ELSEVIER

Predictors of Improved Quality of Life and Claudication in Patients Undergoing Spinal Cord Stimulation for Critical Lower Limb Ischemia

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Background: The aim of this study was to determine predictors of improved quality of life and claudication in patients undergoing spinal cord stimulation (SCS) for critical lower limb ischemia.
Methods: We retrospectively analyzed 101 consecutive patients with few meter claudication and nonhealing ulcer who underwent definitive SCS. These patients were selected among 274 SCS patients treated at our center from 1995 to 2012. All presented with non-reconstructable critical leg ischemia (NR-CLI) and underwent supervised exercise therapy, best medical care and regular ulcers standard or advanced medications for at least 1 month before SCS implantation. We measured self-perceived quality of life using the SF-36 questionnaire. Patients with an improved walking distance of at least 30 meters after SCS had significant improvement on SF-36 questionnaire scores. We considered 30 meters as the cut-off for clinically significant improvement in pain-free walking distance, and we defined this value as functional success. Logistic regression was applied to assess baseline and other patient variables as possible predictors of functional success.
Results: Neither perioperative mortality nor significant complications were found. At a median follow-up of 69 months (range 1−202 months), mortality, major amputation, and minor amputation were 8.9%, 5.9%, and 6.9%, respectively. Functional clinical success was reported in 25.7% of cases. Independent predictors of functional success at univariate analysis included delay between the onset of the ulcer and SCS ($P < 0.001$) and the pain-free walking distance before SCS ($P < 0.002$). The only predictive factor of functional success at multivariate analysis was the delay between the onset of ulcer and SCS (median delay in patients with and without functional success was 3 and 15 months, respectively). In particular, comparable to pain-free walking distance before SCS, the success rate decreased by 40% for each month elapsed from onset of ulcer to SCS.
Conclusions: In our series of patients who underwent SCS, reduced delay between the onset of ulcer and SCS was associated with improved quality of life and walking distance. Larger series are required to confirm these data and to assess clinical implications.

INTRODUCTION

Spinal cord stimulation (SCS) was initially described in 1976 as a treatment for patients with ischemic pain caused by vascular disease.[1] It has been utilized in patients with chronic, stable, symptomatic non-reconstructable critical leg ischemia (NR-CLI) who are in Fontaine stage III or IV.[2,3] NR-CLI is a challenge in vascular medicine, and it has been defined as the condition that occurs when no distal arteries

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can be used as a potential site for bypass, no suitable veins are available as material for graft, and when the patient's comorbidity precludes an operation.[4] NR-CLI patients are usually affected by multiple comorbidities and often have advanced-stage leg ischemia. Sometimes even patients with Fontaine stage IIB, who develop small, nonhealing ulcers (progressing to Fontaine stage IV) with few meter claudication are considered non-reconstructable. Several treatments have been implemented for these patients: best medical therapy; controlled exercise; and, in some cases, SCS.[5] The aim of this study was to evaluate SCS outcomes in this group of patients, focusing on claudication, ulcer healing, and self-perceived quality of life, and also to assess the various predictors of clinical success.

METHODS

In the Department of Vascular Surgery at the Scientific Institute San Raffaele, an observational registry of SCS has been maintained since 1995, when the first stimulator was implanted. We treated a total 274 patients with SCS during the 17-year period from 1995 to December 2012. In all cases, patients had chronic, stable, symptomatic lower limb ischemia (Fontaine stage III or IV). In this study we analyzed patients monitored in our ambulatory, initially showing a clinical condition of Fontaine stage IIB, considered unreconstructable by specialists supported with second-level analysis such as computed tomographic angiography and magnetic resonance angiography. All patients were managed with best medical therapy with cilostazol or pentoxifillin and antiplatelet and pain medication. In addition, they underwent structured exercise programs, regularly monitored with treadmill testing. When these patients developed nonhealing ulcers, moving to Fontaine stage IV, they were assessed for SCS implantation. Inclusion criteria for treatment with SCS were unreconstructable ischemia, ulcers <4 cm, no deep infection, and no bacteremia. Moreover, patients had to be compliant with the treatment and capable of operating the SCS system, free of major cognitive deficits, and with a minimal life expectancy of 1 year.[6] We adopted measurement of local transcutaneous oxygen tension ($TCPO_2$) as criteria for patient selection, considering a baseline value of between 10 and 30 mm Hg as eligible.[4] We excluded patients with non-atherosclerotic CLI, such as Buerger's or Raynaud's diseases, and those who underwent previous treatments with prostaglandin, sympathectomy, or thrombolysis. We also excluded from our study patients who were lost to follow-up, or those who refused regular monitoring with treadmill testing. A total of 101 patients matched the inclusion criteria for our study.

