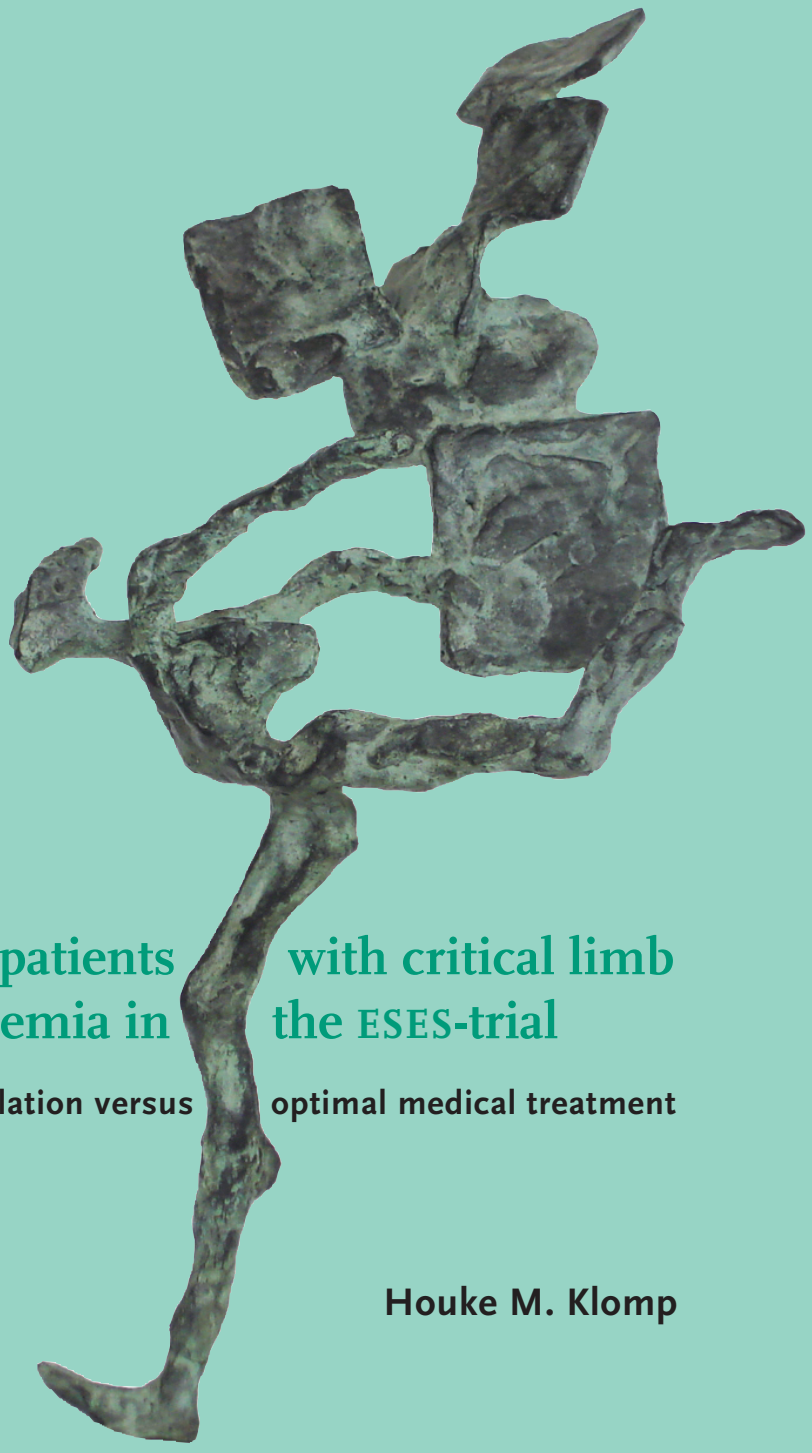

Outcome in patients with critical limb ischemia in the ESES-trial

Spinal cord stimulation versus optimal medical treatment

Houke M. Klomp

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Outcome in Patients with Critical Limb Ischemia in the ESES-trial

Spinal Cord Stimulation versus Optimal Medical Treatment

Uitkomsten bij patiënten met kritiek vaatlijden in de ESES-trial

epidurale ruggenmergstimulatie versus optimale medicamenteuze behandeling

Proefschrift

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op gezag van de
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Chapter I

General introduction and outline

Introduction

Symptomatic arterial disease in the legs is common and asymptomatic disease is even more common[1-4]. However the majority of these patients do not develop disabling intermittent claudication and the risk of major amputation is very small[2,5,6]. The Rotterdam study, a population-based analysis of 7715 patients, documented a frequency of intermittent claudication ranging from about 1% in those between the ages of 55–60 years to 5% in those between the ages of 80 and 85 years. Asymptomatic peripheral arterial disease, as defined by an ankle-to-brachial pressure index of less than 0.90 in either leg, was prevalent in 17% of men and 20% of women aged 55 and older[7].

From the patients with intermittent claudication, 5% to 10% undergo revascularization over 5 years, although there is wide regional variation in this outcome. Limb-threatening ischemia develops in 5% of patients, with 1% to 4% requiring amputation[2,6]. The risk of limb loss is overshadowed by the risk of morbid cardiovascular events and death[8-12].

Most vascular specialists in continental Europe use the Fontaine classification to categorize peripheral arterial disease (PAD). This classification, based on clinical information only, ranges from asymptomatic (I), claudication (II) to rest pain (III) and ischemic skin lesions (IV). Available data indicate that patients do not progress through these stages in an orderly fashion. This can be inferred from longitudinal studies demonstrating only a minority of patients with claudication progressing to Fontaine stages III/IV over time. Some patients progress directly from asymptomatic to stage III/IV.

Hypertension, cigarette smoking and diabetes in particular are powerful risk factors for developing Fontaine stage III/IV peripheral vascular disease, or its Anglo-American equivalent critical limb ischemia (CLI)[3]. If most patients do not progress from claudication into CLI, why do patients progress from mild or no symptoms to CLI? Several possibilities exist. Some patients with marginal circulation in asymptomatic limbs (limited walking activity) suffer progression following occlusion of an important collateral. Some patients with marginally perfused limbs will develop lesions from minor trauma that progress to non healing ulceration and gangrene. In some, acute events can precipitate marked deterioration in lower extremity circulatory states. The most common events are lower extremity bypass occlusion, immobilisation due to fractures or illness, or cardiac events.

Critical limb ischemia occurs when resting blood flow does not meet the basic metabolic requirements of the tissues. Clinically, the patient has pain at rest, ulcerations or gangrene. Despite therapy, only half of these patients will be alive without a major amputation a year after developing critical lower-limb ischemia[6,13,14]. Although numerically far less than claudicants, patients with CLI demand a disproportionately large commitment both in medical effort and economically and represent the major workload for vascular surgical units.

The lack of uniform criteria in reporting studies on CLI weakens the comparison of efficacy of different therapeutic strategies. Thus, to clarify, specify, and homogenize the definition of Fontaine stages III and IV, a consensus document was devised with the input of a number of European vascular specialist societies[6,15]. Chronic CLI in both diabetic and nondiabetic patients was defined by either persistent or recurrent distal extremity pain at rest that required the patient to use analgesics for >2 weeks, with an ankle systolic pressure of <50 mmHg and/or a toe systolic pressure <30 mm Hg, or with ulceration or gangrene of the foot or toes. Later

studies have raised doubts as to whether the ankle or toe pressure cut-off points have been chosen correctly[16]. The problem is that the optimal cut-off is not known, and at present, it is best to describe the pressure ranges (e.g. <50, 50 to 70, and >70 mm Hg). Particularly in diabetic patients, patients with renal disease, patients undergoing chronic steroid treatment, and in the elderly (>80 years), it remains an open question whether a single fixed cut-off point can be defined at all.

One of the greatest problems within modern vascular care of chronic CLI is the poor understanding and risk estimation of the natural history[17,18]. It is well recognized that CLI patients suffer diagnostic delays and poor risk factor modification, which in part contributes to limb loss and poor patient survival. The natural history of chronic CLI has been inferred from older studies, which reported amputation incidences of 60-80% within a year[13,15,19].

Surgical revascularisation procedures (bypass) and catheter-based endovascular interventions with balloon angioplasty or stenting have become the treatment of choice[20,21]. Despite major technical advances in limb salvage procedures, there remain conditions non-suitable for either primary intervention or reintervention after failing reconstructions, most commonly based on absence of suitable autologous vein for distal bypass surgery or major pathology of all crural arteries[10,22,23].

Treatment of such patients with end-stage vascular disease has been restricted to medical treatments. Basic care includes analgesics for ischemic pain and local wound care for ischemic skin lesions. Antithrombotic, hemorrheologic or vasoactive drugs to enhance the (micro)circulation have shown of little value[24].

Intermittent intravenous infusion during several weeks of prostanoids, such as prostaglandin E1 or more stable prostacyclin analogues such as iloprost have been shown to reduce rest pain and heal ischemic ulcerations in placebo-controlled trials, but results have not been consistent[25-28]. There is no evidence that in the long-term the limb is saved.

Hyperbaric oxygen has been used in patients with nonhealing ulcers who, for whatever reason, were not candidates for revascularisation. Only one randomised study of 70 patients with diabetes and ischemic foot ulcers documented a decreased rate of amputation[29]. The use of hyperbaric oxygen is expensive and results at many other institutions have been equivocal[2].

Intermittent pneumatic compression (IPC) aims at leg inflow enhancement and improvement of wound healing in patients with peripheral arterial disease. In small series of patients with tissue loss and nonhealing wounds, IPC has been reported to increase (skin) blood flow and to improve wound healing[30,31].

Gene therapy and cell therapy to stimulate angiogenesis have been tested mainly in phase I and II clinical trials. These studies demonstrated the short-term safety and feasibility of these new approaches[32-35]. Gene induced angiogenesis with vascular endothelial growth factor, holds potential to improve collateral vessel development. Intramuscular vascular endothelial growth factor gene transfer stimulated the formation of new vessels angiographically, improved the ankle pressure or ankle-brachial index, relieved rest pain, and healed ischemic ulcers in patients with end stage peripheral vascular disease. Lower extremity oedema from enhanced vascular permeability seemed to be an untoward effect of vascular endothelial growth factor administration, and gene therapy holds the theoretical potential to induce the growth of malignant cells concurrent with therapeutic angiogenesis[36]. The beneficial results of these studies must be corroborated by subsequent controlled studies before widespread use can be recommended.

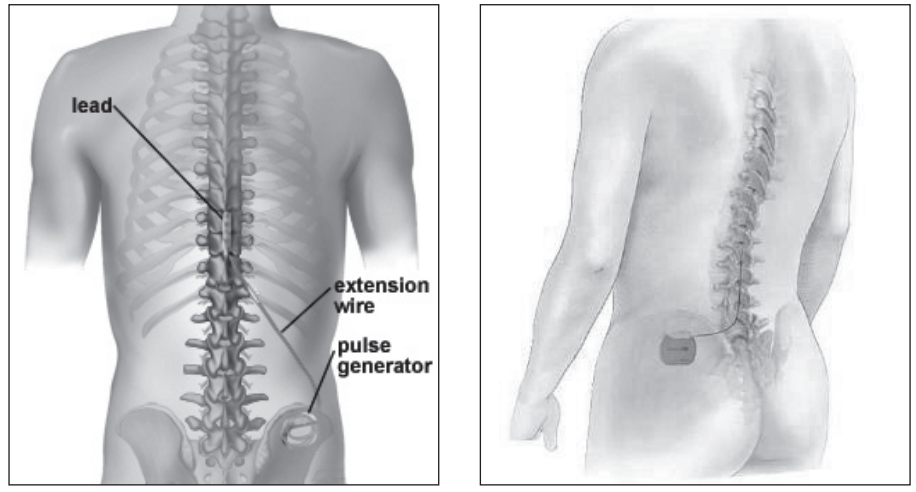

Figure 1: Posterior and lateral view of implantable spinal cord stimulation system with quadripolar lead and pulse generator (battery).

Since 1976, many authors have recommended the use of spinal cord stimulation (SCS) in patients with limb-threatening ischemia[37-55].

Neurostimulation delivers low voltage electrical stimulation to the spinal cord or targeted peripheral nerve to block the sensation of pain. The "Gate Control Theory" as developed by Melzack and Wall[56], proposes that neurostimulation activates the body's pain inhibitory system. According to this theory, there is a gate in the spinal cord that controls the flow of noxious pain signals to the brain. The theory suggests that the body can inhibit these pain signals or "close the gate" by activating non-noxious nerve fibers in the dorsal horn of the spinal cord. Spinal cord stimulation involves implantation of a pacemaker with epidural lead and activates pain-inhibiting nerve fibres in the dorsal columns. This causes paraesthesiae in corresponding dermatomes and suppression of nociceptive activity.

Dorsal column stimulation at Th10-L1 level induces paraesthesia in the lower extremities, thereby alleviating pain of various origins. Change of sympathetic tone and increase of nutritional blood flow have been postulated as possible mechanisms for clinical improvement of ischemia[57-61]. Completely internal neurostimulation systems with power source (battery) and lead(s) have been developed, which can be surgically implanted under local anaesthesia (Figure 1).

A number of studies have been carried out to evaluate the use of SCS for CLI, leading to enthusiastic recommendation of this treatment. Retrospective studies reported excellent pain relief and healing of ischemic skin lesions[37,40,41,62-65]. SCS was thought to prevent or delay amputation and limb salvage was reported to be 68–80% at 1 year and 56–71% at 2 years [39,41,45 66 67]. However until the end of the 20th century, no randomised controlled studies were available. Table 1 and 2 show global results on limb survival in patients with severe peripheral vascular disease treated with SCS in published series.

The best information on whether SCS reduces the incidence of amputation and does more good than harm to patients with severe ischemia of the lower extremity is generated by a randomized controlled clinical trial. We carried out a multicentre randomised trial in the

	Year	n	Fontaine stage	Follow-up [mo]	NOT amputated	Proportion
Tallis	1983[38]	10	II/III/IV	9	8/10	(0.80)
Fiume	1983[68]	21	III/IV	10	10/12*	(0.83)
Augustinsson	1985[39]	34	III/IV	16	27/34	(0.79)
Broseta	1986[40]	41	II/III/IV	25	36/41	(0.88)
Graber	1987[62]	9	III/IV	7	6/9	(0.67)
Bracale	1989[42]	27	III/IV	?	21/27	(0.78)
Franzetti	1989[64]	32	III/IV	> 6	27/32	(0.84)
Sampere	1989[44]	19	III/IV	7	16/19	(0.84)
Bunt	1991[65]	19	III/IV	12	12/15*	(0.80)
Mingoli	1993[69]	76	II/III/IV	26	32/76	(0.42)
Kasprzak	1994[70]	94	II/III/IV	24	73/94	(0.78)
Petrakis	1999[71]	45	III/IV	18	26/45	(0.58)
Petrakis	1999[72]	150	III/IV	71	85/150	(0.57)
Reig	2001[73]	95	II/III/IV	> 6	66/95	(0.69)
Neuhauser	2004[74]	21	II/III/IV	24	15/21	(0.71)

* number of patients evaluated did not match all included patients

Table 1: Descriptive series (SCS in PAD)

	Year	n	Fontainestage	Follow-up [mo]	Limb survival at 1 year	Limb survival at 2 years
Jivegard	1987[41]	32	III/IV	27	68%	59%
Jacobs	1990[66]	20	III/IV	27	80%	56%
Steude	1991[45]	10	III/IV	12	72%	-
Claeys	1994[75]	177	III/IV	36	74%	71%
Horsch	2004[50]	258	II/III/IV	12	78%	-
Brummer	2006[76]	8	**II/III/IV	12	75%	-
Gersbach	2007[55]	87	*III/IV	50	84%	78%

* selected patients with sitting/supine transcutaneous pO2 gradient >15 mmHg

** patients with end-stage renal disease

Table 2: Series (SCS in CLI) with survival analysis

Netherlands that compared spinal cord stimulation in addition to best medical treatment and best medical treatment alone in 120 patients with critical limb ischemia not suitable for further reconstruction.

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Outline of this thesis

The primary question of this thesis was, whether SCS-treatment improved the subsequent health of patients with non-reconstructable CLI more than best medical treatment alone. The randomized trial (ESES-trial) compared the two treatment regimes under clinical practice conditions. The approach was pragmatic and aimed at answering the question which mode of therapy works best, rather than how it works.

The results of the randomized trial in relation to literature data are presented in chronological order. Chapter II describes the design of the trial and its methodological problems. Chapter III describes the most important results: mortality, limb survival. Chapter IV summarizes the data on technical quality of stimulation treatment in the patients who were randomized to receive SCS. Chapter V shows the results of quality-of-life- and pain-assessment. Chapter VI describes the cost analysis of SCS-treatment. In chapter VII subgroup-effects are analyzed and the results of the randomized trial are discussed in relation to published reviews on SCS. Chapter VIII describes a simple prognostic model for the risk of amputation and in chapter IX a potential clinical management strategy is proposed for patients with non-reconstructable critical limb ischemia. A general discussion and summary are presented in chapters X and XI.

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Chapter II

Design issues of a randomised controlled clinical trial on spinal cord stimulation in critical limb ischemia

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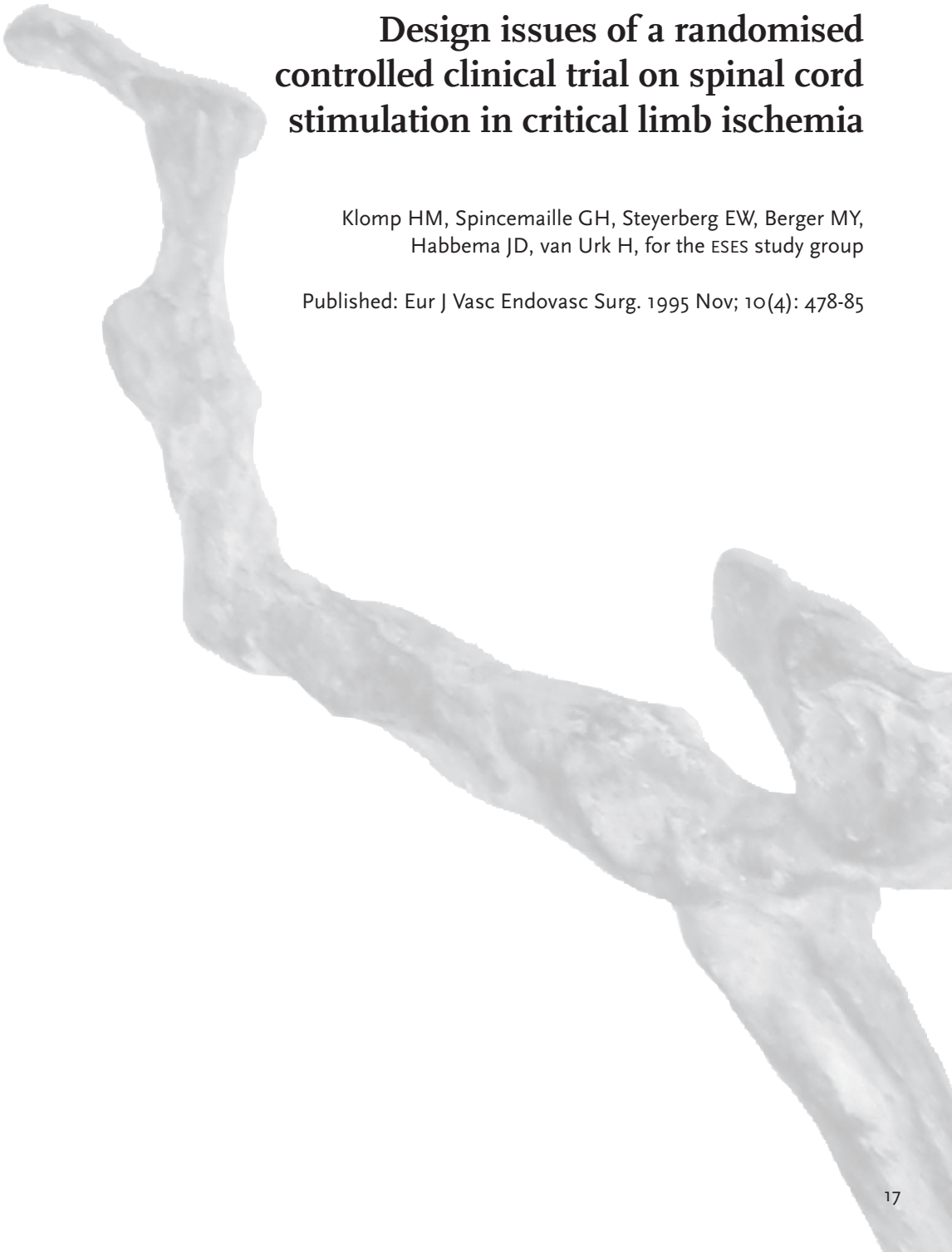

Abstract

Objectives

Review of the design of a clinical study to evaluate the efficacy of epidural spinal cord electrical stimulation (ESES) as compared to best medical treatment in patients with non-reconstructible critical limb ischemia.

Design

Randomized controlled clinical trial of pragmatic type, which was analyzed according to the intention-to-treat principle. The treatment strategies were ESES, in addition to best medical treatment, and best medical treatment alone. Patients were followed for at least 18 months. The ESES-trial was a multicentre trial in 17 hospitals in the Netherlands. Patients with critical limb ischemia, nonsuitable for either primary intervention or reintervention after failing reconstructions, were eligible. Chief outcome measures were limb survival, patient survival, quality of life, cost-effectiveness.

Main results

From November 1991 until May 1994, 120 patients had been enrolled. Using life-table analysis, at one year 76% of these randomized patients were alive: 41% without amputation and 35% with amputation. Quality of life of the trial patients was low, even compared to other severely ill patients groups, such as liver and heart transplant candidates.

Conclusions

Considering the high incidence of death and amputation, 18 months of minimal follow-up seems adequate to detect a clinically relevant outcome improvement from ESES-treatment if present.

Introduction

Chronic critical limb ischemia has an unfavourable natural history, leading to amputation of the limb in 60-80% of patients within a year[1-3]. Surgical bypass or endovascular procedures are the treatment of choice. Despite major advances in limb salvage by vascular repair, there remain patients nonsuitable for either primary intervention or reintervention after failing reconstructions. Until recently, treatment of such patients was restricted to medical treatment: analgesics for ischemic pain, hemorrheologic medication to enhance the (micro)circulation and local wound care for ischemic skin lesions[4-8]. Ultimately however, many of these patients face major lower-extremity amputation, which bears a high risk of disability, prolonged hospitalization and death.

Epidural spinal cord electrical stimulation (ESES) activates the dorsal columns of the spinal cord and causes paresthesias in the lower extremity, alleviating pain of various origins[9]. Moreover, ulcer healing and therefore a limbsaving effect has been suggested[10]. A number of studies have been carried out to evaluate the use of ESES for ischemia of the leg, leading to enthusiastic recommendation of this treatment[11-19]. One year limb salvage was reported to be approximately 80%, two year limb survival about 50%[16,17,20-22]. These studies were uncontrolled or made historical comparisons and a randomized controlled clinical trial was clearly required. In this paper, we describe the design issues of the ESES-trial in the Netherlands.

