

Effects of Spinal Cord Stimulation (SCS) in Patients with Inoperable Severe Lower Limb Ischaemia: A Prospective Randomised Controlled Study

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Objectives: This study was designed to test the hypothesis that spinal cord stimulation (SCS) improves limb salvage in patients with inoperable severe leg ischaemia.

Design: Prospective randomised controlled study with 18 months follow-up.

Setting: Vascular surgical units in two university hospitals.

Materials: Atherosclerotic (n = 41) and diabetic (n = 10) patients having chronic leg ischaemia with rest pain and/or ischaemic ulcerations due to technically inoperable arterial occlusions.

Chief outcome measures: Limb salvage and amount of tissue loss within 18 months, pain relief.

Main results: Twenty-five patients were randomized to SCS and 26 to analgesic (control) treatment. Macrocirculatory parameters were not different in the two groups during follow-up. Long-term pain relief was observed only in the SCS group. At 18 months, limb salvage rates in the SCS and control groups were 62% and 45% (N.S.). Tissue loss was less (p = 0.05) in the SCS group. A subgroup analysis of patients without arterial hypertension showed a significantly lower amputation rate in the SCS vs the control group.

Conclusions: SCS provided long-term pain relief but limb salvage at 18 months was not significantly improved by SCS in this rather small study. The results suggest that SCS may reduce amputation levels in patients with severe inoperable leg ischaemia and be most effective in patients without arterial hypertension.

Key Words: Amputation; Extremity; Ischaemia; Pain; Spinal cord; Stimulation.

Untreated severe chronic lower limb ischaemia usually leads to pain and skin ulcerations and, if the patient survives long enough, to gangrene. Revascularisation procedures, which usually abolish the need for amputation in such patients, are occasionally impossible to perform or fail due to poor outflow conditions. Although amputation may not be immediately necessary in such patients,¹ long-term limb salvage is poor.²⁻⁴ Several conservative treatment modalities have been tried in inoperable patients with severe lower limb ischaemia.^{4,5-7} Electrical spinal cord stimulation (SCS) has been reported to reduce ischaemic pain⁸ and improve ulcer healing⁹⁻¹¹ and microcirculation¹²⁻¹³ in ischaemic limbs. It has been suggested that SCS reduces tissue loss and improves limb salvage in inoperable lower limb ischaemia patients.^{9,14-16} Limb salvage by SCS is unproven,

however, since demonstration of such an effect requires a prospective randomised study. The primary hypothesis to be tested in the present randomised study was that SCS, as compared to conservative analgesic treatment, reduces the amputation rate within 18 months in patients with severe lower limb ischaemia considered inoperable due to poor outflow conditions.

Materials and Methods

Patients

During a 5-year period, patients with severe lower limb ischaemia in two vascular centres were evaluated for participation in this study. The inclusion criteria were severe chronic (duration more than 2 weeks) lower limb ischaemia in atherosclerotic and diabetic patients with rest pain and/or ischaemic ulcerations,

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in whom vascular reconstruction was considered impossible or had failed due to poor outflow conditions. Exclusion criteria were rapidly progressing ischaemia, gangrene of more than one toe, extensive infection and/or extensive non-healing ischaemic ulcerations, poor cooperability, or presence of associated diseases prohibiting the use of SCS. All patients had undergone digital subtraction arteriography. Arterial bypass was performed down to the ankle level during the first 3 years of the study, and down to pedal arteries during the last 2 years. A patient was considered inoperable if no outflow arteries were observed at or above the above mentioned levels, or if angiographically demonstrated outflow arteries at exploration were found to be heavily calcified, or if femorocrural/pedal bypass was possible but no vein was available. The study was approved by the Ethics Committee of the University of Göteborg. During the study period approximately 1000 patients were operated upon for severe lower limb ischaemia at the two centres.

Randomisation, treatment and follow-up

Patients were randomised to either SCS and peroral analgesic treatment (SCS group), or peroral analgesic treatment alone (control group). Peroral analgesics were prescribed as required by the patient: usually with dextropropoxyphen as the first choice and opiates as the second. The randomisation was stratified according to Pocock and Simon¹⁷ for sex, age (cut-off point was 70 years), diabetes and ischaemic ulceration. Management in the control group included pain control by analgesics, and care of ischaemic ulcers by a specially assigned nurse. Whenever relevant, antihypertensive and cardiotropic medications were optimised by an internist.

The patients were scheduled for follow-up visits to the out-patient clinic at 2, 6, 12 and 18 months after randomisation. A few patients who did not attend underwent telephone interviews. Indications for amputation were progressive gangrene, intractable pain, or extensive infection and/or non-healing ulcerations. A decision to amputate was taken by the patient and an independent orthopaedic surgeon, who also performed the amputation. Limb salvage was defined as no amputation, or an amputation on the forefoot only. The extent of amputation was classified in order of increasing handicap as none (no amputation, or minor amputations on the forefoot only), moderate (unilateral below knee amputation), or major (at or above knee level, or any bilateral amputation above ankle level).