At baseline, we recorded patients' demographics, risk factors, disease characteristics, previous revascularizations, analgesic therapy, and self-perceived quality of life based on the 36-item Short-Form Health Survey (SF-36),[7] a multipurpose health assessment with 36 questions used widely to evaluate quality of life (QoL). All patients performed a symptom-limited treadmill exercise test at hospital admission to determine their baseline pain-free walking distance and maximum walking distance. The protocol for treadmill exercise used in this study consisted of walking at 2.5 km/h and 0% grade. Pain intensity was evaluated with the visual analog scale (VAS).[8]

In accordance with our protocol, we performed implantation of temporary electrodes in all cases. We used Itrel II, Itrel III, or Veristrel devices (Medtronic, Minneapolis, MN, USA). All stimulators were placed while in the operating room under local anesthesia and short-term antibiotic prophylaxis with cefazolin 1 g intravenously. Electrodes were placed with the patient in the prone position. We used a Tuohy needle to locate the epidural space. Electrodes were then inserted at the desired level under fluoroscopic guidance. On-table stimulation was undertaken to confirm appropriate paresthesia overlap of the area of pain. The electrodes were then connected to a percutaneous extension cable linked to a portable external pulse generator.

After 1 month, all patients underwent an ambulatory visit to assess the effectiveness of primary treatment. Implantation of an internal impulse generator, as permanent treatment, was proposed for patients with significant pain reduction, amelioration of claudication, good compliance, $TCPO_2$ increase, and wound-healing improvement.[9] Otherwise, patients underwent removal of electrodes and follow-up. All patients were scheduled for assessment at months 1, 6, and 12 for a mean follow-up period of 32 (range 14–41) months. At each follow up visit, we recorded limb survival, walking distance, improvement in wound healing, analgesic drug use, adverse events, pain amelioration, self-perceived QoL, and $TCPO_2$ data. To monitor QoL, we used the SF-36 questionnaire. For all patients who had an improvement in walking distance of at least 30 meters, self-perceived QoL improved significantly according to the SF-36 questionnaire. We therefore considered 30 meters as the cut-off for clinically significant augmentation of pain-free walking distance, and we defined this value as functional success.