Design

The study is designed as a randomized controlled clinical trial. The treatment strategies are best medical treatment alone (standard treatment) versus best medical treatment plus ESES (ESES-treatment), and these are allocated at random to patients that meet the inclusion criteria. The eligibility criteria are shown in Table 1. Seventeen centers collaborated in the study. Patient data are collected on standardized patient-record forms.

The aim is to compare "ESES-treatment" with "standard treatment", in patients with non-reconstructible critical ischemia of one leg. Both treatments will be analyzed with regard to limb survival, patient survival, quality of life and cost-effectiveness. Quality of life is measured by a generic questionnaire (Nottingham Health Profile) and disease-specific questionnaires for mobility and pain. The costs of the alternative treatments will be compared by means of an economic evaluation. We use real cost rather than reimbursement fees. The secondary outcome measures are: use of analgesics, healing of ischemic skin lesions, amputation level, complications, and circulatory measurements. Prognostic factors for both primary and secondary outcomes will be studied.

In a pilot study performed in 1989, 37 patients were randomized, 18 to conservative treatment, 19 to ESES. Amputation-free survival at one year was 67% in the ESES-treatment group versus 47% in the conservative group (p=0.082) with a hazard ratio of 2.3. Based on the pilot-study and the available literature, the sample size of the trial was calculated using a hazard ratio of 2 for amputation in the standard and ESES-treatment group. Assuming a total proportion of endpoints of 50%, a two-sided confidence level (1-α) of 95% and power (1–β) of 80%, at least 56 patients per treatment arm are required[37].

Since November 1991, all patients with non-reconstructible critical limb ischemia visiting vascular surgeons in participating centers were screened for eligibility for the ESES-trial. The planned progress through the study is outlined in Figure 1. To evaluate the clinical course, the patients are followed up for at least 18 months by the surgeon who enrolled the patient. The

Inclusion criteria:	
Critical ischemia of one of the lower limbs in patients, for whom a meaningful vascular reconstructive procedure is considered not to be possible:	
1 a.	Persistent rest pain for at least 2 weeks, being treated with analgesics
b.	and/or ulceration or gangrene of foot or toes
2 a.	Doppler ankle systolic pressure less than 50 mmHg or ankle brachial pressure index (ABPI) less than 35%
b.	For patients with diabetes and incompressible vessels, leading to unreliable ankle pressure: absence of arterial ankle pulsation
3.	Patient informed consent
Exclusion criteria:	
1.	Vascular disorders other than atherosclerotic disease
2.	No rest pain (e.g. only intermittent claudication) and no ulceration or gangrene
3.	Ankle pressure > 50 mmHg and ABPI> 35%, when these pressures can be measured reliably
4.	Palpable ankle pulsations in patients with diabetes and incompressible vessels
5.	Ulcerations deeper than the fascia or with largest diameter > 3 cm
6.	Infected, suppurating gangrene or gangrene with largest diameter > 3 cm
7.	Intractable infection of ulceration or gangrene
8.	Critical ischemia of both legs
9.	Possibility of a meaningful vascular reconstruction
10.	Neoplastic or other concomitant disease with life expectancy <1 year
11.	Presence of a cardiac pacemaker
12.	Impossibility to implant an epidural electrode and stimulator
13.	Previous participation in an ESES-trial or pilot study
14.	Psychosocial incompetence of the patient to satisfy the follow-up schedule

Table 1: ESES-trial eligibility criteria.

follow-up flow chart is shown in Figure 2. Patients receiving ESES-treatment are checked regularly by a neurosurgeon or anesthesiologist for the stimulation settings and possible technical or clinical complications. The intake questionnaire concerning quality of life, pain and medical care is completed by the patient before randomization. In addition to outpatient clinic follow-up, the coordination center mails questionnaires to the patient's home, two to four weeks after each follow-up visit; a postage-free reply envelope is provided.

Organization.

The coordination center receives the patient-record forms and questionnaires and maintains a concurrent database. The study is set up as a multicenter trial with local responsibility. Within each clinic a center-coordinator is responsible for the data collection. A steering and ethical committee supervise trial conduct and progress. Treatment allocation is performed in an independent Research Assistance Institute. The clinician phones the randomization center, which checks eligibility, registers the patient and gives the treatment assignment right away, using randomization software on a personal computer. Stratified randomization as described by Zelen[23] is used. Strata are formed by diabetes and institution, which ensures a balance of ESES- and standard treatment in diabetic and non-diabetic patients and within the participating centers.

Treatment regimes.

Patients allocated to standard treatment receive analgesics, antithrombotic and hemorrheologic drugs, local wound treatment and antibiotics, if indicated. There is a list of recommended medication, but no fixed treatment regimen. The clinician should in particular aim at adequate pain suppression. Sympathectomy and prostanoids were not excluded, but both were used infrequently. Those allocated to ESES treatment additionally receive an implantable spinal cord stimulation system (Itrel II® pulse generator and quadripolar electrode, Medtronic, Minneapolis, MN, USA). The lead is placed in the epidural space and manipulated until the patient experiences pleasant paraesthesia extending down into the painful area of the limb. The pulse generator is implanted in the same session. Again, primary aim is adequate pain suppression.

If pain suppression is inadequate, the effect should be optimized by altering pain medication and/or stimulation settings. In case of technical problems, electrode migration or infection, attempts should be made to resolve the difficulties (by repositioning the electrode, replacing the implant or treating with antibiotics). If such problems cannot be corrected, the system will be removed. These patient receive standard treatment, but are analyzed in the original treatment group.

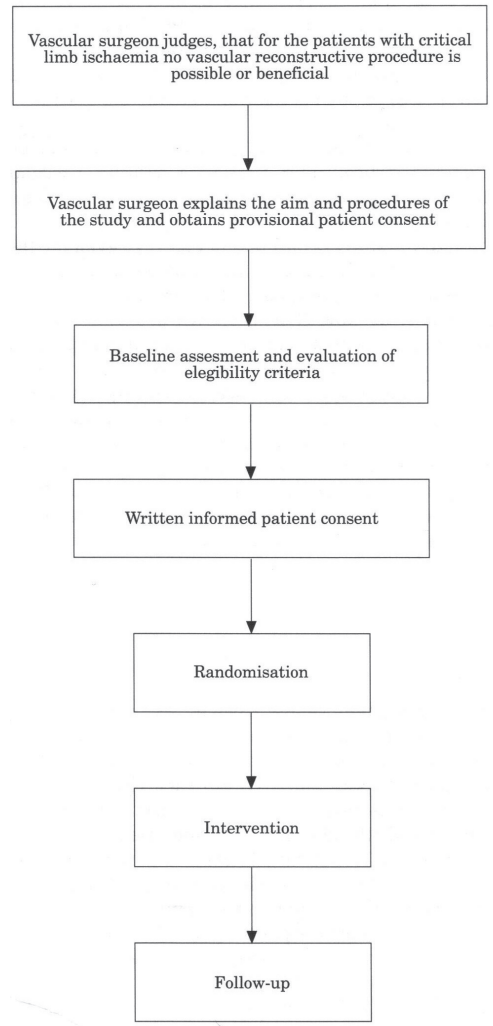

Figure 1: Flow chart of patient progress through the ESES-trial

Progress

Although estimated cautiously, the accrual rate turned out to be lower than expected. Randomization of 120 patients was completed in May 1994. There was quite some variation in the number of recruited patients among the clinics. Two hospitals provided over 30% of the patients. The intake rate is summarized in Figure 3.

A number of baseline patient characteristics are listed in Table 2. Prior to randomization a mean of 2.2 vascular interventions were performed in the critically ischemic legs: none in 22%, one intervention in 23%, two interventions in 22%, three interventions in 13% and four or more interventions in 20% of the limbs. Forty patients (33%) previously had an ipsilateral sympathectomy. Mean ankle pressure in non-diabetic patients was 41.3 mmHg (mean ankle-brachial pressure index was 0.26).

	Vascular surgeon (standard and ESES)				Neurosurg. (ESES)	Coord. center
	Exam	Qu	Dop	µc	Stim	Qu
Intake	±	±	±	±	+	
t=0 Randomisation						
1 month	±		±	±	+	±
3 months	±		±	±	+	±
6 months	±		±	±	+	±
12 months	±		±	±	+	±
18 months	±		±	±	+	±
end of study	±				+	

Abbreviations:
± = ESES treatment and standard treatment groups.
\+ = applies only to ESES treatment group.
Exam = clinical examinations.
Qu = questionnaire on quality of life, pain, medical consumption.
Dop = Doppler ankle pressure measurements.
µc = microcirculatory measurements.
stim = follow-up stimulation settings by neurosurgeon or anaesthesiologists.

Figure 2: Flow chart of follow-up

Patient compliance on completing the questionnaires on quality of life and consumption of medical care was most satisfactory. Completing the list took on average 47 minutes (range 5-300 minutes). We compared the baseline quality of life score of the trial patients with reference values matched on age and sex, taken from a random sample of 2173 people representing the general English population[24]. The general well-being of trial patients proved to be much worse than well-being of the general population. Compared to other severely ill patients (liver and heart transplantation candidates), quality of life was also less, pain being the predominant characteristic[25,26]. The results have been summarized in Figure 4.

By December 1994, 37 patients died and 53 patients underwent major amputation. The Kaplan-Meier plot is shown in Figure 5. The incidence of death and amputation was high, indicating that a clinically relevant outcome improvement from ESES-treatment, if present, should be detectable.

Discussion

The need for controlled studies of promising new treatments in critical limb ischemia has been stressed recently by many authors[27-31]. A number of controversies about the alleged effects of sympathectomy, prostanoids and epidural stimulation continue to exist as mainly uncontrolled reports are published. An adequate concurrent control group is mandatory, as a significant number of patients could be stable or improve with conservative methods. "Limb salvage" with conservative treatment could be as high as 60%[4,5,27,32]. Furthermore, studies of new treatment modalities tend to coincide with considerably more medical care (hospitalized care, control visits), which in itself can cause better results than expected.

The primary question that needs to be answered, is whether ESES-treatment improves the subsequent health of a patient more than best medical treatment alone. This study compares the two treatment regimes under clinical practice conditions. The approach is thus pragmatic and aims at answering the question which mode of therapy works best, rather than how it works[33].

In non-reconstructible critical ischemia, the effectiveness of treatment cannot be expressed

in so-called "hard" endpoints only. Research reports in vascular surgery generally focus on mortality, limb survival and complications, whereas the patients' subjective feelings and quality of life are also important aspects of the patients' clinical condition, affecting the decision whether or not to perform a therapeutical procedure [34]. The ideal outcome would be the patients' health for his or her remaining life. In critical ischemia limb salvage is an important endpoint, but only in combination with an acceptable level of pain and discomfort.

In addition to the "true effects" of the treatments studied, there will be psychosomatic effects, analogous to placebo effects. Whereas in this study the psychosomatic effects can not be equalized between the two groups of patients (a nonfunctioning device should be implanted in patients with standard treatment, which is ethically unacceptable), we include these within the "true effects" and assess psychosocial effects as results as well[33,34]. To minimize the effect of follow-up visits and differences in data collection between ESES- and standard treatment, the measurement of quality of life and pain takes place between two follow-up visits.

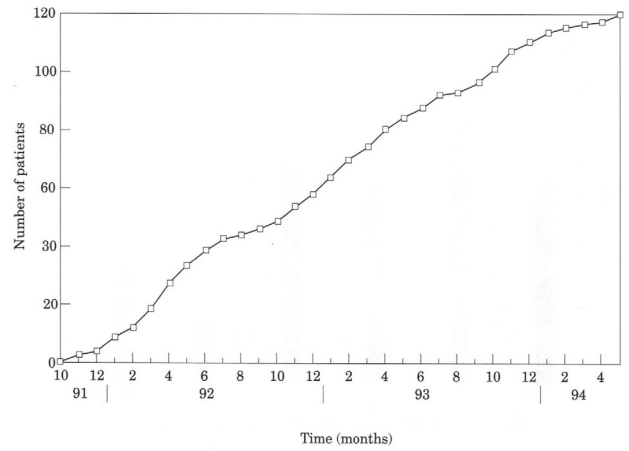

Figure 3: Accrual rate ESES-trial.

If the condition of the limb becomes progressively worse, the vascular surgeon has to decide whether to amputate. This decision is taken on grounds of progressive tissue loss, intractable infection or unbearable pain. This is to some extent susceptible to individual judgement. Center-specific factors are equalized by the stratified randomization. Thus, deferral of amputation can be considered a positive result, if based on an improved condition of the extremity and on an improved health state, additionally taking into account the short life expectancy of the group of patients studied.

The eligibility criteria (Table 1) were drawn according to the "European Consensus Document on Chronic Critical Limb Ischemia"[4]. Toe systolic pressures were not used, since a number of participating hospitals do not measure these. There has always been debate about the definition of critical limb ischemia. This issue has become very prominent since Thompson *et al*.[35] presented data on 148 severely ischemic limbs in non-diabetic patients, presenting with rest pain, tissue necrosis or a combination of these. Ankle systolic pressure was > 50 mmHg in 51% of these limbs. A higher ankle pressure did not correspond with better prognosis. Therefore, many participating surgeons argued for reassessment of the ankle pressure restriction. From March 1993 onwards, patients with ankle pressures 50-70 mmHg (was ≤ 50 mmHg) or ABPI 35-40 % (was ≤ 35 %) were included. Treatment allocation was balanced within this group by

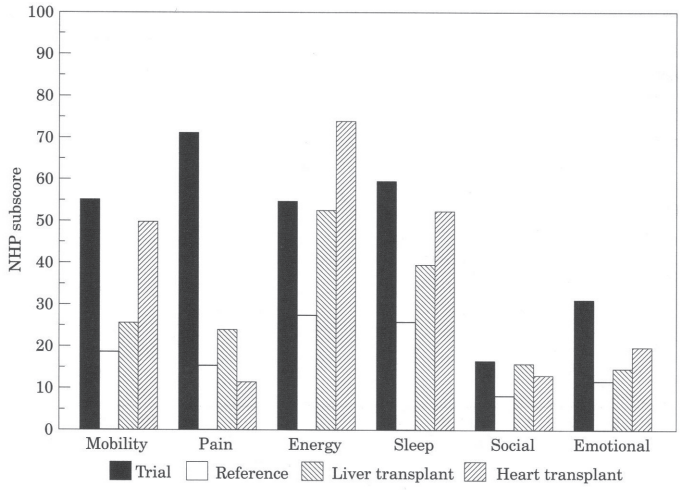

Figure 4: Quality of life, measured by Nottingham Health Profile, in trial patients (1st column) as compared to a reference population (2nd) and to candidates on waiting lists for heart and liver transplantation (3rd/4th). Higher scores correspond with deteriorating health states.

definition as a separate stratum.

For comparability in research, the relevance of stringent definition of critical limb ischemia is obvious. However, the absence of a meaningful vascular (re)intervention means that this trial population is already different from the whole population of patients with critical limb ischemia. Many patients in this trial have a history of multiple vascular reconstructions. Secondly, relaxation of some inclusion criterium may be necessary to ensure the feasibility of a multicenter trial and commitment of its participants[36]. The essential feature is that the trial is representative for the patient group likely to benefit from its findings. Efficacy and safety as regards to clinical outcome will be analyzed according to the intention-to-treat principle. Consequently, all eligible patients, regardless of technical problems or compliance, are included in the analysis. This results in a valid comparison as it relates to actual clinical practice[36].

Since ESES-treatment involves a costly implant, but might decrease the expense of amputation and rehabilitation, the issue of cost versus possible benefit has often been addressed[16,17,29]. A concrete analysis of cost, however, has never been performed. Costs can be classified into direct medical costs (inside and outside the hospital), direct non-medical costs (patient costs) and indirect cost[38]. The viewpoint of the analysis has to be the society perspective, thus all costs and consequences will be taken into account whomsoever they accrue. The costs are calculated per patient as the product of volumes and market prices. Volumes will be determined for all patients, while cost per procedure will be estimated in a smaller sample.

For valuation of the cost, we first identified the fundamental cost items. A detailed cost analysis is necessary to estimate market prices for the important determinants, i.e. those with large volumes or high prices. These are primarily direct medical costs, such as in-hospital-stay, operative procedures (implantation, amputation), outpatient visits, and admission to nursing-home or rehabilitation centre. Prices are valued using department based cost registrations and involve quantification of attendance by health professionals, supplies, equipment, and capital costs in one university hospital and two general hospitals. Prices of admission to a nursing-home or rehabilitation clinic are available from a Dutch national investigation. For less important cost

items, as travel expenses and out-of-pocket payments, charges or expert estimates are used as approximations of the market prices. Finally, the various medical effects (outcome measures as patient- and limb survival and quality of life) will be related to the cost of each treatment. This cost-effectiveness analysis will be performed for the whole group of trial patients, but also for specific patient profiles. If the most effective treatment is also the most expensive, the ratio of cost and effects may need to be compared with other health programs.

In short, this randomized clinical trial will provide insight in the effects of ESES treatment in patients with non-reconstructible critical limb ischemia. Intake of 120 patients is completed and follow-up is proceeding adequately.

	Frequency	%
Male (70.6 years mean age)	70	58
Female (75.3 years mean age)	50	42
Diabetes	45	38
Insulin dependent	19	16
Rest pain	119	99
Ischemic skin lesions	79	64
Contralateral limb:		
Asymptomatic	56	47
Symptomatic	48	40
Amputated	16	13
Smoking:		
Never	37	31
Stopped > 1	38	32
Smoking	44	37
Myocardinal infarction in history	45	38
Angina pectoris	26	22
CVA	15	13
TIA	18	15

Table 2: Baseline characteristics on 120 patients enrolled in the ESES-trial

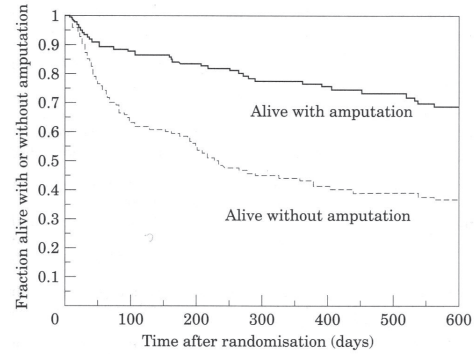

Figure 5 : Kaplan-Meier plot for the whole trial population, the upper line indicating mortality, the lower line indicating amputation. The area between the lines shows the proportion of patients alive with major amputation. The area below the lower line shows the proportion alive without amputation. At 365 days it can be read that 76% of patients were alive: 41% without amputation and 35% with amputation.

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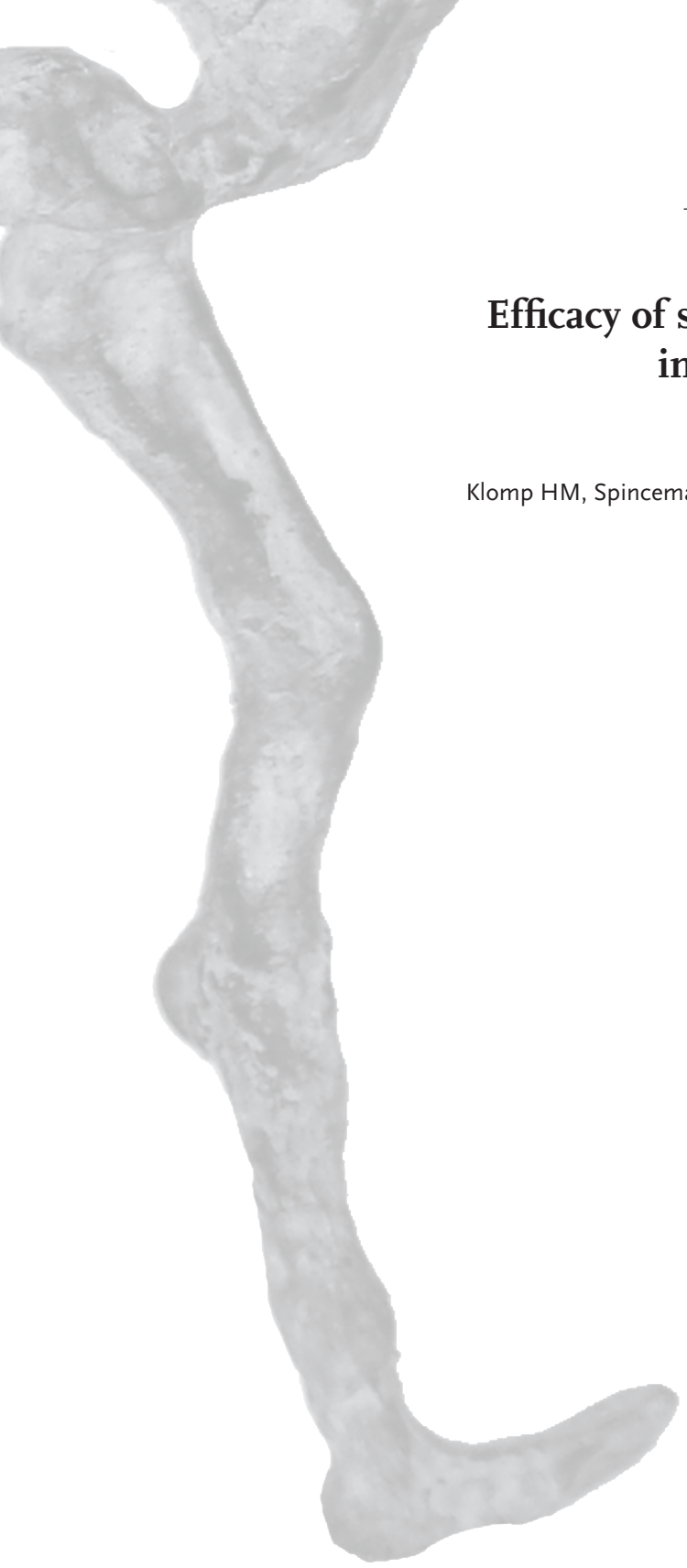

Chapter III

Efficacy of spinal cord stimulation in critical limb ischemia

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Abstract

Background

For patients with critical limb ischemia, spinal cord stimulation has been advocated for the treatment of ischemic pain and the prevention of amputation. We compared the efficacy of the addition of spinal cord stimulation to best medical treatment in a randomised controlled trial.

Methods

120 patients with critical limb ischemia not suitable for vascular reconstruction were randomly assigned either spinal cord stimulation in addition to best medical treatment or best medical treatment alone. Primary outcomes were mortality and amputation. The primary endpoint was amputation-free survival at 2 years.

Findings

The mean (SD) age of the patients was 72·6 years (10·3). Median follow-up (range) was 605 days (244–1171). 40 (67%) of 60 patients in the spinal cord stimulator group and 41 (68%) of 60 patients in the standard group were alive at the end of the study, (p=0·96). There were 25 major amputations in the spinal cord stimulator group and 29 in the standard group, (p=0·47). The hazard ratio for survival at 2 years without major amputation in the spinal cord stimulation group compared with the standard group was 0·96 (95% CI 0·61–1·51).

Interpretation

Spinal cord stimulation in addition to best medical care does not prevent amputation in patients with critical limb ischemia.

Introduction

Critical lower-limb ischemia occurs when resting blood flow does not meet the basic metabolic requirements of the tissues. Clinically, the patient has pain at rest or ischemic skin lesions. Surgical revascularisation or endovascular angioplasty are the preferred treatments. Despite many technical and clinical advances, some patients have end-stage vascular disease -i.e, limb-threatening ischemia that is not suitable for either primary intervention or reintervention.

