δ TcPO2 of greater than 15 mmHg, but also by an absolute dependent limb value of $\geq$20 mmHg. These indicators suggest that even patients with baseline TcPO2 values of less than 10 mmHg can be "recovered" if they still have sufficient microcirculatory reserve capacity. The sensitivity of the procedure is increased by the accompanying TcPCO2 decrease in the postural test. In accordance with literature, the increase in TcPO2 following the stimulation test (5–13 mmHg) had an influence on the outcome. In metabolic investigations, the morphofunctional data provided by capillaroscopy highlighted the percentage of open capillaries poststimulation—which in responders is greater than 50%—as being a significant parameter, although not mentioned in previous studies.

CONCLUSIONS

Spinal neuromodulation is an effective therapy option in the management of patients affected by non-reconstructable chronic critical limb ischemia. The clinical datum of pain relief and the above noted microcirculatory parameters combine to allow a reliable selection of patients that can improve the efficacy of the treatment. Such tests are commonly carried out by specialists in most hospitals, and for this reason should have a clinical utility in evaluating patients with peripheral vascular disease. Given the complexity of microcirculatory reactivity and considering the results of this study, it is our opinion that the selection of patients should be based on more than one microcirculatory parameter.

Authorship Statements

Dr. G. Colini Baldeschi designed the study and approved the final manuscript. Dr. A. Carlizza prepared the manuscript draft.

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COMMENTS

Baldeshi and colleagues have added a valuable piece of information to the clinical knowledge base regarding SCS for ischemic pain. If we can better predict outcomes, we can improve pain relief, improve function, and in some cases salvage limbs.

The paper is very well done, but one must ask "what is the clinical value?" We need better clinical predictors as to whom to implant and more importantly perhaps, when to implant in the ischemic pain patient.

I applaud this excellent work but encourage others to initiate a clinically relevant randomized prospective study on ischemic limb pain and SCS from which we can harvest valuable clinical predictors.

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The study is using as predicting factors tcPO2 and tcPCO2 as well as capillaroscopy as the measurement for the treatment of patients with non reconstructable PVD. This allows the judgment of the microcirculatory reserve capacity.

The authors treated two groups of patients with a total of 40 patients included. The results are satisfying and correspond to the results of former publications (well cited in the paper).

The study of literature is correct. As there do not exist many publications on SCS for this particular indication, PVD, the study demonstrates a high importance and should be accepted for publication in Neuromodulation without further corrections.

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The authors of this report present a nice summary of a group of 40 patients with critical limb ischemia who underwent implantation of spinal cord stimulation (SCS) device specifically for this indication. Although not approved for clinical use in the United States, peripheral vascular disease is one of the most common indications for SCS worldwide, particularly in Europe. And since there is a hope that at some point this indication will be approved in the US as well, it is very important to collect data on technique and outcome, and critically analyze current situation in this field.

The authors' findings are indeed quite impressive. The baseline characteristics of the patients' circulation do appear to correlate with the treatment outcome. Not surprisingly, those with worse baseline characteristics fared worse in terms of amputation rate. However, I disagree with the tone of the authors' conclusions. Based on their experience, it is concluded that certain physiological and morphological data are helpful in patient selection and may improve efficacy of treatment. Indirectly, the authors suggest that those who have less reserves in their vaso-reactivity and are generally worse at baseline, will fare worse with SCS, and therefore may be screened out during the selection process.

I, however, would suggest otherwise. In the worse baseline group (Group B, 18 of 40 patients), 38.8% (7 out of 18) ended up with limb amputation within 12 months after SCS implantation. With "glass half empty" concept, these patients did not benefit from stimulation and therefore entire SCS process was done for nothing. But looking at this worst of the worst group of critical limb ischemia patients, one may assume that without SCS all 18 of them would have required amputation within this timeframe—and therefore, following the "glass half full" approach, it appears that 11 out of 18 (61.2%) were saved from amputation with SCS despite very poor baseline values.

I would encourage researchers to concentrate on this worst group of patients and pursue optimization of stimulation parameters, refinement of stimulation targets and using SCS as a part of a larger procedural approach in order to further decrease rate of unfavorable outcomes.

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Comments not included in the Early View version of this paper.