SCS treatment

In the SCS group, the dorsal epidural space was punctured under local anaesthesia, and a thin multi-electrode lead was introduced and manipulated under fluoroscopic control until the tip reached the target point as assessed by intraoperative electrical stimulation confirming that paraesthesiae were experienced in the ischaemic areas.⁸ The lead was anchored to the supraspinal fascia. A subcutaneous pouch was established in the left iliac fossa for the pulse generator (Medtronic Quad + Itrel II, Medtronic Inc., Minneapolis, U.S.A.). A subcutaneous extension wire connected the lead and the pulse generator. Prophylactic antibiotic treatment was administered.⁸ The patient was usually discharged a few days later after external telemetric programming of the pulse generator. The stimulation parameters generally were: pulse width 210 μ s, frequency 50 Hz and an intensity (voltage) giving comfortable paraesthesiae in the ischaemic areas: one amplitude for upright position and one lower for bed rest were programmed. The patients could start or stop the stimulation as well as switch between the two stimulation intensities and were encouraged to use the stimulator as often as they wished. During follow-up visits, the patients were interviewed regarding function of the stimulator, and in particular regarding the adequacy of paraesthesiae in the ischaemic area. The patients were instructed to contact the responsible physician between follow-up visits if the paraesthesiae disappeared.

Parameters measured

The systolic (SP) and diastolic arm blood pressure, the ankle doppler pressure (AP) and/or the systolic toe pressure (STP) including distal to brachial pressure indices (ABI and/or STPI) were measured at randomisation and, whenever possible, during follow-up visits of unamputated patients. The ischaemic pain was assessed using two techniques. The patients were asked to describe their degree of pain (dummy variables) as slight (1), moderate (2), severe (3), very severe (4) or intolerable (5). Furthermore, the patients were asked to quantify the pain on the visual analogue scale (VAS¹⁸) from 0 (no pain) to 100 (maximally severe pain). The patients also described their feeling of warmth (i.e. skin temperature) in the ischaemic area using the VAS from zero (maximally cold) to 100 (maximally warm). Also these parameters were recorded at follow-up visits in unamputated patients whenever possible.

Statistics

Our previous open study⁹ showed a 10% limb salvage rate in a historical control group as compared to 80% in SCS patients (without partial gangrene prior to SCS). The hypothesis to be tested in the present study was 25% and 70% limb salvage rates at 18 months in the control and SCS groups respectively. A sample size of approximately 50 patients was estimated to be sufficient ($\alpha < 5\%$ and power $> 80\%$). Analysis was performed on an intention-to-treat basis. Limb salvage was calculated at 2, 6, 12 and 18 months and the extent of amputation at 18 months. Changes in distal pressures, pain and VAS scores were studied by the Wilcoxon signed rank test. Limb salvage was analysed using the life table technique.¹⁹ Intergroup comparisons were made using χ^2 or Mann-Whitney *U*-tests. Calculations regarding the extent of amputations included all patients, regardless of whether they survived for 18 months or not.

Results

Twenty-five and 26 patients who met the inclusion and exclusion criteria were randomised to the SCS and control groups, respectively. The two groups were

Table 1. Patient characteristics at randomisation

	SCS (<i>n</i> = 25)	Controls (<i>n</i> = 26)
Age (years \pm s.d.)	73 \pm 12	73 \pm 12
Female/male (<i>n</i>)	11/14	12/14
Ischaemic ulceration present (<i>n</i>)	13	13
Diabetes (<i>n</i>)	5	5
Arterial hypertension (<i>n</i>)*	11	13
Pain (VAS score)	52 \pm 5	55 \pm 5
Pain score (1–5)	3.2 \pm 0.2	3.1 \pm 0.2
Skin temperature (VAS score)	33 \pm 4	35 \pm 3
ABI in ischaemic limbs	0.36 \pm 0.05	0.39 \pm 0.05
Medication (<i>n</i>) with		
Opiates	5	6
Dextropropoxyphen	16	11
Paracetamol	6	11
ASA	2	2

* Data were missing in three patients.

similar regarding clinical characteristics (Table 1). Most patients (Table 2) had critical limb ischaemia according to the recently (1992) published criteria in the second European Consensus Document.²⁰ Three patients who were randomised to SCS never received SCS treatment. In the first case, the patient received a cardiac pacemaker shortly after randomisation which contraindicated SCS, in the second case, rapid deterioration occurred after randomisation, while in the

Table 2. Pressure indices for the two groups

	SCS	Controls	All
CLI (% of all)	21 (84)	24 (92)	45 (88)
ABI	0.33 \pm 0.05	0.37 \pm 0.06	0.35 \pm 0.04
STPI	0.08 \pm 0.02	0.05 \pm 0.01	0.06 \pm 0.01

Values are means \pm SEM. Abbreviations: ABI, ankle to brachial and STPI, systolic toe to brachial pressure index; CLI, critical limb ischaemia according to the second European Consensus Document.²⁰

third case SCS surgery was delayed due to reasons unrelated to the patient. These patients received early amputation at 1, 4 and 7 weeks respectively and are included in the analyses. One patient was reoperated for lead displacement during follow-up. There were no infections, or other complications to SCS during follow-up.