The natural history of non-reconstructable critical limb ischemia is not clear. Many groups suggest that amputation of the limb is necessary in 60–80% of patients within a year[1–6]. Antithrombotic and vasoactive drugs are of little value in the management of critical limb ischemia. Only prostanoids have shown some efficacy, but there is no evidence that in the long-term the limb is saved[3,7–9].

Stimulation of the dorsal columns of the spinal cord causes paraesthesiae in corresponding dermatomes and suppression of nociceptive activity. In the past 15 years, spinal cord stimulation has become an accepted technique to treat neurogenic pain disorders. The benefits of spinal cord stimulation for ischemic disorders -excellent pain relief and healing of ischemic skin lesions- were reported in retrospective studies[10–20]. Spinal cord stimulation was thought to prevent or delay amputation and limb survival was reported to be 68–80% at 1 year and 56–71% at 2 years[10,13,21–24]. However, efficacy has not been confirmed in randomised controlled studies. The only controlled study (n=51) found no statistical difference in the proportion of limbs saved at 18 months between spinal cord stimulation and control groups (62% *vs* 45%)[25]. We carried out a multicentre, randomised clinical trial in the Netherlands that compared spinal cord stimulation and best medical treatment in 120 patients with critical limb ischemia not suitable for further reconstruction.

Methods

The design, randomisation, and other procedures have been described in detail elsewhere[26]. The study took place between November, 1991, and January, 1996, in 17 hospitals in the Netherlands. The protocol was approved by the ethical committees at each centre, and patients gave written, informed consent.

Eligible patients had critical limb ischemia and were not candidates for vascular intervention or reintervention, usually because of insufficient distal runoff or recurrent graft failure. Inclusion criteria were persistent pain at rest for more than 2 weeks or ischemic skin lesions, ankle systolic pressure below 50 mm Hg or, in patients with diabetes and incompressible vessels, absent palpable ankle pulses. Patients with extensive necrosis or infected gangrene and those who were terminally ill, dependent on a pacemaker, or unable to complete the patient questionnaire were excluded. Patients were stratified by diabetes, ankle pressure, and hospital. Randomisation was by a random-numbers table and the list was held independently of the investigators.

Patients were randomly assigned best medical treatment, which was the standard treatment, or spinal cord stimulation treatment, which was in addition to the best medical treatment. Medical treatment included analgesics, antithrombotic drugs such as aspirin or coumarins, vasoactive drugs such as pentoxifylline, buflomedil, or ketanserin, local wound care, and antibiotics, as needed. A list of recommended medication was provided, but there was no fixed treatment regimen. Chemical lumbar sympathectomy and prostanoids were not excluded, but were used in three patients only. The lead of the spinal cord stimulator (Quadripolar, Medtronic, Minneapolis, MN, USA) was placed in the epidural space and manipulated until the

patient experienced pleasant paraesthesiae that extended into the painful area of the limb. The pulse generator (Itrel II, Medtronic, Minneapolis, MN, USA) was implanted at the same time into the subcutaneous tissue of the flank. Patients with a spinal cord stimulator were checked regularly by a neurosurgeon or anaesthetist.

If pain suppression was inadequate, medication, stimulation settings, or both were changed. Lead migration or infection of the stimulator was treated by repositioning the electrode, or treatment with antibiotics, but if these measures failed, the system was explanted.

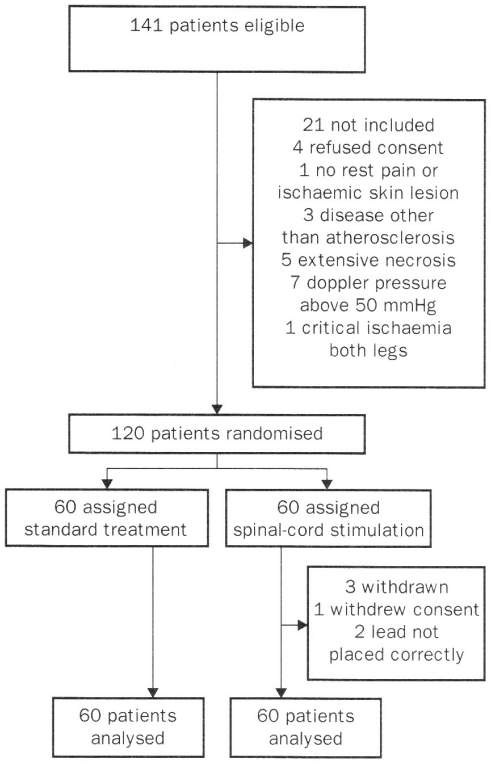


Figure 1: Trial profile

All patients were assessed at months 1, 3, 6, 12, 18, and at the end of the study. Between follow-up visits patients came to hospital as needed. The primary endpoint was limb survival at 2 years. When amputation was indicated, the level of amputation was recorded. Limb survival was defined as absence of major amputation[27]. Major amputations were those at the level of the ankle or higher. Death from progressive gangrene, sepsis, complications, and 30-day perioperative mortality after amputation or implantation was classified as disease-specific mortality.

For assessment of pain, the McGill Pain Questionnaire[28] was used and the pain-rating index (PRI) was the measure of expressed pain. Analgesic use was recorded and quantified by the medication quantification scale (MQS)[29]. An MQS score was calculated from the dose and assigned values of the different analgesics. Major analgesics were narcotic analgesics and minor analgesics were aspirin, paracetamol, and non-steroidal antiinflammatories. The Nottingham

Health Profile[30] (NHP) and EuroQol[31] were used to assess quality of life.

Cost analysis was based on resources used by patients for 2 years after randomisation or until death, if it occurred within 2 years. Costs were classified into direct medical costs—those incurred inside and outside the hospital—direct non-medical costs, and indirect costs[32]. The costs were calculated per patient as the product of volumes and market prices. Volumes of the cost items were collected for all patients. Market prices were estimated in smaller samples. All costs were expressed in 1993 Dutch guilders (ƒ1,00 ~ 0.35 UK£ at the time of this study).

Statistical analysis

Analysis was by intention to treat and included all patients who were randomised. Differences between groups were compared by *t* tests, for continuous variables, and by χ^2 tests for categorical data. Patient and limb survival was estimated with the Kaplan-Meier method and differences were evaluated by the log-rank test. In the analysis of limb survival, patients were censored at death. Healing of ischemic skin lesions could only be assessed in intact legs and thus patients who died or had an amputation were censored. For the analysis of amputation level, patients were censored at death or at amputation on a higher level. Pain and quality-of-life measurements were assessed by ANCOVA and adjusted for baseline differences; $p<0.05$ was deemed statistically significant. The study had 80% power to detect an increase in limb survival by 3 months (hazard ratio 1·8), based on a total sample size of 120 patients at the 95% level of significance.

	Spinal-cord stimulation (n=60)	Standard (n=60)
Demographic		
Age (years)*	73·1 (9·8)	72·1 (10·6)
M/F	33/27	37/23
Other disorders		
Diabetes	22 (37%)	23 (38%)
Cerebrovascualr accident or TIA	13 (22%)	16 (27%)
Myocardial infarction	23 (38%)	22 (37%)
Angina pectoris	12 (20%)	15 (25%)
Vascular		
Smoking		
Stopped for more than 1 year	22 (37%)	16 (27%)
Current	18 (30%)	26 (44%)
Contralateral limb		
Symptomatic	19 (32%)	29 (48%)
Amputated	9 (15%)	7 (12%)
Ischaemic skin lesions	38 (63%)	41 (68%)
Ulceration	23 (38%)	27 (45%)
Gangrene	15 (25%)	14 (23%)
Previous vascular reconstructions		
1 or 2	25 (42%)	29 (48%)
≥3	19 (32%)	20 (33%)
Sympathectomy	21 (35%)	19 (32%)
Ankle systolic pressure (mm Hg)*	35·2 (24·8)	41·6 (21·8)
Ankle-to-brachial pressure index*	0·23 (0·16)	0·28 (0·13)
Pain and quality of life		
Minor analgesic	54 (90%)	50 (83%)
Major analgesic	18 (30%)	21 (35%)
MQS score*	7·0 (5·1)	7·4 (5·2)
Pain rating index score*	22·6 (11·4)	21·6 (11·4)
Quality of life scores		
NHP*	47·7 (19·4)	47·2 (20·0)
EuroQol	54·0 (21·0)	50·7 (20·4)

Data are number (%) or *mean (SD). TIA=transient ischaemic attack.
MQS=Medication quantification scale score. NHP=Nottingham health profile.

Table 1: Baseline clinical characteristics of patients

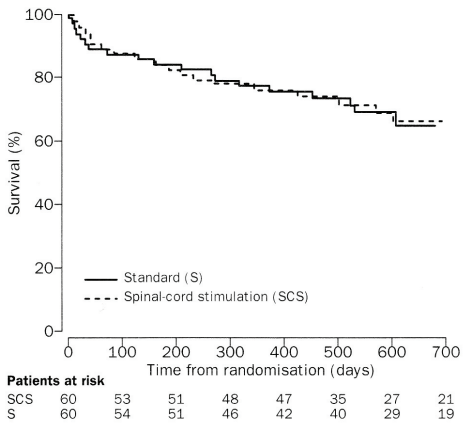
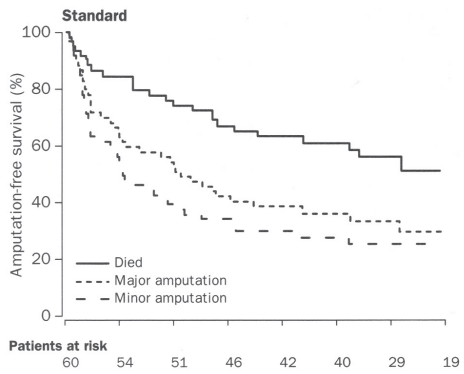


Figure 2: Mortality



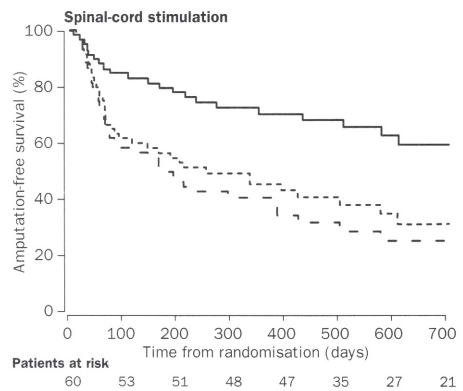


Figure 3: Amputation-free survival in the treatmentgroups (standard=upper graph; SCS=lower graph) by type of amputation.

Results

141 patients were eligible and the flow of patients is shown in Figure 1. 120 patients were randomly assigned spinal cord stimulation or standard treatment. The mean (SD) days in hospital for implantation of the stimulator was 4·9 days (2·3).

The characteristics of the patients at baseline are in Table 1. All patients took analgesics. Median follow-up was 605 days (244–1171). Kaplan-Meier estimates of patient survival were

similar in the two groups (Figure 2): the hazard ratio for the spinal cord stimulation group was 1·09 (95% CI 0·59–2·03). Disease-specific mortality at 6 months was 5% in the spinal cord stimulation group compared with 7% in the standard group; at 2 years these values were 5% and 9% (p=0·45), respectively.

The amputation-free survival rates are shown in Figure 3. The areas between the curves show the proportion of patients alive without major or minor amputation. The hazard ratio for survival at 2 years without major amputation was 0·96 (0·61–1·51).

Kaplan-Meier plots for limb survival are in Figure 4. Most amputations occurred soon after randomisation. The hazard ratio for amputation in the spinal cord stimulation group compared with the standard group was 0·81 (0·47–1·42).

In patients without amputations the cumulative percentage of ulcers healed at 1 year were 45% in the spinal cord stimulation group *vs* 54% in the standard group (p=0·21); the proportions of patients with gangrene were similar (53% *vs* 50%, respectively; p=0·56).

Table 2 shows the percentages of patients with amputations at toe, transmetatarsal, foot, below-knee, and above-knee levels. Overall, at 2 years only 27% of all patients were alive without any amputation; 37% had died. Reasons for amputation were progressive tissue loss (71%), unbearable pain (67%), infection (15%), or combinations of these factors.

Figure 5 shows the pain-rating index. Pain was decreased significantly in both treatment groups at 1 month and 3 months (p<0·001) and did not differ between groups. Pain medication use is summarised in Figure 6. The NHP and Euroqol showed poor quality of life compared with matched reference values of the general population: the two groups did not differ (Figure 5).

In the spinal cord stimulation group, three patients needed lead repositioning within 30 days. During follow-up, 13 lead displacements occurred, and 11 reposition and one reimplantation procedures were done. Infection was reported in three patients. Three batteries failed within 18 months. Because of these difficulties eight patients (13%) had suboptimum stimulation. If only patients with adequate stimulation were analysed, limb survival at 6 months was 67% in the stimulation group and 68% in the standard group; at 2 years these values were 55% and 46%, respectively (hazard ratio 0·78 [0·44–1·39], p=0·39).

In the standard group side-effects were reported in ten patients: upper gastrointestinal bleeding (3), nausea (7), dizziness (2). In the spinal cord stimulation group side-effects occurred

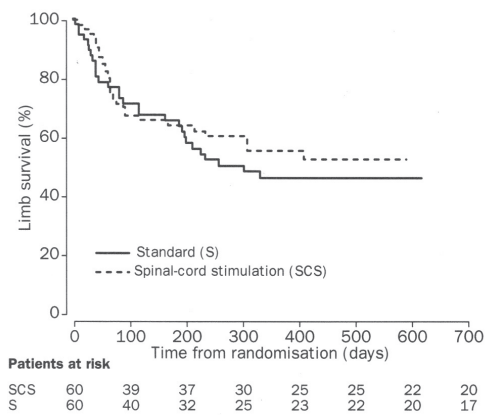


Figure 4: Limb survival

Cumulative events	Spinal-cord stimulation (n=60)		Standard (n=60)		p*
	6 months	2 years	6 months	2 years	
Amputation					
Major	19 (34%)	25 (48%)	18 (32%)	29 (54%)	0·47
Major or death	26 (43%)	38 (67%)	26 (43%)	39 (66%)	0·86
Toe(s)†	4 (9%)	8 (23%)	9 (23%)	9 (23%)	0·57
Forefoot†	2 (4%)	2 (4%)	5 (12%)	5 (12%)	0·21
Foot†	1 (2%)	3 (8%)	1 (2%)	3 (8%)	0·91
Below-knee†	18 (32%)	22 (42%)	16 (29%)	22 (43%)	0·87
Above-knee†	4 (7%)	4 (7%)	5 (9%)	9 (17%)	0·15

*From Kaplan-Meier survival analysis. †Kaplan-Meier estimates of amputation level adjusted for censoring of data at death or at amputation at a higher level.

Table 2: Cumulative amputations (%) at 6-month and 2-year follow-up

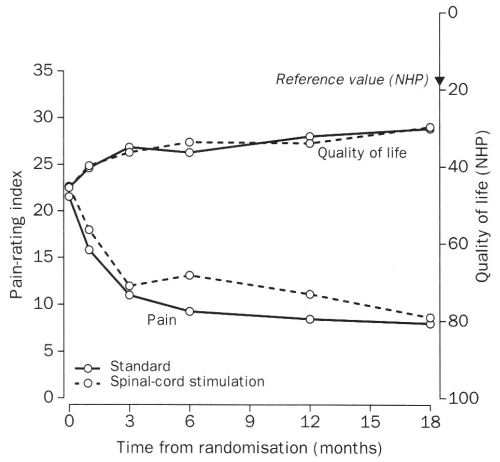


Figure 5: Pain-rating index and quality-of-life index

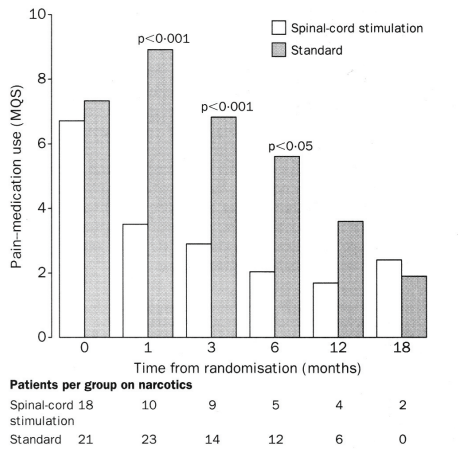


Figure 6: Pain medication use

in four patients: duodenal perforation (1), nausea (2), and pruritus (1).

Most of the costs were from staying in hospital and in rehabilitational facilities. These costs were similar for both groups: mean *f*25,957 and *f*14,870 per patient in the spinal cord stimulation group *vs* *f*27,153 and *f*16,465 in the standard group. The mean cost for operative procedures per patient was *f*18,428 in the stimulator group and *f*918 in the standard group. The cost of implanting the stimulator was *f*15,900. Costs for professional care at home and in homes for the elderly were similar. Outpatient cost, medications, medical supplies, and non-medical costs were a small part of the cost. Total cost at 2 years was *f*80,439 per patient in the spinal cord stimulator group, *f*17,376 (28%) higher than in the standard group (p=0·009). Adjusted for mortality, the mean cost per patient was *f*69,066 in the stimulator group and *f*52,407 in the standard group, p=0·002.

Discussion

In 1991, LoGerfo[33] warned in an editorial about undue clinical acceptance of spinal cord stimulation for management of lower extremity ischemia and stressed the need for randomised clinical trials.

In this trial, we compared two treatment regimens and aimed to answer the question about which mode of therapy works best -rather than how it works[34]. The primary measure of efficacy was limb survival. We did not find that spinal cord stimulation was of benefit above that of best medical treatment. Amputation-free survival was not improved nor was the risk of major amputation significantly reduced. The rates of amputation were similar in both groups and were particularly high during the first 3 months, which shows both the nature of critical ischemia and the limited potential of current treatments. However, a surprisingly high number of patients with critical limb ischemia can, temporarily, be stable or improve with conservative methods:[4,5,9] in the standard group, limb survival was 46% after 1 year.

Studies of new treatment modalities involve more medical care (hospital visits and general attention) in the selected patient population, which can improve outcomes. Therefore, efficacy can only be verified in controlled, preferably randomised, trials.

Patients with a spinal cord stimulator used significantly less pain medication, which

suggests substantial pain relief from this treatment. Nevertheless, similar pain reduction was seen in the standard group. Although spinal cord stimulation may be of great benefit for ischemic pain, the effect is not stronger than adequate conservative pain treatment. Amputation also reduces pain, on average by 40%. The high frequency of amputations during the first 3 months thus accounts for at least 22% of the observed pain reduction in this period.

Spinal cord stimulation was associated with a substantial number of complications in our patients. In other similar patient groups, such as those with peripheral vascular disease, patients have had complications from spinal cord stimulation: failure (3–4%), infection (3–5%), lead dislocation and breaks (11–36%), cerebrospinal-fluid leak (1%), and meningitis (0·5%)[10,21–24]. Most complications could be adequately corrected. Additional analysis did not show that the treatment effect of spinal cord stimulation was superior in patients with adequate stimulation.

Conservative treatment probably was the cause of potentially life-threatening gastrointestinal problems in four patients (three in the standard treatment group). Although these events may not be exclusively attributed to medication, elderly patients who use combinations of aspirin, non-steroidal anti-inflammatory drugs and anticoagulants are at risk of gastrointestinal complications.

The calculated costs over 2 years were 28% higher in the spinal cord stimulator group than in the standard group: most of this was the cost of staying in hospital and rehabilitation. The initial costs in the spinal cord stimulator group were high, all other costs evolved similarly in both treatment groups.

We found that in patients with critical-limb ischemia, a treatment regimen of best medical treatment and spinal cord stimulation was no more effective than best medical treatment alone in preventing amputations and costs more. Medication can provide pain relief to that achieved with spinal cord stimulation.

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Chapter IV

Technical data and complications of spinal cord stimulation

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Abstract

Background

This study was done to evaluate the effect of spinal cord stimulation (SCS) on critical limb ischemia and to report technical problems and complications.

Methods

One hundred and twenty patients with critical limb ischemia were eligible for randomization between medical treatment and medical treatment plus SCS. Sixty received a spinal cord stimulator (Itrel II; Medtronic, Minneapolis, Minn., USA). Primary outcome measures were limb salvage and pain relief.

Results

The mean pain reduction in both treatment groups was 50% (from 5 to 2.5 on the visual analog scale). The 2-year limb survival was 52% (SCS) versus 46% (standard treatment; p=0.47). The number of patients undergoing major amputations in the SCS group with intermediate TcpO2 values was half of that in the standard group (14 *vs.* 28; 24 *vs.* 48%; p=0.17). Implantation was successful in 51 patients. Technical problems such as loss of stimulation due to lead displacement occurred in 13 patients (22%), local infection at the site of implantation occurred in 3 patients (5%), resulting in a total complication rate of 27%. Premature depletion of the battery occurred within 2 years in 3 patients (5%). There were no lead fractures, epidural infections, hematoma or cerebrospinal fluid leakage.

Conclusions

Training of physicians and better reliability of the hardware should reduce the frequency of technical problems. Lead displacement remains the major technical problem. The search for prognostic factors of limb salvage is important. One microcirculatory measurement (TcpO2) seems to have a prognostic value, which remains to be described more precisely.

Introduction

Over the last 10 years, many attempts have been undertaken to improve limb survival in patients with critical limb ischemia. The most important treatment options were the use of prostaglandins and spinal cord stimulation (SCS).

Good to excellent effects of SCS on pain in patients with critical ischemia have been described[1–8]. Some suggested that SCS also might have an important effect on limb salvage[1,9,10]. Final conclusions on the efficacy of SCS in critical limb ischemia were difficult to reach in the absence of randomized trials. The only randomized study was published by Jivegard[11] some years after the start of the Dutch randomized study and was not conclusive regarding limb salvage. When SCS is compared with other treatment options, it is important to realize that SCS is a technique still in evolution. The aim of new hardware development is to improve stimulation coverage of the pain region and reduction of technical problems and failures. Any discussion on the effectiveness of SCS is therefore related to the actual state of the hardware. A better understanding of the mechanisms of SCS may influence the selection of patients eligible for this treatment. With these restrictions in mind, a randomized study was designed to answer those questions.

Materials and Methods

One hundred and twenty patients were selected on the basis of clinical symptoms and macrocirculatory data, as described in the European Consensus Document on Critical Limb Ischemia[12]. They were randomized between medical treatment and medical treatment plus SCS. Randomization was performed by a random numbers table, and the list, which was available around the clock, was held in an independent research institute. Inclusion criteria were critical limb ischemia and nonreconstructible peripheral arterial occlusive disease (Table 1). Data were collected at intake and 1, 3, 6, 12, 18 and 24 months. Outcome measures were limb salvage, pain relief and quality of life. Patient and limb survival was estimated with the Kaplan-Meier method at 1 and 2 years follow-up. Pain was evaluated using the visual analogue scale (VAS), the Pain Rating Index (PRI) of the McGill Pain Questionnaire (MPQ), which is the sum of the scores of the sensory, affective and evaluative categories of the questionnaire, and the pain score of the Nottingham Health Profile (NHP). The normative values of the NHP (women aged 55–59 years) for the subscore of energy are 18.6, pain 14.5, emotional reactions 7.7, sleep 11.7, social isolation 3.4 and physical mobility 3.7. The mean value of the six dimensions is 9.9[13].

The SCS hardware used consisted of a lead, an extension cable and a pulse generator (Quad lead; Itrel II, Medtronic, Minneapolis, MN, USA). The stimulation parameters were controlled by telemetry using an external programmer[14]. Implantation was performed as a one-stage procedure under local anesthesia in the operating room.