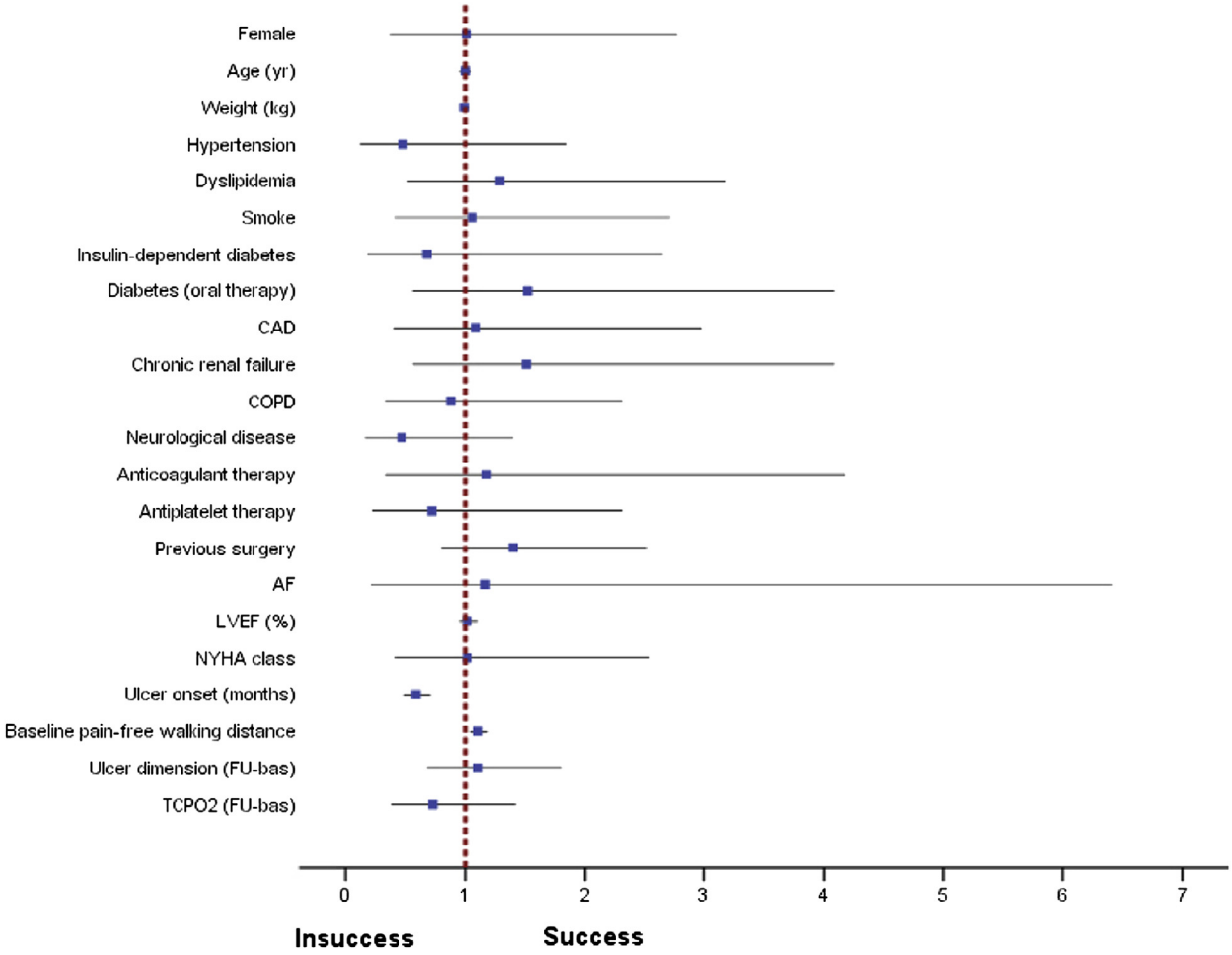

Fig. 1. Results obtained by univariate analysis for all variables considered. The elapsed time between onset of ulcer and implantation and pain-free walking distance preimplantation, independently of each other, were the only predictors of success (considered as an increase of at least 30 meters in pain-free walking distance at follow-up).

Logistic regression was applied to assess baseline and other patient variables as possible predictors of functional success.

The multivariate model is stepwise and includes all variables with $P < 0.10$ at univariate analysis. Results are shown as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical software (Stata/SE, version 12.1; StataCorp, College Station, TX, USA) used for analysis. All statistical tests were two-tailed with $P < 0.05$ considered significant. SPSS software for Windows was used for construction of the graphs.

RESULTS

A total of 103 patients were given temporary SCS. All patients were in Fontaine stage IV and had ulcers of <4 cm. There were no patients with non-atherosclerotic CLI, such as Buerger's or Raynaud's diseases, and no previous treatments with prostaglandin, sympathectomy, or thrombolysis.

We implanted a total of 44 (42.8%) temporary Itrel II, 51 Itrel III (49.5%), and 8 Versitrel (7.7%) devices, with equal distribution in the two groups. After 1 month, 101 patients were considered eligible for implantation of an internal impulse generator, as permanent treatment. Two patients underwent SCS removal for inefficacy of treatment, lowering of $TCPO_2$, and worsening of pain.

Neither perioperative mortality nor significant complications were reported. Six patients, 2 of them diabetics, underwent major amputation of the target limb (defined as amputation above the knee) at 11 and 18 months of follow-up, respectively, for worsening of ischemia and related symptoms. Four diabetic and 3 nondiabetic patients underwent minor amputation for worsening of

pain due to ulcer progression and infection. Functional clinical success after SCS was reported in 25.7% of the patients. Late mortality was 8.9% at a median follow-up of 69 (range 1–202) months. None of the deaths observed were attributable to SCS or its complications.

Figure 1 shows the results obtained by the univariate analysis for all variables considered. The elapsed time between onset of the ulcer and SCS and pain-free walking distance before SCS, independently of each other, were the only predictors of success. Specifically, the median delay between onset of the ulcer and SCS in patients with and without functional success was 3 (range 2–5) and 15 (range 12–15) months, respectively. With increased time (in units per month) between the onset of ulcer and SCS, the probability of success decreased (for each unit) by 41%, and pain-free walking distance preimplantation increased the likelihood of success by 11% (for each additional meter).