Mean VAS scores for skin temperature were similar in the two groups at randomisation (Table 1), and did not significantly change with time. An insignificant increase in ABI with time was observed in both groups (Fig. 1). The STPI was higher than the baseline value in both groups at 2 months and in the SCS group also at 18 months (Fig. 2), but there was no significant difference between the two groups. Using the VAS, significant long term pain relief was observed in the SCS but not in the control group (Fig. 3). Using the semi-quantitative pain score (1–5), pain relief ($p < 0.05$) was observed throughout follow-up in the SCS group, but never in the control group.

In the SCS-group, nine patients (36%) were amputated within 18 months versus 14 (54%) in the control group. There were eight deaths in each group.

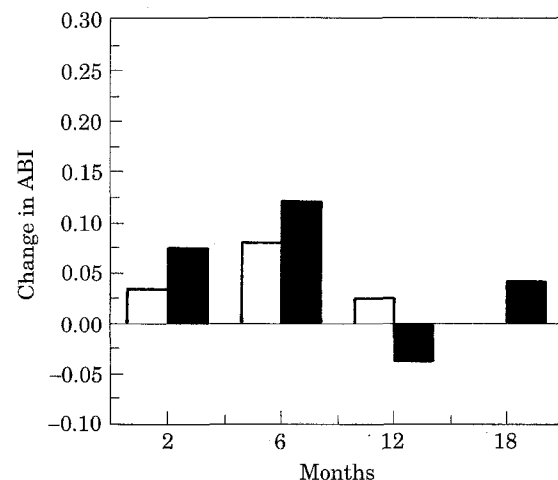


Fig. 1. Change in ankle-brachial index (ABI) during follow-up as compared to the randomisation value: control (□); spinal cord stimulation (■). There were no significant changes in either group (Wilcoxon rank sum test).

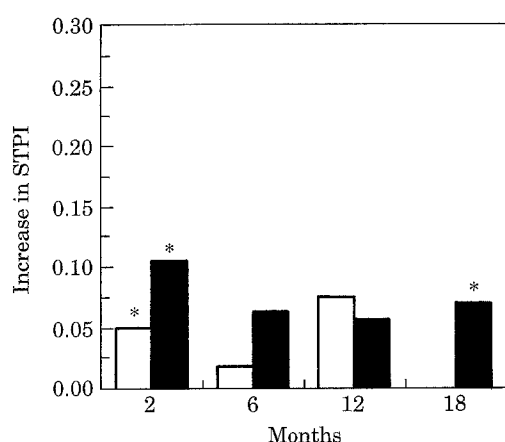


Fig. 2. Increase in systolic toe pressure index (STPI) during follow-up: control (□); spinal cord stimulation (■). * $p < 0.05$ vs randomisation value (Wilcoxon rank sum test). There were too few (< 5) observations in the control group at 18 months for analysis.

Ten of these 16 non-survivors died after having reached amputation as primary endpoint. At 18 months, there was an insignificantly higher limb salvage rate (62% vs. 45%) in the SCS vs the control group (Fig. 4). None, moderate and major amputations within 18 months were observed in 16, 8 and one patient in the SCS group vs 11, 8 and 6 in the control group. ($p = 0.05$, χ^2 test).

Subgroup analysis of amputation rates at 18 months in patients without arterial hypertension surviving and followed for 18 months demonstrated a higher ($p = 0.045$, Mann-Whitney U -test) amputation rate in the control group (nine out of 13) as compared to the SCS group (three out of 11). Subgroup analysis in patients with critical limb ischaemia (Table 2) demonstrated that 63% and 33% of the surviving

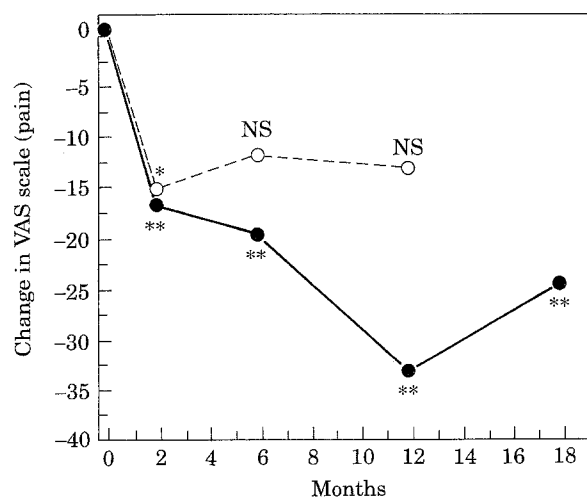


Fig. 3. Change in VAS score for pain during follow-up: control (○); spinal cord stimulation (●). There were too few (< 5) observations at 18 months in the control group for analysis. * $p < 0.05$; ** $p < 0.01$