Implantation problems, stimulation parameters, complications and adverse events were monitored during follow-up. TcpO2, laser Doppler fluxmetry and capillary microscopy were used to evaluate microcirculation. Ubbink *et al.*[16] categorized patients according to the status of their baseline skin microcirculation into good (TcpO2 above 30 mm Hg), intermediate (TcpO2 between 10 and 30 mm Hg) and poor (TcpO2 below 10 mm Hg).

Baseline data were general characteristics of the population, circulatory measurements and pain. Technical data related to SCS were time between randomization and implantation, localization of the tip of the lead, stimulation parameters and adverse events. Parameter adjustments secondary to lead repositioning or replacement were registered as a minor

	n	%
Female	27	45%
Male	33	55%
Age, years	73.1 (SD = 9.8)	
Diabetes	22	37%
Other leg		
Symptomatic	19	32%
Amputated	9	15%
Smoking		
Stopped for 1 1 year	22	37%
Still smoking	18	30%
CVA/TIA	13	22%
Myocardial infarction	23	38%
Angina pectoris	12	20%
Ulcerations/gangrene	38	63%
Previous vascular surgery		
None	15	25%
1 or 2	25	42%
> 3	19	32 %
Sympathectomy	21	35%
Ankle pressure, mm Hg		35.2 (SD = 24.8)
Ankle-brachial index, mm Hg		0.23 (SD = 0.16)

Table 1: Characteristics of patients randomized for SCS.

complication. Data were analyzed with the *t*-test for continuous variables and the χ^2 test for categorized variables. Two-sided *p*-values less than 0.05 were considered statistically significant. Based on the number of patients selected for the study, this study had a statistical power (1-ß) of more than 80% to detect an increase in median limb survival from 3 to 6 months with an α–level of 5%.

Results

One hundred and forty-one patients were evaluated. Twenty-one were not randomized: 4 refused informed consent, 1 had no rest pain, 3 had other diseases than atherosclerosis, 5 had extensive necrosis, 7 had a Doppler pressure above 50 mm Hg, and 1 had critical ischemia in both legs. Baseline data are shown in Table 1. Sixty of the 120 eligible patients were randomized for SCS-treatment.

The mean (SD) in-hospital stay for implantation of the stimulator was 4.9 days (2.3). Median follow-up was 605 days (244–1,171). Limb survival at 6 months was 66% in the SCS group and 68% in the standard group. At 1 year, limb survival was 60 versus 46%, and at 2 years it was 52 versus 46% (*p*=0.47).

At intake, the VAS score of all patients was between 4.7 and 5, the NHP pain score between 69 and 75, and the PRI of the MPQ between 21 and 24. All scores declined over time (Figure 1) by 30–50% with no significant difference between groups. Looking at the best pain reduction at 1 month follow-up, 19 patients had a reduction of more than 50%, 27 patients had a reduction less than 50%, and pain was worse in 15 patients. After amputation, pain intensity dropped by 70–80%, reducing the pain score from 3.9 to 1.8 in the standard group and from 2.6 to 1.4 in the

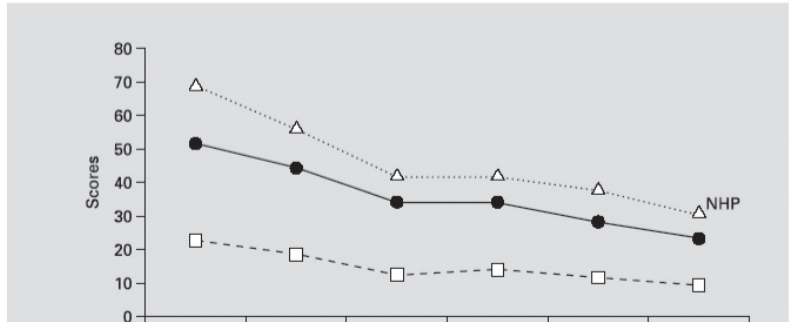
SCS group (*p*<0.001).

Patients with a poor skin perfusion had a high amputation rate of 80% for SCS and 71% for standard treatment. Patients with good microcirculation had a good outcome irrespective of the treatment given. Amputation frequency in patients treated with SCS and an intermediate TcpO2 value was half of that in the standard group (24 *vs.* 48%), indicating the possible prognostic value of categorization on limb salvage[15].

Initial implantation problems occurred in 9 patients. One patient refused implantation after randomization. Proper lead positioning resulting in paresthesias covering the pain region was not secured in 4 patients (7%), mainly due to technical problems while navigating with the lead in the epidural space. In 6 patients (10%), positioning was not optimal because paresthesias overlapped the pain region only partially. A renewed intervention corrected this problem successfully in 2, but failed in 4.

Baseline technical data are summarized in Table 2. The tip of the lead was situated between the vertebral level Th11–L1 in 41 patients. Stimulation parameters were within the normal ranges of amplitude (lower than 3.7 V), pulse width (210 µs) and pulse rate (between 60 and 85 pps). A unipolar electrode combination was used in 49% of the patients. In 20 patients with a follow-up of 18 months, the mean amplitude rose from 3.3 to 3.8 V (SD ± 1.8). The increase was mainly due to changes in electrode combinations and not to an increased demand to maintain the intensity of paresthesias.

Multiple changes of electrodes used to stimulate were performed to correct loss of adequate stimulation in 21 patients which could be attributed to either a slight change in position of the lead, a technical failure of one of the electrodes or a migration of the lead. Where there was a



	0	1	3	6	12	18
● VAS	51.8	43.6	33.7	33.5	27.6	22.5
□ PRI-MPQ	22.61	17.89	11.87	13.18	11.14	8.76
△ NHP Pain	69.76	56.2	41.42	41.88	37.14	30.8

Follow-up in months (0, 1, 3, 6, 12, 18). VAS was measured as a value between 0 = none and 100 = maximal pain. PRI-MPQ is the pain rating index of the McGill Pain Questionnaire which is the sum of the sensory, emotional and affective parts of the list of synonyms. The NHP Pain is the combination of different questions in the questionnaire related to pain. The higher the values are in both measures (NHP and MPQ), the worse the condition of the patient. The data of patients under conservative treatment are comparable. Important is the parallel evolution over time in the different scores.

Figure 1: Different pain scores for patients under SCS treatment.

Location of tip of the electrode	
Th_{11}–L_1	81%
Above Th_{11}	12%
Below L_1	4%
Stimulation parameters	
Pulse amplitude, V	2.9 (SD = 1.4)
Pulse width, µs	211 (SD = 12.5)
Frequency, pps	72 (SD = 20)
Electrodes used	
Bipolar	37%
Rostral anode	20%
Rostral cathode	80%
Unipolar	49%
Both (changing over time)	14%

Table 2: Location of the tip of the electrode and baseline stimulation parameters

minimal change in position, changing the electrode combination would usually restore loss of adequate stimulation. The electrode configuration was changed in 8 patients as the only action to restore successful stimulation. This was considered to be a minor adverse event.

Major adverse events such as technical and medical complications included migration of the lead, infection and early depletion of the battery and are listed in Table 3. Migration of the lead was considered as a major adverse event, necessitating hospitalization and additional surgical intervention to restore adequate stimulation. Surgical repositioning was done with the lead left in place in 12 patients, and 1 lead had to be removed and replaced by a new one (Table 4). No lead fractures were observed. Because of these difficulties, 8 patients (13%) had suboptimal stimulation.

Problems with wound healing or erosion of the skin underneath the pulse generator were not seen. Three patients had an infection of the subcutaneous pocket of the pulse generator. One patient had the device explanted and died shortly afterwards of cardiac failure due to a bad general condition. The second patient was successfully treated with antibiotics after evacuation of the abscess in the pocket of the pulse generator, which was reimplanted later. The third patient, in whom a pulse generator was left in place after a below the knee amputation, had an infection at the site of the stimulator; removal of the stimulator solved the problem. Two patients reported discomfort at the site of the pulse generator, which was left in place long after amputation was performed. The devices were explanted. In 3 cases still under follow-up, an earlier than expected battery depletion occurred within 2 years (613 and 548 days) after randomization. In 1 case a new pulse generator was implanted (Table 4).

Discussion

The conclusion of the randomized multicenter trial indicated that SCS was not more effective in preventing amputations and reducing pain than an optimal medical treatment[15]. This statement is certainly quite provoking, as several clinicians involved in SCS reported better results of SCS for this indication. Non-randomized studies and some experimental data suggest that SCS influences the peripheral microcirculation. Adding microcirculatory measurements and particular TcpO2 to the inclusion criteria may be the key to better patient selection.

A further improvement in the results of SCS can be expected if the technical adverse events

are reduced. The positioning of the lead in the epidural space is not always easy if one wants to cover the pain region with paresthesias. Leads with different electrode geometry were developed to overcome these problems[7–19]. One alternative is the use of more than one lead with multiple electrode contacts.

The frequency of lead repositioning reported to restore optimal stimulation using multichannel devices was between 15 and 25%, which was comparable with our results[14]. Lead fracture was not seen in our study (Quad lead, Medtronic), but is reported in the literature as up to 23% for percutaneously inserted leads. These reports generally refer to older types of leads.

Early battery depletion occurred in 2 patients, who had initially a high intensity of stimulation (4.5 and 5 V). Three other cases had high initial settings, which might have resulted in an early depletion. Early amputation resulted in discontinuation of the stimulation therapy.

	Follow up, months						Total
	0	1	3	6	12	18	
Implant failure	6						6
Displacement		7	5		1		13
Infection		2		1			3
Lead fracture		0					0
Battery EOL						3	3
Total	6	9	5	1	1	3	25

Implant failure: mostly due to problems such as failure to position the lead in the epidural canal. Displacement: position change of the lead in lateral or rostrocaudal direction after correct initial positioning of the lead. Battery EOL: depletion of the battery.

Table 3: Complications

	Follow-up, months					Total
	1	3	6	12	18	
Lead						
Replacement		9	4		1	14
Reimplantation	2	1				3
Pulse generator						
Temporary removal		1				1
Definitive removal	0	1	4	3	1	9
Total	2	12	8	3	2	27

Replacement: percutaneous trial to reposition the lead. In cases of failed percutaneous reposition, a complete new percutaneous reimplantation was performed. Temporary removal of the lead or pulse generator was due to infection, and definitive removal was necessary because of depletion of the battery in 3 patients.

Table 4: Measures taken to correct the complications and interventions scheduled to restore normal stimulation

For patients with critical ischemia a mean battery life of 3–5 years is generally sufficient because of the high number of dropouts due to amputation and mortality within a period of 2 years.

Other complications mentioned in the literature were infection, epidural hematoma and leakage of cerebrospinal fluid. Infection was reported with a frequency of 2–12%[14]. Treatment usually consists of removing the system, followed by antibiotics for 1 or 2 weeks. Our infection rate was 5%. In 2 cases, the pocket became infected months after an amputation when the stimulator was no longer used. It seems therefore wise to explant the device once it is no longer used, certainly in patients such as these with skin lesions and diabetes who are more susceptible to infections. Neither epidural hematoma nor leakage of CSF was encountered in this study.

A possible factor responsible for a lower than expected successful implantation was the high incidence of degenerative disease of the spine in a group of patients at this age.

Technical improvement will accompany better and more reliable leads, as these remain the critical part for successful long-term use of the SCS system. Lead fracture became rare after the introduction of the larger and stiffer leads, but displacement remains a frequent problem (24%). Regular adaptation of stimulation parameters and, if needed, percutaneous or surgical repositioning of the lead makes this therapy difficult and demanding to prolong a good result over time. A regular outpatient clinic is necessary. Infections are rare, but, if present, compromise the outcome of the therapy. Battery life of the pulse generator is sufficient for this population. It can be enhanced by proper parameter settings to reduce energy consumption. For other indications better and newer battery technology extending the battery life is needed.

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Chapter V

Pain and quality of life in patients with critical limb ischemia

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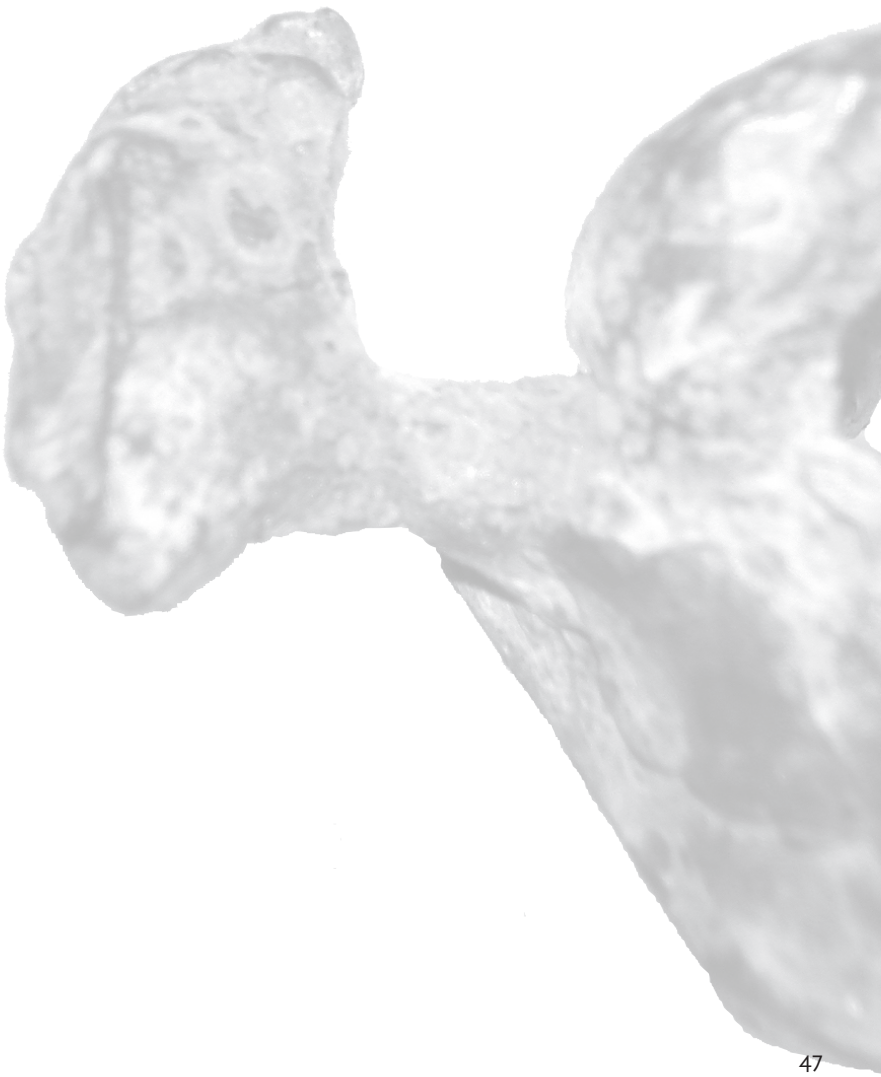


Abstract

Background

The objective was to carry out an assessment of pain and quality of life of patients with critical limb ischemia during the follow-up of a multicentre randomized trial in more detail than previously reported.

Methods

In a multicentre clinical trial 120 patients were randomized between medical treatment and medical treatment plus spinal cord stimulation. Patients were selected on the basis of clinical symptoms and macrocirculatory data as described in the European consensus document on critical limb ischemia. Data were collected at intake and then 1, 3, 6, 12 and 18 months later. Outcome measures were limb salvage, pain relief and quality of life. Patient and limb survival was estimated with the Kaplan–Meier method. Pain was evaluated using the visual analogue scale (VAS), the McGill pain questionnaire, the pain score of the Nottingham Health Profile (NHP) and the use of analgesics. Quality of life was evaluated using the NHP, the EuroQol and mobility subscore of the Sickness Impact Profile.

Results

The 2-year limb survival was 52% for SCS treatment and 46% for standard treatment (p=0.47). Pain relief was considerable in both treatment strategies (p<0.005) with no significant differences between the strategies. The improvement occurred within the first few months and remained stable during further follow-up. Patients with SCS used fewer non-narcotic and narcotic drugs (p<0.001 at t=1 and t=3, p<0.002 at t=6). The overall scores of quality of life improved significantly (p<0.05), with no difference in score between treatments. The subscores of mobility and energy of the NHP in non-amputated patients were significantly better in the SCS group (p<0.005). Amputation had a negative effect on mobility, but relieved pain substantially (p<0.05).

Conclusions

In contrast to the existing literature, the randomized trial revealed no major difference in overall pain and quality of life assessment between treatment groups. Patients treated with SCS used substantially fewer analgesics.

Introduction

Morbidity and mortality are considerable in patients once critical limb ischemia is diagnosed. The 5-year mortality in patients with lower limb ischemia exceeds 50%. In a study with elderly patients, the 1-, 3-, and 5-year survival rates were 59%, 28% and 23%, respectively, which were markedly poorer than the expected survival rates of the age- and sex-matched Japanese population at 1, 3 and 5 years, being 93%, 79% and 65%, respectively[1]. It was estimated that a major amputation of the ischemic limb is performed in >50% of patients within a year once critical limb ischemia is diagnosed[2]. The major reasons for amputation are non-healing skin ulcers, gangrene and pain. The primary therapy is vascular reconstruction. In patients for whom vascular reconstruction is no longer a possibility, pain medication and vasoactive drugs are used to reduce pain and avoid limb amputation. It is believed that pain relief plays a major role in reducing the risks for amputation. Better mobilization will have a beneficial effect on distal blood flow. In addition good local skin care can stabilize and even improve the local condition of the threatened distal limb region[3]. A number of publications described a good to excellent effect of SCS on pain[4-13]. Some of these publications suggested that limb salvage may be an important effect of SCS. However, these studies were primarily directed to the effect of SCS on pain relief. In order to solve the question of limb salvage, a randomized study was undertaken. Other outcome measures were pain relief and quality of life.

Methods

Study design

The study took place between November 1991 and January 1996 in 17 hospitals in The Netherlands. A total of 120 patients were enrolled during the intake period, which ended in 1994. Data were sampled at intake and at 1, 3, 6, 12 and 18 months post randomization. The follow-up period for all patients was at least 1.5 years. Patients with atherosclerotic vessel disease were eligible if they were diagnosed as having critical ischemia as defined by the European consensus and if no vascular reconstructive surgery was possible[14,15]. Inclusion criteria are summarized in Table 1. Patients were eligible if all inclusion criteria, and none of the exclusion criteria, were met. Randomization was performed by a random numbers table and the list was held in an independent research institute, which was available around the clock. The clinicians could phone the randomization centre, which step-by-step checked eligibility, registered the patient and assigned treatment. Randomization was stratified for presence or absence of diabetes and institution. Patients were randomized between medical treatment and medical treatment plus spinal cord stimulation. Medical treatment included proper care for wound ulcers, pain medication (minor and major analgesics), antithrombothic drugs such as aspirin and coumarins, and vasoactive drugs such as pentoxyfilline, buflomedil, or ketanserin. There was no fixed treatment regimen. Chemical lumbar sympathectomy and prostanoids were not excluded but were used in only three patients. The spinal cord stimulation consisted of the implantation in one session of a complete system containing a lead, an extension cable and a pulse generator (Itrel II, Quad lead, Medtronic, Minneapolis, MN, USA). Those who were allocated to SCS were seen at each follow-up period by the anesthesiologist or the neurosurgeon responsible for the technical and surgical care of the implant. This implies that patients with SCS were seen more often by a physician than those with only medical treatment.

Inclusion criteria:
Critical ischemia of one of the lower limbs in patients, for whom a meaningful vascular reconstructive procedure is considered not to be possible:
1 a. Persistent rest pain for at least 2 weeks, being treated with analgesics
b. and/or ulceration or gangrene of foot or toes
2 a. Doppler ankle systolic pressure less than 50 mmHg or ankle brachial pressure index (ABPI) less than 35%
b. For patients with diabetes and incompressible vessels, leading to unreliable ankle pressure: absence of arterial ankle pulsation
3. Patient informed consent
Exclusion criteria:
1. Vascular disorders other than atherosclerotic disease
2. No rest pain (e.g. only intermittent claudication) and no ulceration or gangrene
3. Ankle pressure > 50 mmHg and ABPI> 35%, when these pressures can be measured reliably
4. Palpable ankle pulsations in patients with diabetes and incompressible vessels
5. Ulcerations deeper than the fascia or with largest diameter > 3 cm
6. Infected, suppurating gangrene or gangrene with largest diameter > 3 cm
7. Intractable infection of ulceration or gangrene
8. Critical ischemia of both legs
9. Possibility of a meaningful vascular reconstruction
10. Neoplastic or other concomitant disease with life expectancy <1 year
11. Presence of a cardiac pacemaker
12. Impossibility to implant an epidural electrode and stimulator
13. Previous participation in an ESES-trial or pilot study
14. Psychosocial incompetence of the patient to satisfy the follow-up schedule

Table 1: Inclusion and exclusion criteria

Assessment measures

Quality of life

The Nottingham Health Profile (NHP) is an established measure of perceived health and detailed descriptions of its features and shortcomings are well documented[16-18]. It is divided into two parts. Part I has 38 yes/no questions divided into six different dimensions of health: pain (P), sleep (S), energy (E), mobility (M), social isolation (I) and emotional behaviour (B). Each dimension has a score with a maximum of 100 (worst score). Part II comprises seven general yes/no questions referring to the effects of health on occupation, ability to perform tasks around the home, personal relationships, sex life, social life, hobbies and holidays. Each question is attributed a value of 1 on affirmation and 0 in case it is not applicable. The NHP has simple instructions, is easy to answer and administer, even by mail. The questionnaire is short, acceptable to the patient and reliable to the clinician and has been used successfully in community surveys and in clinical settings. The Dutch version was validated by Erdman[19]. In the present study only the first part of the NHP was used. Normative values of the NHP (women aged 55–59 years) for the subscores are: for energy 18.6, pain 14.5, emotional reactions 7.7, sleep 11.7, social isolation 3.4 and physical mobility 3.7. Mean value of the six dimensions is 9.9[17].

The EuroQol is a short questionnaire of five items that contribute to the state of health:

mobility, ability to perform self-care, ability to do usual activities, pain/discomfort and anxiety/depression. Each item contains three questions. The maximal (worst) score if each factor is scored is 100. The score system requests information about the patient's situation during the previous week. For analysis, a linear index was used[20,21].

3. SIP — mobility score: the SIP is a well-evaluated, 136-item measure, organized into 12 subscales. The physical dimension contains items measuring a broad range of ADL, mobility and complex physical activities. Only the mobility subscore was used as a comparison with the mobility score of the NHP. The score ranged from 0=normal to 100=the worst possible score[22].

Pain evaluation

The visual analogue scale (VAS) is a simple method of measuring the 'intensity' of pain. The scale is a line, on which the left represents 'no pain at all' (score 0) and the right 'unbearable pain' (score 10). The number between 0 and 10 expresses the intensity of pain. The brief pain inventory which scores pain intensity at different moments gives an impression of the maximal and minimal pain over time[23-26]. Pain relief of >50% was considered to be good, a 25–50% reduction was seen as moderate, and a reduction less than 25% was considered unsuccessful.