These two variables were subsequently introduced in a multivariate model to evaluate their relationship. The analysis showed that the only predictive factor was the delay between the onset of ulcer and SCS (Fig. 2). In particular, comparable to pain-free walking distance before implantation, the probability of success decreased by 40% for each month elapsed from onset of ulcer to implantation.

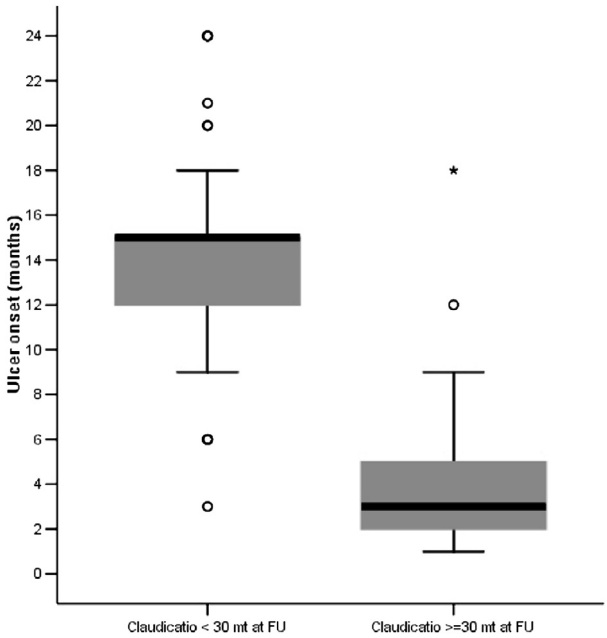

Fig. 2. The x-axis shows improvement of claudication and the y-axis shows the months elapsed between the onset of ulcer and implant. For each category, there is a ''box'' that identifies the first and third quartile and the ''whisker,'' which extends to each of the extreme values of the interval. The median is represented by the horizontal line within (or at the ends) the box. The points and stars outside the box represent the outlier values and the strong outlier values, respectively.

DISCUSSION

The vast majority of studies on outcomes of SCS in patients with lower limb critical ischemia have addressed rest pain reduction and limb survival.[10–13] Less analgesic uptake in patients treated with SCS has been reported.[3]

Only a few studies have reported the impact of SCS on claudication, mostly as a transition from rest pain to claudication, or on patient QoL.[14–16] Claudication is usually the first symptom described, and it is clearly an important determinant of QoL, particularly before the development of rest pain.

QoL was a major point of interest in this study, and our analysis showed significant improvement in self-perceived QoL in patients who had an increase of 30 meters in pain-free walking baseline distance—likely an expression of both pain reduction and amelioration of daily activity. In our study we observed that this target was achieved in about 25% of the patients overall, and QoL and claudication improved significantly if the median time between the onset of ulcer and SCS implantation was 3 months. This finding is of much interest because SCS has not been clearly shown to ameliorate limb salvage and patient survival,[10] and indications and timing of SCS are still strongly debated.[4] The role of best medical therapy and structured exercise program must be strongly considered in terms of increase in walking distance, prevention of rest pain, and amputation in patients with peripheral arteriopathy, but the rate of failure of these noninvasive is not negligible.[17,18] In recent years, the use of percutaneous transluminal angioplasty (PTA) of the tibial arteries has been proposed in these patients,[19] but middle- and long-term patency and outcomes are controversial.[20,21]

We have found that SCS may be very beneficial in specific subgroups of patients, poorly studied before, for specific functional targets, such as claudication and QoL. We hope our findings will initiate further study.

To detect the best candidates for SCS, most investigators have been in agreement that $TCPO_2$ should be used extensively as a patient selection criterion for SCS, showing the correlation between pain amelioration and microcirculation quality in the trial period and long-term outcome.[5,22,23] This

suggests the need for a valid tissue substrate for the vasodilation action of SCS, and the fact that pain reduction stimulates patients to walk, which leads to improvement of collateral pathways. In our series, $TCPO_2$ improvement during the trial period was one of the main inclusion criteria for definitive SCS. A recent study by Colini-Baldeschi and Carlizza[23] also demonstrated that the morphofunctional data provided by capillaroscopy highlighted the open capillary percentage poststimulation as being a significant parameter and should be evaluated in future studies.

In conclusion, in our series of patients who underwent early stimulation after ulcer onset, we found improved walking distance and QoL compared with patients who underwent late stimulation. Similar to pain-free walking distance before implantation, the probability of success decreased significantly for each month elapsed from onset of ulcer to implantation. Larger series are needed to confirm our findings and to assess the clinical implications.

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