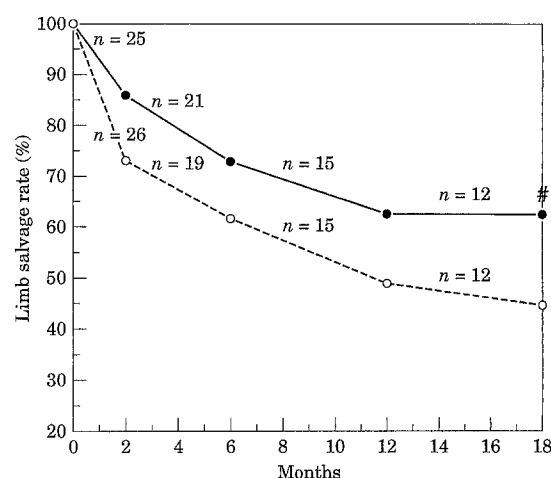


Fig. 4. Limb salvage rates in SCS and control groups within 18 months: control (○), spinal cord stimulation (●). N.S. vs. control group. The number of patients entering each interval is depicted.

patients were unamputated after 18 months ($p = 0.08$, Mann-Whitney U -test) in the SCS and control groups respectively.

Discussion

This study includes patients with technically inoperable severe chronic lower limb ischaemia and, using amputation and death as endpoints, evaluates the effects of spinal cord stimulation (SCS) and peroral analgesics as compared to peroral analgesic treatment alone. Limb salvage at 18 months was not significantly improved by SCS (62% vs. 45%), but the extent of amputations was smaller ($p = 0.05$). Mortality was similar in the two groups. During follow-up, there was significant long-term pain relief only in the SCS group whereas distal perfusion pressures were similar in the two groups. Subgroup analysis in patients without arterial hypertension showed a decreased amputation rate at 18 months in response to SCS.

The limb salvage rate in the SCS group (62%) was slightly lower than postulated in the hypothesis (70%) to be tested. Three patients randomised to SCS for various reasons did not receive SCS but were included in the intention-to-treat analysis. If these patients had been excluded, the limb salvage rate at 18 months would have been 69.9% in the SCS group. By contrast, the limb salvage rate in the control group was significantly higher than we expected. It is possible that this is partly due to intensified care of ischaemic ulcers and optimal adjustment of antihypertensive drugs.

We performed no microcirculatory assessments in this study. No significant macrocirculatory effects by SCS were observed in comparison with the control group. The trend towards increasing pain relief with time in the SCS compared to the control group may suggest that improved blood flow is one mechanism explaining the pain relief. SCS is reported to improve microcirculatory parameters such as capillary density, capillary red blood cell velocity (RBCV) and peak RBCV in patients with severely ischaemic legs who experience pain relief by SCS (denoted as responders), suggesting improved skin blood flow by SCS in responders.¹⁶ Transcutaneous oxygen tension increases in response to SCS¹¹ supporting this notion. Dooley found arterial dilatation in response to SCS.²¹ Roldan, using Doppler recordings, observed increased maximum speed and a tendency towards normalisation of the pulse wave form in response to SCS in limb ischaemia patients.¹³ Cardiac output (CO) is reported to increase in response to transcutaneous nerve stimulation,²² a method supposed to activate mechanisms partially similar to those of SCS. The effects of SCS on cardiac output in patients with severe lower limb ischaemia is not reported.

A reduced amputation rate at 18 months in response to SCS was observed in this study in patients without arterial hypertension. Interestingly, better results by SCS in non-hypertensive as compared to hypertensive patients were also observed in the study of Broseta and associates:¹⁰ six out of 10 hypertensive patients were amputated during SCS treatment, as compared to none out of 11 non-hypertensive patients. The present study failed to show a significant overall improvement in limb salvage by SCS. Based on the present results, more than 300 patients would be needed to demonstrate a limb-saving effect by SCS with the present inclusion and exclusion criteria.

It can be concluded that SCS gives long-term pain relief in patients with severe lower limb ischaemia and that the level of amputation may be lowered by SCS. The present results further demonstrate that physiological long-term effects of SCS as well as limb salvage must be evaluated in randomised controlled studies. The present data suggest that improved limb salvage by SCS can be expected in normotensive patients, but further prospective randomised studies are needed to evaluate the significance of this observation.

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