The McGill Pain Questionnaire (MPQ) is a measure of pain 'magnitude', looking at not only pain intensity but also at the other dimensions of pain: emotion, cognitive-evaluative and sensitivity[27-29]. The questionnaire is divided into two parts: the pain assessment questionnaire and the home recording card. Only the first part with the pain descriptors has been validated. A Dutch language version does exist (MPQ-DV)[30]. The questionnaire looks at the subjective perception of pain qualities and can be used in a dynamic way for a length survey[25]. The pain descriptors are divided into categories, the descriptors in a category differing only in intensity. The sum of the words used by the patient for a given category produces the score for the subclass. The global Pain Rating Index (PRI) of the MPQ is the sum of the scores of the sensory, affective and evaluative categories. Only the first part of the MPQ has been used in the present study. This weights sensory aspects of pain more heavily than affective and evaluative aspects. In limb ischemia, the sensory aspect is important and more or less equivalent to the intensity of pain. Subscale patterns of the MPQ are highly interrelated. It is believed that differentiating groups of patients on the basis of subscales is inappropriate[31].

A Medication Quantification Scale (MQS) consisting of two components was used to evaluate the use of analgesics[32]. The first component is the detriment weight (DW), based on the potential harmful effects in case of long term use. The detriment weight originally included eight classes of medications prescribed frequently for the management of pain. Light analgesics such as aspirin and paracetamol have a DW=1; morphine and morphine analogues have a DW=6. The second element is the dosage level based on the daily dosage ranges recommended by the manufacturer. The score ranged from 0 (<1 dose per week) to 4 (supratherapeutic dose). In the case of morphine, 1–20 mg/d was considered as a dosage level of 1, and 71–120 mg/d had a value of 3. For narcotics, the dosage levels were based on the morphine equivalent in milligrams. The MQS for each medication is obtained by multiplying the detriment score of its class by the dosage level. If the patient was taking multiple medications, the MQS score for each medication was summed to obtain the total MQS score. As an example: a patient taking amitriptyline 75 mg/d (DW=2, dosage level=2. MQS=4), and morphine 60 mg/d (DW=6, dosage level=2, MQS=12) has a total MQS of 4 + 12 = 16.

CHARACTERISTICS	SCS (*n*=60)		Standard (*n*=60)	
male/female	33/27	(55/45%)	37/23	(62/38%)
age [year]*	73.1	± 9.8	72.1	± 10.6
diabetes	22	(37%)	23	(38%)
'other leg'				
symptomatic	19	(32%)	29	(48%)
amputated	9	(15%)	7	(12%)
smoking				
quit > 1 yr	22	(37%)	16	(27%)
still smoking	18	(30%)	26	(44%)
CVA or TIA	13	(22%)	16	(27%)
myocardial infarction	23	(38%)	22	(37%)
angina pectoris	12	(20%)	15	(25%)
ischemic skin lesions	38	(63%)	41	(68%)
gangrene	24	(40%)	23	(38%)
vasc.reconstructions				
0	15	(25%)	11	(19%)
1 or 2	26	(42%)	29	(48%)
> 3	19	(32%)	20	(33%)
sympathectomy	21	(35%)	19	(32%)
ankle systolic pressure [mmHg]*	35.2	± 25	41.6	± 22
ankle-to-brachial pressure index*	0.23	± 0.16	0.28	± 0.13

Data are given number (%) or *mean ± SD.

Table 2: Intake values of both treatment groups.

Statistics

Based on the number of patients selected for the study, this study had a statistical power (1-β) of more than 80% to detect an increase in median limb survival from 3–6 months with a α-level of 5%. The power was primarily calculated for differences in limb survival. Baseline differences were tested with the *t*-test for continuous variables and the chi-square tests for categorized variables. Differences between SCS and standard treatment in quality of life scores during follow-up were tested with covariance analysis, where the covariate was the baseline measurement of the quality of life instrument; *p*-values less than 0.05 were considered statistically significant. Differences in scores at the different time intervals of follow-up between treatment modalities were analyzed.

Results

One hundred and forty-one patients were eligible. Twenty-one were not randomized: 4 refused informed consent, 1 had no rest pain, 3 had other diseases than atherosclerosis, 5 had extensive necrosis, 7 had a Doppler pressure above 50 mmHg and 1 had critical ischemia in both legs. Patients' characteristics at intake were not statistically different for the two treatment modalities (Table 2). In case of SCS treatment, the mean (SD) hospital stay before implantation of the stimulator was 4.9 days (2.3). Median follow-up was 605 days (244–1171). Limb survival at 6 months was 66% in the SCS group and 68% in the standard group. At 1 year limb survival was 60 *vs* 46% and at 2 years limb survival was 52 *vs* 46% (*p*=0.47). The hazard ratio was 0.81 (95%CI:0.47–1.51). In the SCS treatment group 13 lead displacements occurred and 11 repositions and 1 re-implantation procedure were done. Infection was reported in three cases and three batteries failed within 18 months. Because of these difficulties, eight patients (13%) had suboptimal stimulation. All patients were analyzed following the intention to treat principle[33].

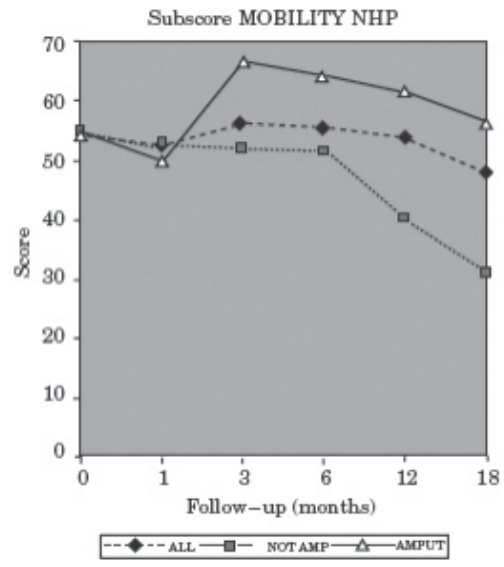


Figure 1: Mean NHP mobility score in patiens treated with SCS. The scores vary between 0=normal and 100=the worst possible score. Only the SCS patients were represented. In the table below the scores of the patients with a standard treatment are given and can be compared with SCS.

Quality of life

The mean value of the overall NHP score at intake was 47 (SE=2.6, *n*=58) for the standard treatment and 48 (SE=2.6, *n*=57) for the SCS group. Between 3 and 6 months follow-up there was a decline of mean values to 34 (SE=3, *n*=41) for the standard group and 35 (SE=2.6, *n*=44) for the SCS group, which remained unchanged until the end of the follow-up period at 18 months. The global NHP score may obscure effects in subdimensions. However, there were no differences in values of mobility between SCS and conservative treatment (Table 3), nor for pain, energy, sleep, social isolation and emotional reaction. Patients undergoing SCS who were not amputated, showed better mobility and energy scores after 12 months than did the conservatively treated non-amputated patients ($p<0.01$). In case of amputation, mobility was reduced (Figure 1; Table 3).

The EuroQol (EQ) simple linear index showed a similar improvement over time as the NHP. Initial values of the EQ were 51 (*n*=58, SE=2.9) in the standard group and 54 (*n*=56, SE=2.8) in the SCS group. The decrease at *t*=12 was 43 in the standard group and 41 in the SCS group. Patients who underwent an amputation early in the trial had worse initial EQ scores than those amputated later. Scores after amputation worsened to 66 at *t*=1 (*n*=8, SE=8.2) in the standard group and 61 (*n*=4, SE=4.9) in the SCS group. Gradually, over a period of months, scores regained values comparable to those of non-amputated patients.

The mean value of the mobility index of the Sickness Impact Profile at intake was 36 (SE=1.9, *n*=58) for the standard treatment and 34 (SE=1.7, *n*=57) for the SCS group. During follow-up the scores declined but the difference was not significant nor was there a difference between treatment modalities.

Follow-up	0	1	3	6	12	18
Cons all	54	52.5	52	51	54	51
Non-amp		48	49.6	44.5	50.5	49
Amputated		75	58.5	60.5	57	51.5
n	60	43	38	36	23	17
SCS all	54.5	52.5	56	50.5	53.7	47.7
Non-amp		52.8	52	51.5	40	30.7
Amputated		49.9	66.5	64	61.2	56.2
n	60	50	39	37	29	17

SCS = Spinal cord stimulation treatment, Cons = conservative medical treatment,
n = numbers of patients alive and amputation free at each follow-up period

Table 3: Mean mobility score for both treatments. Follow-up in months.

Follow-up (months)	0	1	3	6	12	18
CONS						
All (mean values)	51.3	38.3	33.4	25.6	29.8	25.2
Not amp		38.4	37.7	27.9	42.6	35.6
Amput		38	20.2	21.3	21.7	18.5
n	58	47	47	42	38	24
SCS						
All	51.8	43.6	33.7	33.5	27.6	22.5
Not amp		45.2	40.3	39.3	34	37.7
Amput		25.9	15.6	21.3	23.5	14.5
n	57	47	46	44	42	27

Scores are between 0 = none and *100* = maximal pain. Data are mean values. As for other pain measurements the overall scores hide the differential effect between amputated and not amputated patients. *n* = number questionnaires received for each period. *All* = all patients censored at time to follow-up. *Not amp* = patients not amputated at time of follow-up and *Amput* = patients amputated at time of follow-up.

Table 4: Visual Analogue Score of patients in both treatment groups.

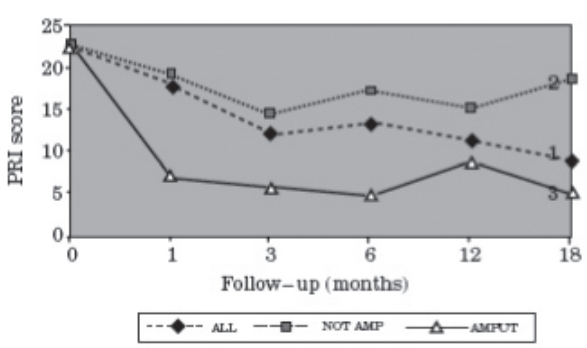
Pain relief

VAS score

At intake the VAS score for the SCS treatment was 5 (*n*=60, SE=0.4), with a mean minimum pain score of 2.5 (SE=0.3) and mean maximum pain score of 8 (SE=0.2). The scores were similar for the standard group. During follow-up, a narrowing of the range between the lower and upper mean scores was observed. At *t*=6 months, the VAS score in the SCS group was 3 (*n*=44, SE=0.4) with a minimum score of 2 (SE=0.3) and a maximum score of 5.3 (SE=0.5). In the standard group, mean pain scores declined from 5 (*n*=58, SE=0.2) to 2.5 (*n*=23, SE=0.5) at 18 months ($p< 0.0001$). Reductions in pain scores and range were similar for the SCS- and standard treatment group. Pain reduction of more than 50% comparing intake values with the value at *t*=1 was observed in 19 patients (20%), reduction less than 50% in the majority of patients (55%) and pain was worse in 24% of the patients. After amputation the pain scores declined to values between 3.9 and 1.8 in patients receiving standard treatment and to 2.6 and 1.4 for SCS treatment ($p< 0.001$).

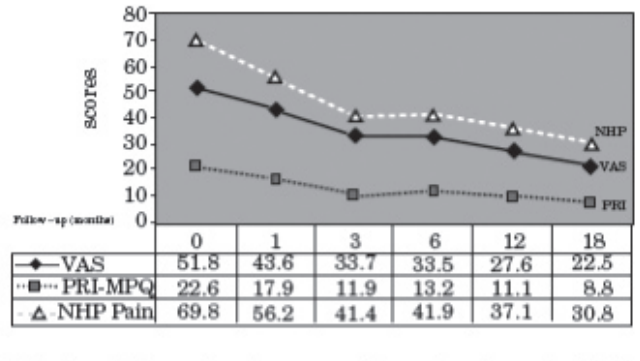
McGill pain questionnaire

The pain-rating index (PRI), part I of the McGill, was used and represents the sum from the sensorial, affective and evaluative indices. Intake values of the PRI did not differ between



Mean values of pain-rating index (PRI) of the SCS treated patients. Group 1 = all patients, 2 = patients not amputated, and 3 = amputated patients.
X-axis = follow-up in months, Y-axis = PRI value. The higher the score the worse the pain intensity. The difference between amputated and non-amputated patients is statistically significant.

Figure 2: McGill Pain Questionnaire.



Follow-up in months (0-18). VAS = visual analogue score measured as value beteen 0=none and 100 = maximal pain.
PRI-MPQ = pain rating index of the McGill Pain Questionnaire which is the sum of the sensory, emotional and affective parts of the list of synonymes. The NHP Pain is the combination of different questions in the questionnaire related to pain. The higher the values are in both measures (NHP and MPQ) the worse is the condition of the patient. The data of the patients under conservative treatment are comparable and summarized in Tables 3,4,5. Important is the parallel evolution over time in the different scores.

Figure 3: Different pain scores for patients under SCS treatment

standard treatment and SCS: for standard treatment 21.5 (*n*=58, SE=1.5) and SCS treatment 22.6 (*n*=57, SE=1.5). The difference between intake and one month follow-up (T0–T1) for the standard treatment was 32% (p=0.005) and slightly less for the SCS. After 3 months the scores declined to values between 8 and 13 for both treatment modalities, remaining unchanged until the end of follow-up. In the case of amputation the differences between intake and follow-up were more pronounced in both groups. The values dropped by 70–80% to nearly normal as compared to intake (p=0.001) (Figure 2; Table 5). Likewise, the pain score of the NHP at intake was 72 (*n*=58, SE=3.5) for the standard treatment and 70 (*n*=57, SE=3.9) for the SCS treatment and declined to 36 (*n*=24, SE=6) and 31 (*n*=27, SE=6) respectively at 18 months. This reduction of 50% was significant ($p<0.001$), and similar in both groups. Pain relief in non-amputated patients was substantially less.

Patients who underwent an amputation had significantly lower pain scores than non-amputated patients in both treatment groups ($p< 0.01$). The evolution in time of the three pain measurements is given in Figure 3. There is a remarkable parallel evolution during follow-up.

MQS score

For an overview, analgesics used at intake were divided into three categories: (1) paracetamol and aspirin (ASA); (2) nonsteroid anti-inflammatory drugs (NSAID); (3) morphine and morphine analogues. Analgesic medication use for both treatment groups is shown in table 6.

Scoring the use of drugs was carried out using the Medication Quantification Scale (MQS). At intake, the mean MQS of the standard group was 7.35 (SE=0.68) and for the SCS group was 6.68 (SE=0.65) (Table 6). During follow-up there was a significant difference between the two treatment modalities. Patients receiving SCS used less non-narcotic and narcotic drugs (Table 7).

Discussion

For the study of quality of life and pain, a number of questionnaires and scales are available. All of them, uni- or multi-dimensional, are subjected to critic related to their clinical relevance. As Carlsson[24] stated: 'The patient should complete each scale without having the possibility of comparing with previous estimates'. However, the reliability of a pain relief score calculated as a difference between two estimates on the absolute scale may be low, because the double influence of the measurement error, which may be different in different patients. When assessing efficacy of treatment, attention should therefore focus on several complementary

Follow-up	0	1	3	6	12	18
Cons all	21.5	15.8	10.9	9.2	8.5	8.1
Non-amp		15	13	12.5	13	13
Amp		18	4.2	4	5.8	5.8
n	60	43	38	36	23	17
SCS all	22.6	17.9	11.9	13.2	11.1	8.7
Non amp		18.9	14.2	17.1	15	18.5
Amp		7	5.8	4.7	8.8	5
n	60	50	39	37	29	17

Mean values for pain-rating index (PRI) of the conservatively treated patients (Cons) and the stimulated patients (SCS). Follow-up in months. *n*= patients amputation free and alive at time of follow-up.

Table 5: McGill Pain Questionnaire.

Drugs	Standard	SCS
Paracetamol	41 (68%)	43 (72%)
NSAIDS	21 (35%)	22 (37%)
Morphine and analogues	21 (35%)	18 (30%)
MQS (mean ± SD)	7.3 ± 5.2	6.7 ± 5.0

Medication used in both treatment modalities at intake. The difference is not significant. Although in the article of Steedman (35) drugs were divided into six classes, for the purpose of comprehensibility they were reduced to three classes in this table. Only a minority of patients used drugs as muscle relaxants, benzodiazepines and barbiturates.

Table 6: Medication quantification scale at *t*=0.

Follow-up	Standard	SCS	*p*-value
t = 0	7.3±0.7	6.7±0.6	NS
t = 1	8.9±0.9	3.5±0.6	<0.001
t = 3	6.8±0.8	2.8±0.7	<0.001
t = 6	5.6±0.9	2.0±0.5	0.002
t = 12	3.6±0.8	1.7±0.5	0.055
t = 18	1.9±0.7	2.4±1.0	0.70

Table 7: Mean ± SE for the quantification of the use of analgesic drugs in both groups.

indices of pain relief, as well as on the individual's tendency to bias his estimates"[24]. Graham reported that the reliability of the McGill pain questionnaire was high[34]. In this study the different pain scales (VAS, McGill PRI and the NHP pain score) were compared and revealed a strong correlation (p<0.001).

Critical limb ischemia is an extremely high burden for the quality of life of these patients. Other chronic diseases such as severe angina pectoris, hip disease and rheumatoid arthritis revealed comparable results for pain and restriction of mobility [30,35]. Other studies that analyzed 'general well being' reported that patients with limb ischemia had fear of pain and amputation and suffered from a restricted mobility[25,36-38].

Quality of life

Mean scores on quality of life (NHP) in patients with peripheral vascular disease 'amenable to surgery' and who were surgically treated were 30.3 for energy, 22.6 for pain, 13.9 for emotional

reactions, nine for social isolation, 24.7 for sleep and 22 for physical mobility, with an overall score of 20.4[16,39]. This was well below, and thus better than the scores in patients with critical ischemia 'not amenable to surgery' studied in this trial.

Augustinsson reported on quality of life in patients with SCS for ischemic pain using the Sickness Impact Profile (SIP) and a Mood Adjective Checklist (MACL). Seventeen of the 54 patients had critical ischemia (22%). Functions of daily life were reported as unchanged. In a supplementary short (1 month) prospective study on 23 patients, of whom 13 had ischemic pain, clear improvements were seen in sleep, rest and emotional behaviour (p< 0.01)[40]. Humphreys reported on the QoL of a large group of patients with peripheral vascular disease using the Rosser classification and the EuroQol. In a subgroup of 10 patients with critical ischemia no change in QoL was found comparing the situation before and six months after amputation; this reflected the problem of rehabilitation[21,39].

Pain relief

In this study the pain relief was reported using the VAS, the PRI of the McGill pain questionnaire and the pain weighted scores of the NHP. All these measures revealed an important reduction in pain, which was seen from the first month follow-up on. There was, however, no difference between treatment strategies. Augustinsson reported 'excellent' pain relief, which according to his classification was more than 66% pain relief in 15% of his patients[40]. Broseta mentioned 'substantial' pain relief (75–100%) in 78% (29/37) of the patients[5]. Mingoli reported pain relief in 75% of patients at 2 years with infrequent use of analgesics[41]. Meglio noted more than 50% pain relief (mean 90.1%) in 85% (34/40) of the patients treated[42]. Bunt reported a pain relief of 75% or more in 11 of 15 patients (73%)[11].

The existing literature, in which no randomized study was available at the start of this study, remains responsible for the impression that pain relief is almost complete in most patients with SCS. Careful analysis indicates that only a small percentage (15–20%) has 'excellent' (>75%) pain relief.

Excellent pain relief after a trial period of stimulation was considered as a predictive factor for long-term success. No scientific data were available confirming this hypothesis. A trial stimulation period was therefore not incorporated in the study design. Subsequent simulation of a trial stimulation with our data proved to be negative. Data on pain relief were compared between time of implantation and 1 month follow-up. Although limb survival was lower in patients without good pain relief, there was no difference in survival between a good reaction on stimulation or a good reaction on pain medication.

Another element in the evaluation of pain relief is the reduction in medication. A useful method is the medication quantification technique, which gives the physician a better insight on the kind and quantity of drugs taken by the patient[32]. We consider this method adequate, but could not find data to compare our results in the literature. Several authors described the influence of hypertension on limb survival. Patients having hypertension seemed to have a worse outcome[13,43]. This analysis was also performed in the Dutch randomized trial. Although there was a tendency towards an imbalance in the numbers of patients between treatment (p=0.07), no statistical significant difference was found. The hazard ratio for the risk of amputation in the presence of hypertension was 0.72 (p=0.25).

Conclusion

Both treatments resulted in a significantly positive effect on pain and quality of life. The overall outcome measures of well-being did not differ between the two treatment modalities. Minor inconsistent differences in subscores of the NHP were seen between the treatment groups. Patients under SCS treatment used significantly fewer analgesics. Amputation was very successful regarding pain relief, but decreased the mobility of the patient, rendering rehabilitation more difficult. A trial period of stimulation is not needed if limb survival is the endpoint of the study. In the case of critical limb ischemia a follow-up period of 18 months seems adequate because most amputations and complications occurred well within this period.

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Chapter VI

Cost-effectiveness of spinal cord stimulation for non-surgical management of critical limb ischemia

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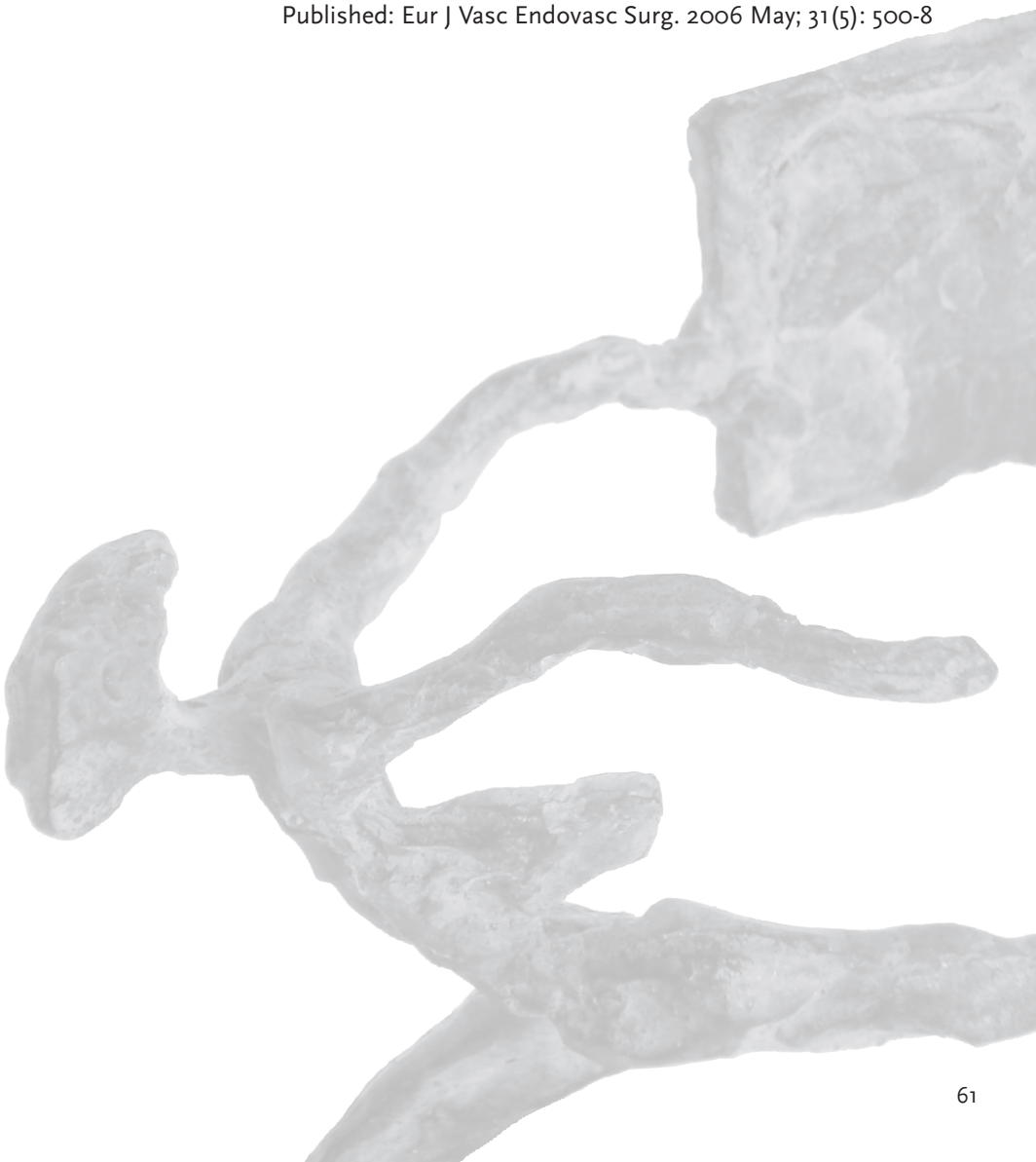


Abstract

Objective

To quantify the costs of treatment in critical limb ischemia (CLI) and to compare costs and effectiveness of two treatment strategies: spinal cord stimulation (SCS) and best medical treatment.

Methods

One hundred and twenty patients with CLI not suitable for vascular reconstruction were randomised to either SCS in addition to best medical treatment or best medical treatment alone. Primary outcomes were mortality, amputation and cost. Cost analysis was based on resources used by patients for 2 years after randomisation. Both medical and non-medical costs were included.

Results

Patient and limb survival were similar in the two treatment groups. Costs of in-hospital-stay and institutional rehabilitation constituted the predominant part (±70%) of the total costs of medical care in CLI. Cost of SCS-implantation and complications (€7,950 per patient) exceeded by far cost due to amputation procedures (€410 per patient). The total costs of treatment were €36,600 per patient over 2 years for the SCS-group vs. €28,700 for best medical treatment alone (28% higher for SCS-group, p=0.009).

Conclusions

Total costs of treatment in CLI are high. Major components are hospital and rehabilitation costs. In contrast to recent reviews, there were no long-term benefits of SCS-treatment. Therefore, cost-effectiveness is reduced to cost minimisation and SCS-treatment is considerably more expensive than best medical treatment.

Introduction

Critical limb ischemia (CLI) threatens the survival of an extremity and often causes lifelong disablement from a painful leg. Lower-extremity amputation bears a high risk of disability, prolonged institutionalization or death[1–4]. Compared with amputation, revascularisation is associated with lower perioperative morbidity and mortality. Limb preservation should be the goal, yet many patients with critical leg ischemia are poor candidates for the preferred therapeutic options of percutaneous transluminal angioplasty or surgical revascularisation.

Many authors have recommended the use of spinal cord stimulation (SCS) in patients with limb-threatening ischemia in whom vascular reconstructionis not an option[5–19]. SCS involves implantation of a pacemaker with epidural lead activating the dorsal columns of the spinal cord. Dorsal column stimulation at Th10-L1 level induces paraesthesia in the lower extremities, thereby alleviating ischaemic pain. Pain relief has been reported as excellent in CLI and limb survival far better than expected (68–80% after 1 year)[6,8,12,20,21]. In a multicentre randomised trial[22], we found that SCS-treatment was no more effective than best medical treatment alone in preventing amputations. Recently, however, several reviews concluded that SCS is beneficial (in selected patients)[18,19,23]. Since these reviews contain major weaknesses and the available information on costs in CLI involved is very limited[24–26], we present a reconsideration of the evidence together with a detailed analysis of costs.

If costs were considered in CLI, often these were 'roughly' calculated using charges/fees and with little information about the differentiation of the costs. This may result in bias.

We aimed to study the total direct and indirect medical costs of critical limb ischemia within theframework of a randomised trial. We present estimates of the full cost price, based on real resource use, in substantial patient groups.

Methods

Study design

The trial design has been published[22,27]. In brief, patients with CLI as characterized by persisting rest pain or ischaemic skin lesions[1] were eligible, if vascular reconstruction was not possible. From 17 hospitals in The Netherlands, 120 patients were enrolled from 1991 until 1996. The ethical committees at each participating centre approved the study protocol, and patients gave written informed consent. The treatment strategies SCS in addition to best medical treatment ('SCS-treatment') and best medical treatment alone ('standard treatment') were allocated at random to eligible patients using balanced block randomisation.

Treatment

Standard treatment included analgesics, antithrombotic and haemorrheologic drugs, local wound care and antibiotics, if indicated. There was a list of recommended medication, but no fixed treatment regimen. Those patients allocated to SCS treatment additionally received an implantable spinal cord stimulation system. A quadripolar lead (Medtronic) was placed in the epidural space and connected to an Itrell II pulse generator (Medtronic). Both treatment regimens initially aimed at adequate pain suppression. During follow-up, the treatment effect was optimised by altering medication, stimulation settings or both. Patients receiving SCS-treatment were checked regularly by a neurosurgeon or anaesthesiologist.

All patients were assessed before randomisation, at 1, 3, 6, 12, 18 months after randomi-

sation, and at the end of the study. After each follow-up visit, patients completed a questionnaire on consumption of health resources. Between follow-up visits patients came to the hospital as often as necessary. The primary outcome measure was limb survival, defined as absence of 'major' amputation (on level of foot or higher)[28].

Background of the costanalysis

The viewpoint of the cost analysis was societal, thus all costs and consequences were taken into account. Cost analysis was based on recorded resource use by patients for 2 years after randomisation or until death, if this occurred within 2 years. The costs were calculated per patient as the product of volumes and market prices. Volumes of the cost items were collected for all patients. Market prices were estimated in smaller samples. All costs were converted to 1993 Euros (*f*100= €45.38), according to the calculation factor of the The Nederlandsche Bank (www.dnb.nl). Costs were not discounted given the short time perspective (2 years per patient). In the successive time periods (0–1, 1–3, 3–6 months after randomisation, etc.) volumes of resource use per patient were calculated from the observed volumes divided by the number of patients at risk. This method was an adaptation of the product-limit method as used in survival analysis[29] .

Use of resources

Costs were classified into direct medical costs (inside and outside the hospital), direct non-medical costs and indirect costs[30]. The components of the medical costs in CLI are summarized in Table 2. Direct non-medical costs consisted of travel expenses and out-of-pocket expenses on home adaptations (e.g. removal of thresholds for wheelchairs, bathroom adaptations). Indirect non-medical costs involved non-professional help to patients externally to the health sector (e.g. transportation by relatives and friends or domestic help). We did not include costs caused by loss of production due to absence from work, since the majority of patients were retired from work.

Hospital admissions were classified as directly related to CLI (wound care, amputations, complications), related to CLI (other vascular events, including cardio-and cerebrovascular events) or not related to CLI. In The Netherlands, nursing homes have adequate facilities for rehabilitation; therefore, temporary stay in nursing homes is common for elderly amputees. As for homes for the elderly, only new admissions (after randomisation) were taken into account.

Volume information on outpatient visits, direct medical cost items outside the hospital and nonmedical care was primarily collected from patient questionnaires. Data on operative procedures, in-hospital stay and rehabilitation, and medication usage were available from the case-record-forms filled in by the surgeons. Furthermore, information was checked in hospital administrations and hospital information systems.

Costing resources

For evaluation of the costs, we first identified the fundamental cost items. A detailed cost analysis was performed to estimate market prices for the important determinants, i.e. those with large volumes or high prices. These were primarily direct medical costs, such as in-hospital-stay, operative procedures, and admission to nursing home or rehabilitation clinic. For minor cost items, as travel expenses and out-of-pocket payments, charges or expert estimates were used as approximations of the market prices.

Hospital admission prices were assessed in detail, using cost registrations to quantify attendance by health professionals, supplies, equipment, and capital costs (fixed annual costs of running the unit). We estimated prices of lower limb amputations by recording the presence and time of various health professionals during amputation procedures. Registrations were performed in one university hospital and two general hospitals. Prices of supplies, equipment, and capital costs were obtained from a detailed department based cost registration. These data were available from the hospital information system. The price of implantation of the SCS device was estimated using presence of personnel and time registrations during 20 consecutive implantation procedures; yet the main costs of SCS-implantation arose from the price of the Itrell II pulse generator and Quad lead (€7,200). The prices of outpatient visits were based on department based cost registrations. Prices of admission to a nursing home or rehabilitation clinic were available from other Dutch national investigations[31,32]. Prices for rehabilitation were adjusted according to expert opinion on the amount of medical care consumed by vascular amputees in relation to the average patient in a rehabilitation clinic.

Statistical analysis

All data were recorded on standardized forms and entered in a concurrent database. Analysis of both clinical outcome and cost was by 'intention to treat' and included all randomised patients. Patient and limb survival were estimated and compared with Kaplan–Meier analysis and log-rank tests. In the analysis of limb survival, patients were censored at death. Cost differences between groups were analysed by Mann–Whitney test. For all hypothesis tests, *p*-values are stated, with $p<0.05$ interpreted as statistically significant.

Characteristics	SCS (*n*=60)	Standard (*n*=60)
Male/female	33/27 (55/45%)	37/23 (62/38%)
Age [year]	73.1±9.8	72.1±10.6
Diabetes	22 (37%)	23 (38%)
'Other leg'		
Symptomatic	19 (32%)	29 (48%)
Amputated	9 (15%)	7 (12%)
Smoking		
Quitted >1 year	22 (37%)	16 (27%)
Still smoking	18 (30%)	26 (44%)
CVA or TIA	13 (22%)	16 (27%)
Myocardial infarction	23 (38%)	22 (37%)
Angina pectoris	12 (20%)	15 (25%)
Rest pain only	22 (37%)	19 (32%)
Ischaemic skin lesions	38 (63%)	41 (68%)
Gangrene	24 (40%)	23 (38%)
Vasc. reconstructions		
Nil	11 (18%)	15 (25%)
1 or 2	25 (42%)	29 (48%)
O3	19 (32%)	20 (33%)
Sympathectomy	21 (35%)	19 (32%)
Ankle systolic pressure [mmHg]	35.2±25	41.6G22
Ankle-to-brachial pressure index	0.23±0.16	0.28±0.13

Data are number (%) or mean±SD.

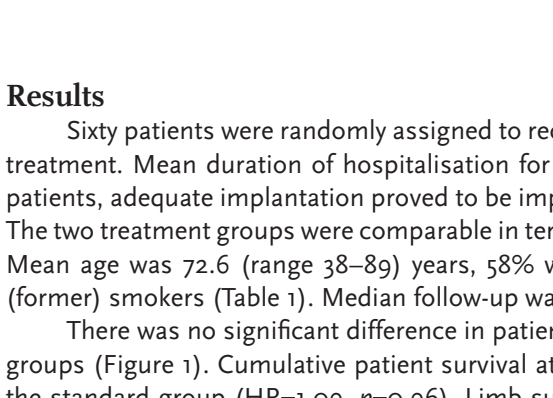
Table 1: Baseline characteristics of the SCS and standard treatment groups

Results

Sixty patients were randomly assigned to receive SCS-treatment and 60 to receive standard treatment. Mean duration of hospitalisation for SCS-implantation was 4.9 (±2.3) days. In two patients, adequate implantation proved to be impossible, and one patient refused implantation. The two treatment groups were comparable in terms of demographic and clinical characteristics. Mean age was 72.6 (range 38–89) years, 58% were males, 38% had diabetes, and 68% were (former) smokers (Table 1). Median follow-up was 2 years (range 8–59 months).

There was no significant difference in patient and limb survival between the two treatment groups (Figure 1). Cumulative patient survival at 2 years was 64% in the SCS-group *vs.* 63% in the standard group (HR=1.09, p=0.96). Limb survival at 2 years was 52 and 46%, respectively (HR=0.82, p=0.47). Analysis of amputation levels revealed no significant differences. In the SCS-group, 18 complications (lead displacements or inadequate stimulation) were treated by operative repositioning procedures.

In Table 2, the unit costs for applicable cost items are summarized, with separate information for university and general hospitals. Table 3 shows how long the patients spent in hospital, rehabilitation centre and nursing home in both treatment groups. Most in-hospital days (over 80%) were directly related to CLI. Only four intensive care unit days were noted (in the standard group). Although in the SCS-group patients spent less days in rehabilitation clinics, there were more admissions to nursing homes. Consequently, the costs of rehabilitation (in clinics and nursing homes together) were similar (€6,760 vs. €7,480 at 2 years). Costs of in-hospital-stay and institutional rehabilitation constituted the predominant part of the total costs of medical care in CLI. Table 4 shows mean cumulative costs per patient according to cost type for both treatments.



The upper curves indicate patient survival for both treatment groups ('SCS' and 'standard' treatment); the lower curves indicate amputation free survival. The area between the upper and lower curves represents the proportion of patients alive with major amputation. Patients at risk: at 12 months 47/44, at 24 months 21/19.

Figure 1: Mortality and amputation in CLI.

Obviously, cost for operative procedures was much higher in the SCS-group because of implantation of the SCS-device (€7,770). In the first month after randomisation more in-hospital days in the SCS-group occurred, due to hospitalisation for the implantation procedure. Over a 2-year period, cost of SCS-implantation and complications (€7,950 per patient) far exceeded the cost due to amputation procedures (€410 per patient). Outpatient cost was higher for SCS-treatment, because of check-ups by the neurosurgeon or anaesthesiologist. In the SCS-group more patients moved to homes for the elderly, while in the standard group more patients

Direct medical cost items	Cost components	Unit cost [Euro]	
		University hospital	General hospital
In hospital			
Inpatient care (per day)	Time/attendance registration, department-based cost registration		
General ward		181	151
Intensive care unit		1150	1027
Operative procedures	Time/attendance registration, department-based cost registration		
Amputation (toe)		266	117
(Forefoot)		430	235
(Foot)		554	382
(Below-knee)		667	406
(Above-knee)		695	554
SCS-implantation	Time/attendance registration, SCS-implant, department based cost registration	7823	7760
SCS-complication treatment		715	685
Outpatient clinic (per visit)	Department based cost registrations	32	30
Routine tests on general ward (per day)	Registration in patient sample (n=18)	17	
Medication use on general ward (per day)	Department of vascular surgery	10	
Rehabilitation			
Consultation (follow-up (per Z days)	Estimates based on reimbursement fees	55+Z x 10	
Day-programme (per day)	Estimates based on reimbursement fees	59	
Outside hospital			
Rehabilitation centre (per day)	National Hospital Institute report	227	
Nursing home (per day)	Ministry of Health report	101	
Home for the elderly (per day)	Ministry of Health report	48	
Medical supplies, e.g.			
Crutches (per pair)	Public Health Service prices	41	
Standard wheel-chair	Public Health Service prices	559	
Below-knee prosthesis	Manufacturer's prices	1682	
Medication use (per individual patient)	Standard dose prices of recorded medicine	Spec.	
General practitioner (per visit)	Reimbursement fee	34	
Professional care, e.g.			
Day-care (per day)	Ministry of Health report	55	
Domestic social service (per hour)	Institute Medical Technology Assessment, Rotterdam	16	
Nurse (per hour)	Ministry of Health report	34	
Direct non-medical cost items			
Travel expenses (per travelled kilometre)	Kilometre price (car/public transportation/taxi)	0.20/0.09/0.60	
Time lost working	See text	–	
Out-of-pocket expenses	Social Services (for the handicapped)	150–340	
Indirect non-medical cost items			
Non-professional help (per hour)	Institute Medical Technology Assessment, Rotterdam	5.5	

Table 2: Unit costs of relevant cost items in critical limb ischemia

received professional care in their own home. Again, combined societal costs for homes for the elderly and domestic professional care were comparable in SCS-and standard group (€6,120 vs. €5,040). For both medication and medical supplies, costs were lower in the SCS group by about 30%. Direct and indirect nonmedical costs had little impact, but were somewhat higher for SCS-treatment. Fig. 2 shows the total cost and its components over 2 years. After 2 years of treatment, costs of SCS-treatment per patient were €7,900 (28%) higher as compared to standard treatment (€36,600 *vs.* 28,700, p=0.009).

Since, mortality was high (23% of the patients died within 1 year, 36% within 2 years), a considerable proportion of patients did not contribute to the cost increase during the entire time period of 2 years. Adjusted for mortality, mean costs per patient were €31,400 for the SCS group and €23,800 for the standard group, thus 32% higher for SCS-treatment (p=0.002).

Type of institution	Cumulative days (2 years)	
	SCS (n=60)	Standard(n=60)
In-hospital-stay		
Directly related to CLI	2523	2544
Related to CLI	480	537
Unrelated to CLI	186	39
Rehabilitation centre	623	1047
Nursing home	1607	1040

Table 3: Days spent in hospital, rehabilitation centre or nursing home in both treatment groups within 2 years after randomisation

Time (months)	Hospital	Operations	Rehab	Eld. home	Homecare	Medication	Outpatient	Non-med	Total
1 SCS	2,694	7,808	17	185	171	55	123	110	11,163
3	5,425	8,041	548	545	490	253	287	260	15,849
6	7,126	8,083	3,081	1,240	816	608	420	402	21,776
12	8,586	8,131	4,740	2,547	1,549	1,092	607	599	27,851
18	10,290	8,376	5,869	3,339	1,916	1,362	772	813	32,736
24	11,799	8,376	6,759	3,803	2,316	1,483	995	1,031	36,563
1 Standard	1,695	72	54	142	306	112	98	102	2,581
3	3,982	189	1,095	308	953	439	225	215	7,405
6	6,740	278	3,839	536	1,639	1,117	351	324	14,824
12	10,990	417	6,253	814	2,559	1,806	587	470	24,167
18	11,740	417	7,323	1,226	3,197	1,958	677	555	27,093
24	12,342	417	7,484	1,341	3,695	2,010	749	627	28,665

Cost components are shown as: *hospital*: cost of hospital admission, in-hospital stay; *operations*: cost of the SCS-device and implantation, amputations; *rehab(ilitation)*: cost of admission to rehabilitation center or nursing home; *eld(erly) home*: cost of admission to home for the elderly; *homecare*: cost of professional day care, general practitioner, district nurse, professional domestic help; *medication* (and supplies): cost of medication use and medical supplies; *outpatient* (consultation): cost of outpatient visits, consultation for rehabilitation, prosthesis (fitting); *non-medical:* cost of non-professional help, travel expenses, out-of-pocket expenses.

Table 4: Cumulative mean cost per patient (Euro)

Discussion

Over 2 years, the costs of SCS-treatment were about €7,900 (28%) higher as compared to best medical treatment alone. Initial costs in SCS-treatment were high due to device implantation. Since all other costs evolved similarly in both treatment groups, SCS-treatment remained the more expensive therapy during follow-up. Survival and amputation-free survival were similar in the two treatment groups of patients with CLI; therefore, cost-effectiveness is reduced to cost-minimisation analysis. Based on limb survival (HR=0.82), the 'number needed to treat' (NNT) to save one limb was estimated at 14, resulting in €110,000 per limb saved. Using for example a health value (utility) for below-knee amputation of 0.61[33], this would correspond to at least €280,000 per QALY gained. Hence, from a societal perspective and with consideration of cost-effectiveness, a conservative approach as in best medical treatment is warranted.

Generally, total costs of treatment (€36,600 *vs.* €28,700 per patient over 2 years) were high. Costs of in-hospital-stay and institutional rehabilitation constituted the predominant part of the total costs of medical care in CLI. Compared with the average age-and sex-specific health care expenditure per Dutch person (€5,150 annually, €10,300 over 2 years), costs are three times higher.

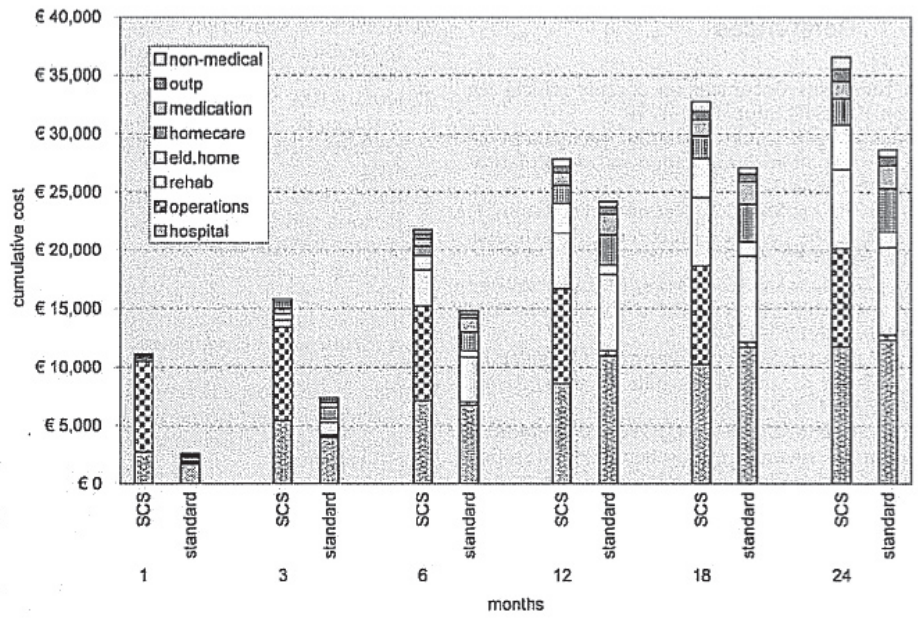


Figure 2: Components of cumulative mean cost per patient over 2 year.

The TransAtlantic Inter-Society Consensus (TASC) document expressed concern about the lack of good quality data concerning cost-effectiveness of interventions in peripheral arterial occlusive disease (PAOD). Nonetheless, several groups reported data on (hospital) costs of CLI, revascularisation procedures and amputation[24–26,34–40]. On average, longterm costs following revascularisation for CLI were estimated at $23,000–28,000. Hospital costs were approximately $11,000 for successful revascularisation ($9,000–11,000 for angioplasty, $11,000–15,000 for surgery), compared with $22,000 for failed revascularisation. Each additional procedure

increased the cost by $9,000. The costs for revascularisation and primary amputation were similar when the costs of a prosthesis and rehabilitative therapy were included. Primary amputation costs were reported between $17,000 and 21,000, secondary amputations lead to higher cost ($25,000–28,000).

For all important cost items, we estimated real costs rather than reimbursement fees or charges. Cost of in-hospital-stay was assessed in detail, since this was the main element of total costs of treatment. Over 80% of in-hospital days were directly related to CLI. Meticulous cost evaluation was also performed for operative procedures, but cost of amputation proved to be relatively unimportant compared to SCS-implantation. Although some differences were observed between the treatment groups as to the rehabilitation facility (rehabilitation clinic or nursing home) and the type of home care (home for the elderly or domestic professional care), combined costs for rehabilitation and home care were comparable. Due to the Dutch health care structure, costs are somewhat higher in university hospitals than in general hospitals. This does have some influence on (total) costs in university hospitals (~10% higher), however, due to stratified randomisation this does not modify either cost comparisons between two groups or costs components (%).

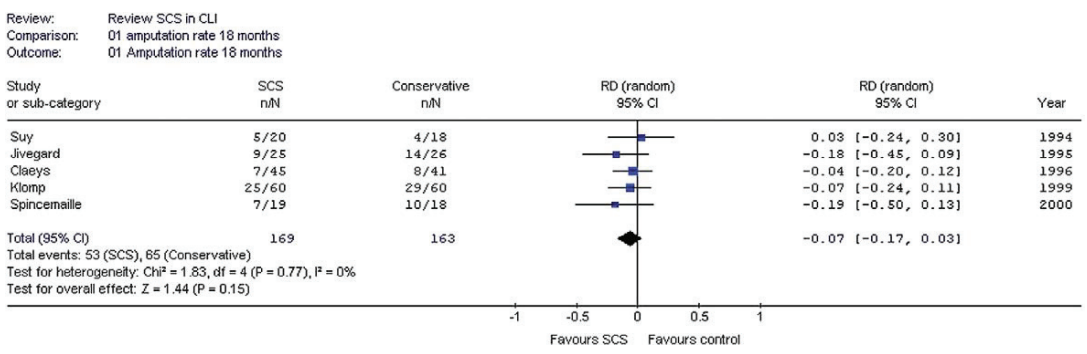


Figure 3: Meta-ana;ysis of randomised studies on SCS in critical limb ischemia

A common problem when using clinical trials for any kind of cost assessment arises from the fact that the clinical protocol mandates more visits, consultations and examinations than otherwise used in clinical practice.[41] For a treatment in a research setting, there will generally be more costs, compared to daily practice. In this study, costs from protocol-driven medical care may have arisen in the outpatient costs. However, these were very limited and comprised less than 3% of the total costs.

With hindsight, all individual randomised studies on SCS for peripheral vascular disease, including the one described in this article, were underpowered. This was mainly due to the assumption that limb survival in the control group would be much lower (based on the literature data 20–40% at 1 year) and that 20–30% improvement in limb survival would be attained readily. However, the conservative (i.e. best medical) treatment groups showed much better outcomes.

A recent 'systematic review'[18,19] included six studies, with patient numbers varying from 27 to 120 patients. The most important problem of this review was the inclusion of a 'controlled' (non-randomised) study by Amann.[17] In this study, patients were classified according to transcutaneous pO2 measurements and did or did not receive SCS treatment based on this TcpO2 classification and trial stimulation. Over 30% of the patients in the 'control' (conservative)

arm underwent amputation within 2 weeks, illustrating intense selection bias. This study should be seen as a prognostic study using TcpO2 measurements, rather than an adequate comparison of treatments. Remarkably, the limb survival curves were quite comparable after the initial period. In addition, amputation data input was incorrect for two studies[22,42], the use of data from a subgroup of the smallest study[43] is artificial, and for at least three studies[42–44] concealment of treatment allocation was dubious. The value of any meta-analysis is totally dependent on lack of bias in its component studies[45]. Hence, in a meta-analysis of clinical trials, it is important to restrict inclusion to randomised trials, ideally with adequate concealment of treatment allocation, intention-to-treat analysis and objective outcome assessment. Figure 3 shows a meta-analysis performed with amputation data input of all (*n*=5) randomised studies at 18 months, generating a risk difference for amputation of -0.07 [95% CI: -0.17 to +0.03] *p*=0.15 with corresponding relative risk estimate of 0.80 [95% CI: 0.60–1.06]. As regards these estimates, one should make allowance for dubious concealment of treatment allocation in three studies, which usually is associated with exaggeration of treatment effects by 40%[46,47].

In conclusion, practical benefit from SCS as compared to best medical treatment alone in terms of (limb) survival has not been established. If SCS is beneficial, the magnitude of the effect is small. The NNT to save one limb would be approximately 13, resulting in costs of around €100,000 per limb saved. In view of the high costs associated with limb-threatening ischemia and its treatment, initial high costs of future therapy developments seem acceptable, particularly if substantial benefit is expected and leads to a decrease of in-hospital days and rehabilitative institutionalisation.

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Chapter VII

Efficacy of spinal cord stimulation in subgroups of patients with critical limb ischemia

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Systematic review and meta-analysis of controlled trials assessing spinal cord stimulation for inoperable critical leg ischemia (Letter)

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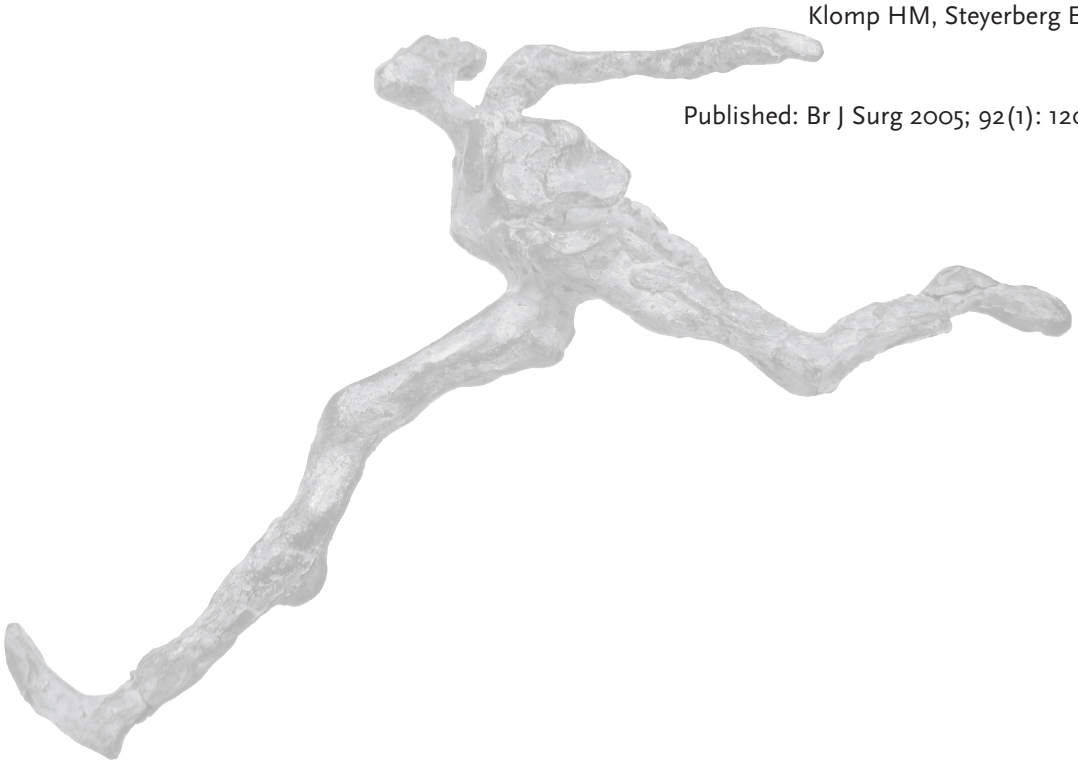

Abstract

Background

The use of spinal cord stimulation (SCS) has been advocated for management of ischemic pain and the prevention of amputations in patients with inoperable critical limb ischemia (CLI), although data on benefit are conflicting. Several reports described apparently differential treatment effects in subgroups. The purpose of this study was to analyze the data on efficacy of SCS and to clarify preselection issues.

Method

Five randomized trials have been performed with a total number of 332 patients. Primary outcome measures were mortality and limb survival. In the largest multicentre randomized trial (*n*=120), comparing SCS-treatment and best medical treatment alone in patients with inoperable CLI, we determined the incidence of amputation and its relation to various pre-defined risk factors. We used Kaplan-Meier and Cox regression analysis to quantify prognostic effects and differential treatment effects.

Results

Meta-analysis yielded a relative risk for amputation of 0.79 and a risk difference of -0.07 (*p*=0.15). The risk factor analysis clearly showed that patients with ischemic skin lesions (ulcerations or gangrene) had a worse prognosis, i.e. higher risk of amputation (RR 2.30, *p*=0.01). We did not observe significant interactions between this prognostic factor (or any other) and the effect of SCS. The analysis did not indicate a subgroup of patients who might specifically be helped by SCS.

Conclusions

Meta-analysis including all randomized data shows insufficient evidence for higher efficacy of SCS-treatment as compared to best medical treatment alone. Although some factors provide prognostic information as to the risk of amputation in patients with CLI, there are no data supporting a more favorable treatment effect in any group.

Introduction

The fate of patients with critical limb ischemia (CLI) is influenced by treatment as well as by a number of other variables[1-3]. Prospective studies provide an excellent basis to identify risk factors for amputation. In the modern practice of vascular surgery, few studies addressed the natural history of CLI. It was inferred from older surveys and studies in patients in whom arterial reconstruction could not be undertaken for various reasons, that major amputation of the limb was necessary in 60-80% of patients within a year[1,4-9]. In an attempt to reduce this high incidence of amputation, several authors have recommended the use of spinal cord stimulation (SCS) for patients with CLI in whom a meaningful vascular reconstruction is not possible[10-15].

SCS involves implantation of a pacemaker with epidural lead activation of the dorsal columns of the spinal cord. Stimulation at Th10-L1 level induces paraesthesia in the lower extremity, alleviating ischemic pain. Change of sympathetic tone and increase of nutritional blood flow have been postulated as possible mechanisms for clinical improvement of ischemia. Since 1976, multiple articles[10-17] have been published on the alleged success of SCS in severe peripheral vascular obstructive disease. SCS was reported to improve limb survival in (nonoperable) CLI[11,13-15,18,19]. However, these reports mainly involved patient series without control groups. A small randomized trial (51 patients) from Sweden[20] showed a decreased amputation rate in response to SCS only in a subgroup of patients without arterial hypertension. Other randomized (preliminary) studies, including the multicentre randomized ESES-trial in the Netherlands[21-24] did not show significant effects on limb salvage. Recent reviews suggested that SCS may have a positive effect on limb salvage in selected patients[25,,26].

In this paper, we analyze the evidence on spinal cord stimulation in patients with critical limb ischemia. Furthermore, we focus on various risk factors for amputation and the treatment effect of SCS in clinical subgroups.

Methods

Study design of the randomized trial (ESES-trial)

The trial design and procedures have been described in detail elsewhere[27]. Eligible patients had critical limb ischemia and a meaningful vascular reconstruction was not possible. Inclusion criteria were persistent rest pain for more than 2 weeks or ischemic skin lesions, ankle pressure below 50 mm Hg or, in patients with diabetes and incompressible vessels, absent palpable ankle pulses. From 17 hospitals in the Netherlands, 120 patients were enrolled from 1991 until 1996. The ethical committees at each center approved the study protocol, and patients gave written informed consent. The treatment strategies SCS in addition to best medical treatment ('SCS-treatment') and best medical treatment alone ('standard treatment') were allocated at random to eligible patients. Randomization was stratified for diabetes, hospital and ankle pressure.

Treatment

Standard treatment included analgesics, antithrombotic drugs (aspirin, coumarins), hemorrheologic drugs (such as pentoxifylline, buflomedil, and ketanserin), local wound care and antibiotics, if indicated. There was a list of recommended medication, but no fixed treatment regimen. Analgesic use was recorded and quantified by the medication quantification scale (MQS)[28]. Chemical lumbar sympathectomy and prostanoids were not excluded, but were used in three patients only. The patients allocated to SCS-treatment additionally received an implantable

spinal cord stimulation system. A quadripolar lead (Medtronic, Minneapolis, MN) was placed in the epidural space and connected to an Itrell II pulse generator (Medtronic, Minneapolis, MN). Both treatment regimens initially aimed at adequate pain suppression. During follow-up the treatment effect was optimized by altering medication, stimulation settings or both. A neurosurgeon or anesthesiologist checked patients receiving SCS-treatment regularly.

Follow-up

All patients were assessed at 1, 3, 6, 12, 18 months after randomization and at the end of the study. Between follow-up visits patients came to the hospital as often as necessary. The primary end point was limb survival at 2 years. Limb survival was defined as absence of major amputation[29].

Prognostic factors

Besides demographic parameters as age and sex, comorbidity variables were recorded: diabetes, smoking, hypertension, history of myocardial infarctions, history of cerebrovascular accidents (CVAs) or transient ischemic attacks (TIAs). Previous vascular reconstructions were summarized as the number of vascular and endovascular reconstructions at the affected limb. Clinical parameters were: presence of ischemic skin lesions (ulcerations, gangrene), ankle pressure and ankle-to-brachial pressure index (ABPI). We studied not only the prognostic weight of these variables for the risk of amputation, but also their potential influence on the effect of treatment. In a multivariable analysis, the treatment effect was estimated after simultaneous adjustment for risk factors that emerged from our analysis with *p*-value < 0.20 or were regarded important in the literature[1,2,13,20,30-35].

Meta-analysis

We searched PubMed, Google and the registers of controlled trials. A combination of medical subject headings and key words were used: "spinal cord stimulation", "vascular", "peripheral vascular disease". This search strategy yielded 417 studies, mainly uncontrolled patient series (*n*=9-177). Eligible studies were randomized controlled trials comparing spinal cord stimulation with any conservative therapy for treatment of chronic severe peripheral vascular disease (critical limb ischemia) in adult patients. Combination of the above search strategy with “randomized trial” generated 6 reports of randomized trials[20,22-24,36,37]. Three of those described the same patient population[24,36,37]. Bibliographies of manuscripts were reviewed to identify other potentially relevant articles. One additional report of a separate patient population was found, published in a book[21]. Consequently 5 randomized studies are available, with patient numbers varying from 37 to 120 patients[20-24]. One prospective study[19] described 112 patients, who did or did not receive SCS on the basis of transcutaneous pO2 measurements. This was a prognostic study using TcpO2 measurements, not an adequate comparison of treatments. One other study[11] (*n*=34) used historic controls and was excluded as well.

Primary outcome measures were mortality and limb survival. Quality assessment included several criteria: report of settings and locations where the data were collected and dates defining the period of recruitment, randomization (whether the sequence was truly random, for example, computer generated, random number tables), concealment of allocation (whether a randomization method described would not allow the investigator or participant to know or influence the intervention group before an eligible participant was entered), and completeness of

accrual and follow-up. Blinding after allocation was not used in any trial. We categorized risk of bias as low in one study[24] (all criteria met), moderate in two[20,22] (one or more criteria met), and high in two[21,23] (no criteria met).

The meta-analysis contained the full data of the available 5 randomized studies (*n*=5)[20-24]. All studies randomized patients with CLI not suitable for (further) vascular reconstruction. Control treatment consisted of medical treatment, more or less similar among the studies, although medication use was observed and reported adequately only in one[24]. In the German study, additional prostaglandin therapy was given to both groups and the primary outcome was ulcer healing[22]. All authors reported mortality and major amputation rates (*n*=5 at 12 months, *n*=4 at 18 months, *n*=3 at 24 months).

Statistical analysis of the randomized trial

All data were recorded on standardized forms and entered in a concurrent database. Analysis of clinical outcome was by intention to treat and included all patients who underwent randomization. Patient and limb survival were estimated with the Kaplan-Meier method and treatments were compared using log-rank tests. In the analysis of limb survival, patients were censored at death. Cox proportional hazards model was used 1) for analysis with prognostic factors and 2) for analysis of interactions between prognostic factors and treatment. Hazard ratios (HRs) were estimated to quantify the effect of prognostic factors. When the HR was greater than 1, the risk of amputation or mortality was higher with the prognostic factor present than without this factor. In multivariable analyses, we selected prognostic factors with a *p*-value < 0.20 and the variable indicating SCS-treatment. For all hypothesis tests, p<0.05 was considered statistically significant.

CHARACTERISTICS	SCS (*n*=60)		Standard (*n*=60)	
male/female	33/27	(55/45%)	37/23	(62/38%)
age [year]*	73.1	± 9.8	72.1	± 10.6
diabetes	22	(37%)	23	(38%)
'other leg'				
symptomatic	19	(32%)	29	(48%)
amputated	9	(15%)	7	(12%)
smoking				
quit > 1 yr	22	(37%)	16	(27%)
still smoking	18	(30%)	26	(44%)
CVA or TIA	13	(22%)	16	(27%)
myocardial infarction	23	(38%)	22	(37%)
angina pectoris	12	(20%)	15	(25%)
ischemic skin lesions	38	(63%)	41	(68%)
gangrene	24	(40%)	23	(38%)
vasc.reconstructions				
0	15	(25%)	11	(19%)
1 or 2	26	(42%)	29	(48%)
> 3	19	(32%)	20	(33%)
sympathectomy	21	(35%)	19	(32%)
ankle systolic pressure [mmHg]*	35.2	± 25	41.6	± 22
ankle-to-brachial pressure index*	0.23	± 0.16	0.28	± 0.13

Data are number (%) or *mean ± SD.

Table 1: Baseline characteristics of the spinal cord stimulation (SCS) and standard treatment groups.

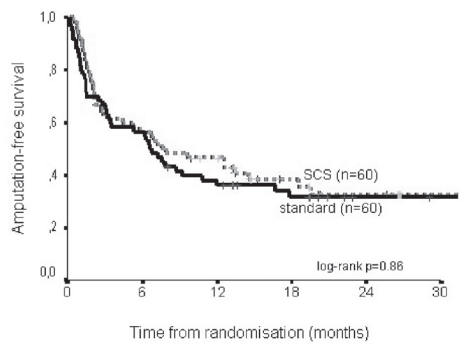

Figure 1: Amputation-free survival for spinal cord stimulation (SCS) and standard treatment groups.

Statistical analysis of the meta-analysis

The meta-analysis data were summarized in Review Manager (RevMan) as relative risks or risk differences. Due to clinical, methodological, and statistical heterogeneity of the studies, random effects models were used. We did not do a sensitivity analysis because of the small numbers of included trials.

Results

In the ESES-trial, 60 patients were randomly assigned to receive SCS-treatment and 60 to receive standard treatment. The groups were comparable in terms of demographic and clinical characteristics (Table 1). Median follow-up was 2 years (range 244-1171 days). The mean age was 72.6 year, nearly 40% of the patients were diabetics, and over 60% had ulcerations or gangrene in addition to rest pain. There was extensive comorbidity: 24% of the patients had had a CVA or TIA, 37% had a myocardial infarction, 23% had episodes of angina pectoris and 68% were (former) smokers. Many patients had had (multiple) vascular reconstructions on the affected limb. Mean Doppler ankle pressure was 38 mmHg, mean ABPI was 0.26.

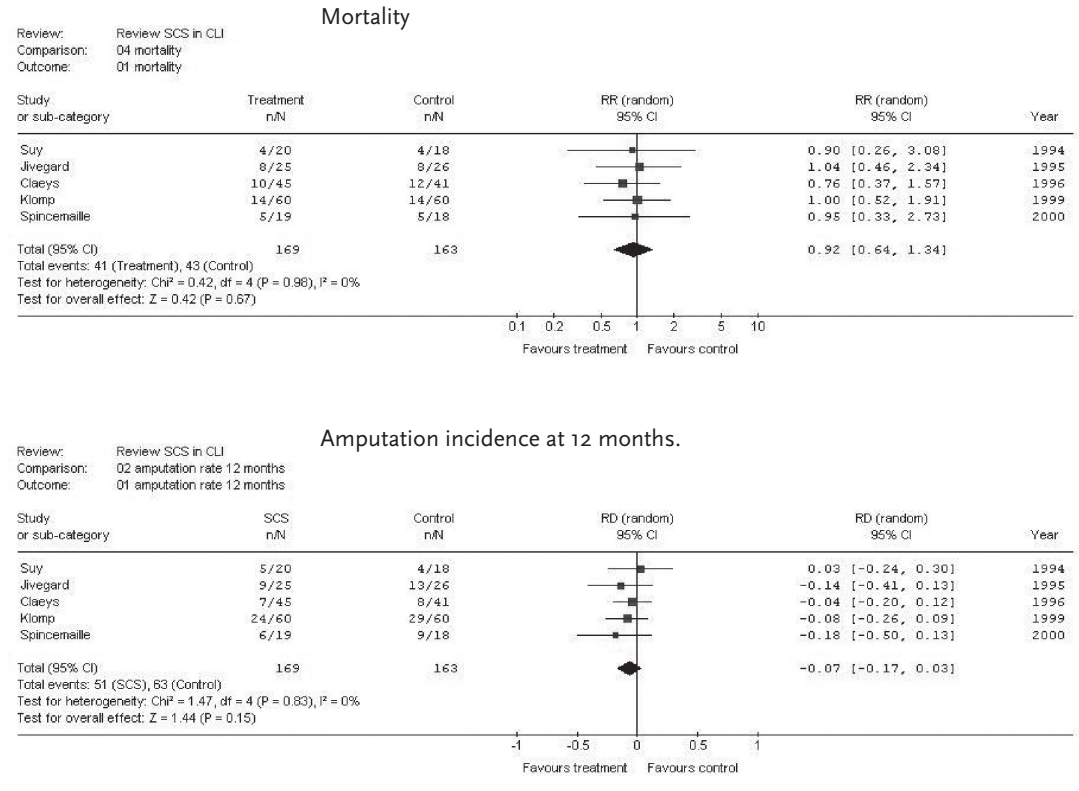

Figure 2: Meta-analysis of randomized trials on spinal cord stimulation (SCS) in critical limb ischemia (CLI) (n=332) Top, Mortality. Bottom, Amputation incidence at 12 months.

Mortality and limb survival

These data were presented previously. Mortality was comparable in both treatment groups: at six months 17% in both groups, and at two years 36% in the SCS-group *vs.* 37% in the standard treatment group (log rank, p=0.96). At 6 months, limb survival was 66% in the SCS-group *vs.* 68% in the standard group, at two years 52% *vs.* 46% (log rank, p=0.47). The relative risk for amputation in the SCS-group as compared to the standard treatment group was 0.81 [95% CI: 0.47 to 1.42]. As a composite measure, amputation-free survival is shown in Figure 1.

Meta-analysis

Five randomized trials included 332 patients, 169 received SCS-treatment, 163 control treatment. Mortality was comparable in both groups (41 of 169 versus 43 of 163, p=0.67). Figure 2 shows the analysis for limb survival at 12 months (51 of 169 vs. 63 of 163, p=0.15), generating a relative risk of 0.79 [95% CI: 0.59 to 1.06] with an absolute risk difference of -0.07 [95% CI: -0.17 to +0.03].

Risk factor analysis

The prognostic significance of the studied variables for the risk of amputation is summarized in Table 2. The analysis did not show a significant prognostic influence for age, sex, diabetes,

FACTOR	HR	95% Confidence interval	*p-value*
Ischemic ulceration	2.20	1.2 - 3.9	0.016
Gangrene	2.48	1.4 - 4.3	<0.001
Smoking	1.27	0.9 - 1.7	0.12
Previous vascular reconstructions (per number more)	1.10	0.9 - 1.2	0.18
CVA/TIA	1.45	0.8 - 2.6	0.22
Hypertension	0.98	0.8 - 1.2	0.86
Ankle pressure (per 10 mmHg increase)	0.92	0.8 - 1.1	0.25
ABPI (per 10% increase)	0.87	0.8 - 1.1	0.47
Angina	1.38	0.8 - 2.4	0.29
Myocardial infarction	0.97	0.6 - 1.7	0.91
Age	0.99	0.8 - 1.3	0.93
Female sex	1.02	0.6 - 1.8	0.94
Diabetes	1.03	0.6 - 1.7	0.97

Table 2: Hazard ratio (HR) for amputation with p-values of 14 pre-defined variables.

FACTOR	HR	95% Confidence Interval	*p-value*
ischemic skin lesions	2.77	1.4 - 5.4	0.003
smoking	1.19	0.9 - 1.7	0.16
previous vasc. reconstructions	1.16	0.9 - 1.3	0.19
SCS-treatment	0.88	0.5 - 1.4	0.64

Table 3: Impact of prognostic factors and the estimation of the treatment effect in the multivariable analysis.

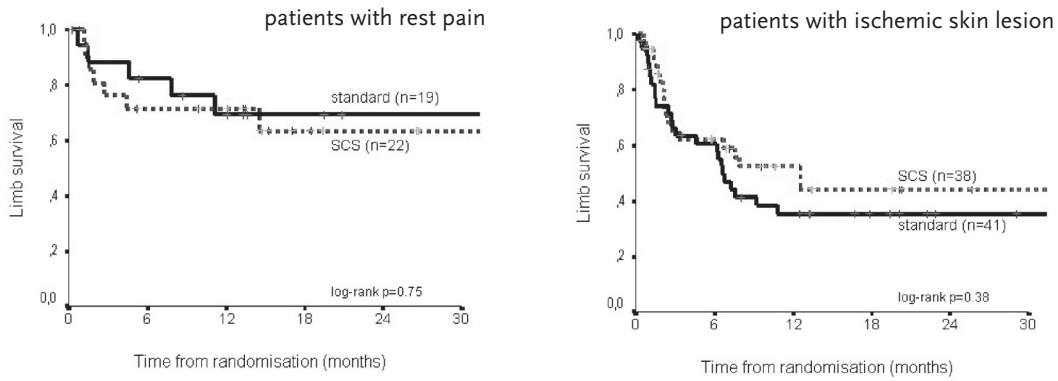

Figure 3: Limb survival according to treatment (SCS versus standard) in the subgroup of patients with rest pain (left, *n*=41) compared with the subgroup with ischemic skin lesions (right, *n*=79).

hypertension, history of myocardial infarction or cerebrovascular symptoms, previous vascular reconstructions, ankle pressure or ABPI. A risk factor with moderate effect was smoking (HR 1.27, *p*=0.12). Patients with ischemic skin lesions (ulcerations or gangrene) obviously had a worse prognosis, i.e. higher risk of amputation (HR 2.30, *p*=0.01). Figure 3 shows limb survival in both treatment groups for patients with rest pain alone and patients with established ulcers and gangrene. For the pooled groups of patients, limb survival at six months was 76% in patients with rest pain and 62% in patients with ischemic skin lesions, at two years 65% and 40% respectively (*p*<0.01).

Subgroup analysis

As mentioned above, the overall risk of amputation in the SCS-treatment group was not significantly different as compared to standard treatment. This hazard ratio for the treatment effect was subsequently estimated with adjustment for each prognostic factor. No substantial deviations were observed from the overall effect as tested by interaction terms of prognostic factors with the treatment effect.

Multivariable analysis

Finally, we performed a multivariable analysis to estimate the treatment effect after simultaneous correction for relevant prognostic factors. The results are summarized in Table 3. Relevant factors were selected from the risk factor analysis combined with the available literature[34,38,39]. Risk factors included were smoking, ischemic skin lesions and the number of previous vascular interventions. The presence of ulcerations and gangrene had a strong effect on amputation risk (*p*=0.003). When adjusted for these baseline characteristics, the hazard ratio for amputation of SCS *vs.* standard treatment was estimated at 0.88 (*p*=0.64).

Discussion

The conclusion of our randomized trial[24] was that SCS was no more effective than best medical treatment alone in preventing amputations. Even so, a debate emerged whether a subset of patients might in fact be helped by SCS. It was stated "that the best candidates for the

procedure are those with ischemic rest pain without tissue loss" or that "SCS-treatment appears beneficial to a subgroup of CLI patients"[25,26,40]. A systematic review[41] suggested improvement of limb survival in patients treated with SCS and expansion of the indication in CLI.

This review included 6 studies[19-24]. One of these was a nonrandomized study by Amann[19] in which patients with CLI were classified according to transcutaneous pO2 measurements and did or did not receive treatment based on this TcpO2 classification and trial stimulation. Over 30% of the patients in the "control" (No-SCS) arm were amputated within 2 weeks (!), illustrating intense selection bias. This study should be seen as a prognostic study using TcpO2 measurements, not as an adequate comparison of treatments. Remarkably, the limb survival curves were quite comparable after the initial weeks.

Patients with "Buerger's disease" were excluded from the smallest study[21] which is unjustifiable and compromises objectivity. The diagnosis was not specified, clinical criteria[42] did not apply (for example the age-criterion <45 years is not met in this study) and it was not a stratification factor. In the other randomized studies, it was not an explicit exclusion criterion (except in the study of Claeys[22]) and there are no data that a treatment effect of SCS, if any, is particularly different in patients with Buerger's disease. Furthermore, the selected data for the "amputation rate after 12 months" were incorrect for two studies. The main conclusion of this review, that SCS is significantly better than conservative treatment alone in achieving a reduction in amputation risk, is not justified. Meta-analysis of the five available randomized studies yields a relative risk reduction of –0.07 (*p*=0.15). Quality of life and pain scores were only assessed in the largest randomized trial[24] and were not improved in those who underwent SCS.

So, is there no effect? In retrospect, all individual randomized studies were underpowered. This was mainly due to the assumption that limb survival in the control group would be much lower (based on the literature data 20-40% at one year[1,4-9]) and that 20-30% improvement in limb survival would be easily reached[14,18,43-45]. However, the conservative (medical) treatment groups did much better. This observation is supported by data of Marston *et al.*[46], showing that limb salvage can be achieved in most patients with arterial insufficiency and uncomplicated chronic nonhealing limb ulcers when treated in a dedicated wound program, even in patients with ABPI< 0.50.

Based on expected standard limb survival at 1 year of at least 45%, a one-sided log-rank test with sample size of *n*=120 achieves 80% power at the 5% significance level to detect a difference of 18% (i.e. limb survival improvement to 63%). With a sample size of *n*=332 the detectable difference is 11% (i.e. limb survival to 56%). The meta-analysis being tested for equivalence at 80% power at 5% significance level allows for a maximum difference of 10% at 12 months (using a one-sided equivalence test of proportions). Consequently, taking into account probable exaggeration of treatment effects due to unclear concealment of treatment allocation in some studies[47], the possible beneficial effect of SCS in terms of incidence of amputation would be small, most likely between 5-7%. The number needed to treat to avoid one amputation would be at least 14, costing over €110.000 per limb saved (≈ over €200,000 per QALY gained)[37,48].

Can a subset of patients be identified who might in fact be helped by SCS? This study confirms the general impression that the amputation rate is higher in CLI patients with ischemic skin lesions than in those with rest pain alone. Prognostic factors for amputation were ischemic ulceration, gangrene, and maybe smoking and the number of previous vascular interventions. In a multivariable analysis, the presence of ischemic skin lesions proved to be the most important risk factor. However, we found no subgroups with significantly different (better or worse) treatment effects of SCS. From earlier studies it was implied that SCS might be a beneficial therapeutic alternative particularly in those patients without established gangrene[10,14,25,43]. This idea was born

from the observation, that the amputation rate was highest in patients with gangrene, suggesting that SCS had no limb-saving effect in those patients. However, retrospective data collection and lack of a well-defined control group limits attempts to identify risk factors and especially factors that modify treatment effects. As the results of this study show, the presence of ischemic skin lesions is indeed an important risk factor for amputation. If SCS has any effect, our study suggests that this effect was especially present in those very patients with ulcerations and gangrene (HR 0.75, p=0.30). This subgroup finding in itself is not sufficiently convincing to restrict SCS to those patients with ischemic skin lesions. On the other hand, if SCS has a constant relative effect among subgroups, the absolute benefit will be largest in those at highest risks, i.e. those with ischemic skin lesions.

The same line of reasoning applies to microcirculatory measurements. Although several classifications and cut-off values provide good prognostic information as to the risk of amputation in patients with CLI[49], this is not necessarily associated with differential treatment effects. If a higher benefit from SCS is expected in subjects with CLI with preserved flow reserve, this treatment effect should be tested in a *randomized* fashion. Since the costs of SCS-treatment are considerable (costs of SCS-treatment per patient were €7,900 (28%) higher as compared to standard treatment[24]) and the mean complication incidence was reported to be 20%[41,50], the benefit from SCS should exceed 15-20% in our view.

Jivegard[20] found a reduced amputation rate at 18 months in response to SCS in patients without arterial hypertension. We could not confirm this finding. Hypertension was not a significant prognostic variable; the hazard ratio was estimated at 0.98 (p=0.86), suggesting similar risks of amputation in hypertensive and non-hypertensive patients. In this study, the treatment response to SCS in patients without hypertension was similar to the overall (lack of) treatment response. Whereas diabetic patients are more likely to develop CLI and have a higher mortality rate[1,51], in this study their risk to be amputated is similar to other patients, once CLI is present. Similar treatment effects were observed in diabetic and non-diabetic patients. Likewise, we did not observe a significantly worse prognosis for patients with (failed) previous vascular reconstructions.

Conclusion

In summary, while the general idea still is that "untreated CLI" usually leads to amputation, in fact a surprisingly high number of patients with chronic CLI can, temporarily, be stable or improve with adequate medical (including analgesic) treatment. SCS probably does not substantially improve outcome in terms of (limb) survival. Patients with ischemic skin lesions (ulcerations or gangrene) have a higher risk of amputation than do patients with rest pain alone. We could not identify a subgroup of patients who might specifically be helped by SCS. If clinically important benefits are expected in subgroups of patients with CLI, randomized studies with adequate power are required.

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Letter:

In September's leading article, Ubbink and Legemate make a plea for evidence-based surgery: "systematic acquisition of unbiased evidence is essential to support daily (surgical) practice"[1]. We could not agree more. However, their systematic review of controlled trials assessing spinal cord stimulation (SCS) for inoperable critical leg ischaemia is an unfortunate example. The quality of controlled trials is of obvious relevance to systematic reviews. If the raw material is flawed, then the conclusions of systematic reviews will be compromised and arguably invalid.

The review by Ubbink *et al* describes six studies, with numbers varying from 27 to 120 patients. The "study descriptions" section is very concise, but incomplete. One (randomized) study was never reviewed (Suy), one study was not randomized (Amann), one study was stopped prematurely (Spincemaille), and for at least three studies, concealment of treatment allocation was dubious. Unclear concealment of treatment allocation in trial is associated on average with exaggeration of treatment effects by 40 percent[2]. Besides, the selected data for the "amputation rate after 12 months" are incorrect for our study[3], and the use of data from a subgroup in the smallest study (Suy) is unjustifiable.

The same meta-analysis, performed with the proper amputation data from the 5 randomized studies, generates a risk difference of -0.07 (95% CI: -0.17 to +0.03) instead of -0.13 (95% CI: -0.20 to -0.04). The main conclusion, that SCS is better than conservative treatment alone in achieving a reduction in amputation risk, is not justified. If SCS is beneficial, the magnitude of the effect is very small.

The problem with systematic reviews and meta-analyses is that they have the stamp of high-brow research and best possible evidence, while in fact they should be scrutinized just as carefully as any other research report.

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Chapter VIII

Prognostic model for amputation in critical lower limb ischemia

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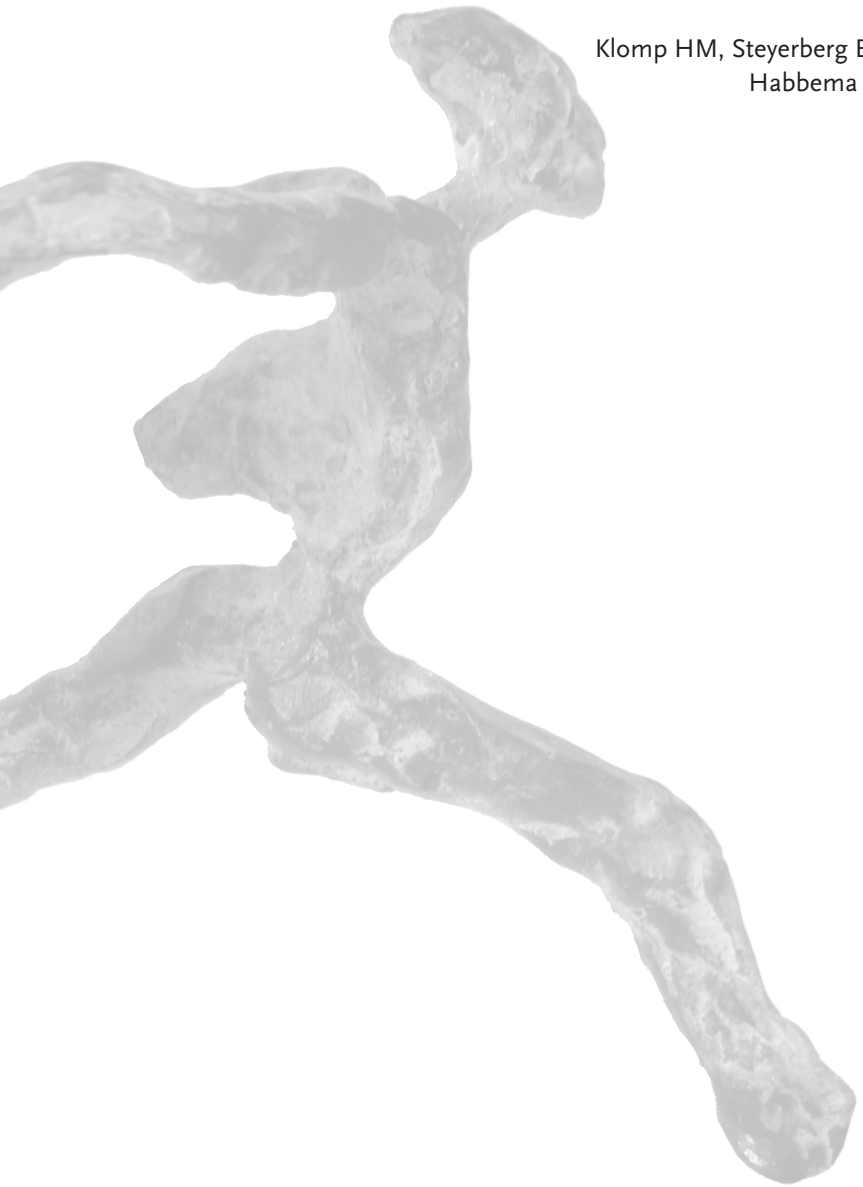

Abstract

Introduction

In a (negative) multicenter randomized trial on management for inoperable critical lower limb ischemia, comparing spinal cord stimulation and best medical treatment, a number of pre-defined factors were analyzed for prognostic value. We included a radiological arterial disease score, modified from the SVS/ISCVS runoff score. The purpose of this analysis was to evaluate clinical factors and commonly used circulatory measurements for prognostic modeling in patients with critical lower limb ischemia

Methods

We determined the incidence of amputation and its relation to various pre-defined risk factors. A total of 120 patients with critical limb ischemia were included in the study. The integrity of circulation in the affected limb was evaluated on 5 levels: suprainguinal, infrainguinal, popliteal, infrapopliteal and pedal. A total radiological arterial disease score was calculated from 1 (full integrity of circulation) to 20 (maximally compromised state). We used Cox regression analysis to quantify prognostic effects and differential treatment (predictive) effects.

Results

Major amputation occurred in 33% of the patients at 6 months and in 51% at 2 years. The presence of ischemic skin lesions and the radiological arterial disease score were independent prognostic factors for amputation. Patients with ulcerations or gangrene had a higher amputation risk (hazard ratio 2.38, p=0.018 and 2.30, p=0.036 respectively) as well as patients with a higher radiological arterial disease score (hazard ratio 1.17 per increment, p=0.003). We did not observe significant interactions between prognostic factors and the effect of spinal cord stimulation.

Conclusion

In patients with critical lower limb ischemia, the presence of ischemic skin lesions and the described radiological arterial disease score can be used to estimate amputation risk.

Introduction

The fate of patients with critical limb ischemia (CLI) is influenced by treatment as well as by a number of other variables[1-3]. Prospective studies provide an excellent basis to identify risk factors for amputation. In the modern practice of vascular surgery, it is difficult to study the natural history of CLI. Older studies in patients with CLI not undergoing re-vascularization showed that major amputation of the limb is necessary in a majority of patients within a year[4-8]. However Marston et al[9] showed that limb salvage can be achieved in most patients with arterial insufficiency and uncomplicated chronic non-healing limb ulcers when treated in a dedicated wound program.

Several authors have recommended the use of spinal cord stimulation (SCS) for patients with CLI in whom a meaningful vascular reconstruction is not possible[10-13]. Although many retrospective and some prospective series reported better (than expected) limb survival in CLI[10, 14-16], these results have not been substantiated in randomized studies[17-21]. Later reviews claimed that SCS might be a beneficial therapeutic alternative particularly in those patients without established gangrene or after selection of patients using microcirculatory measurements such as transcutaneous oximetry[12, 22, 23].

The objective of this analysis was to evaluate the impact of demographic, clinical and commonly used circulatory parameters on outcome in a prospectively followed cohort of patients with inoperable CLI. In the largest randomized trial[20], a number of predefined factors were analyzed for prognostic value. For calculation of a radiological arterial disease score, the proposed system of the Ad Hoc Committee on Reporting Standards of the Society for Vascular Surgery and the International Society for Cardiovascular Surgery (SVS/ISCVS) was used[24]. This angiographic scoring system grades the quality of vessels distal to a planned bypass site and calculates an overall runoff score. We applied this system to a lower limb radiological arterial disease score and compared its prognostic ability to other factors.

Methods

The trial design and procedures have been described in detail elsewhere[20,25]. Eligible patients had CLI and a meaningful vascular reconstruction was not possible. The arterial anatomy of the lower extremities was assessed by digital subtraction angiography with use of either stepping techniques with a single contrast material bolus or multiple contrast material injections. The need for additional images and selective catheterizations was left to the angiographers performing the examinations. No attempt was made to standardize the angiographic technique. All the centers participating in this study used the same non-reconstructability criteria. These were absence of a suitable autologous vein for distal bypass grafting surgery or the absence of all three crural arteries on a selective angiogram, which was a prerequisite for judgment of the calf and foot arteries. The angiogram should delineate contrast down to the distal foot and the adequacy was validated by an independent vascular surgeon. Inclusion criteria were persistent rest pain for more than 2 weeks or ischemic skin lesions, ankle pressure below 50 mm Hg or, in patients with diabetes and incompressible vessels, absent palpable ankle pulses or toe pressure below 30 mmHg.

From 17 hospitals in the Netherlands, 120 patients were enrolled from 1991 until 1996. The ethical committees at each center approved the study protocol, and patients gave written informed consent. The treatment strategies SCS in addition to best medical treatment ('SCS-treatment') and best medical treatment alone ('standard treatment') were allocated at random

to eligible patients. Standard treatment included analgesics, antithrombotic drugs (aspirin, coumarins), cardiovascular risk factor control, hemorrheologic drugs (such as pentoxifylline, buflomedil, ketanserin), local wound care and antibiotics, if indicated. There was a list of recommended medications, but no fixed treatment regimen. Chemical lumbar sympathectomy and prostanoids were not excluded, but were used in three patients only. The patients allocated to SCS treatment additionally received an implantable spinal cord stimulation system. A quadripolar lead (Medtronic, Minneapolis, MN, USA) was placed in the epidural space and connected to an Itrell II pulse generator (Medtronic, Minneapolis, MN, USA). Both treatment regimens aimed at adequate pain suppression.

All patients were assessed at 1, 3, 6, 12, 18 months after randomization and at the end of the study. Between follow-up visits patients came to hospital as often as necessary. Limb survival was defined as absence of major amputation (amputation above the level of the foot)[26]. The Nottingham Health Profile (NHP) and EuroQol were used to assess quality of life. For further assessment of pain, the McGill Pain Questionnaire was used and the pain-rating index (PRI) was the measure of expressed pain. Analgesic use was recorded and quantified by the medication quantification scale (MQS). During follow-up (at 1, 3, 6, 12 and 18 months), over 90% of the quality-of-life questionnaires were adequately completed by the patients using reminding letters, if necessary.

Prognostic factors

A number of predefined factors were collected by the treating physicians of the participating hospitals before randomization. Demographic data included age and sex. Clinical data included diagnosis of diabetes, smoking status, hypertension (systolic blood pressure ≥160 mmHg), history of myocardial infarctions and history of cerebrovascular accidents (CVA) or transient ischemic attacks (TIA). Previous vascular reconstructions were summarized as the number of vascular and endovascular reconstructions at the affected limb. Presence of ischemic skin lesions was categorized to ulcerations or gangrene. A number of patients with ischemic skin lesions had ulceration(s) as well as gangrene. These data were used separately in this analysis. Circulatory

Arterial segment	Artery	Value	×weight	Subscore	
A. Suprainguinal	Common iliac	[0–4]	×3	(a1)	
	External iliac	[0–4]	×2	(a2	
	Internal iliac	[0–4]	×1	(a3)	
	Common femoral	[0–4]	×3	(a4) ± (a1+a2+a3+a4)/9	A [0–4]
B. Infrainguinal	Superficial femoral	[0–4]	×2	(b1)	
	Deep femoral	[0–4]	×1	(b2) ± (b1+b2)/3	B [0–4]
C. Popliteal	Popliteal	[0–4]		(c)	C [0–4]
D. Infrapopliteal	Anterior tibial	[0–4]	×1	(d1)	
	Posterior tibial	[0–4]	×1	(d2)	
	Peroneal	[0–4]	×1	(d3) ± (d1+d2+d3)/3	D [0–4]
E. Pedal arch	Arch	[0–3]		(e)	E [0–3]
'Base resistance'					1+
Total radiological arterial disease score				A+B+C+D+E+1 [1–20]	

For four segments (A–D), angiographic disease was scored by weighting of the degree of occlusion in the main arteries. Points assigned as: 0 = no evidence of disease; 1 = mild disease (stenosis < 20%); 2 = stenosed (20–50%); 3 = severely stenosed (51–99%); 4 = occluded.
For the pedal arch (E), points were assigned as: 0 = completely patent arch; 2 = partially occluded arch; 3 = completely occluded arch.
A 'base resistance' of 1 is added as arbitrary intrinsic resistance of the normal vascular bed, leading to a radiological arterial disease score ranging from 1 to 20.

Table 1: Calculation of radiological arterial disease score.

measurements included the radiological arterial disease score, the ankle pressure and ankle-brachial index (ABI). The angiograms were reexamined by an independent observer (CHAW) to calculate the radiological arterial disease score, constructed similar to the runoff score of the Ad Hoc Committee on Reporting Standards of the SVS/ISCVS. The integrity of circulation in the affected limb was evaluated on 5 levels: suprainguinal, infrainguinal, popliteal, infrapopliteal and pedal. A total score was calculated from 1 (full integrity of circulation) to 20 (maximally compromised state) as explained in Table 1.

We studied not only the prognostic weight of these variables for the risk of amputation, but also their potential influence on the effect of SCS-treatment. In a multivariable analysis, the treatment effect was tested as well as the impact of risk factors that emerged from our analysis with p-value < 0.20 or were regarded important in the literature[4,18,27-32].

All data were recorded on standardized forms and entered in a concurrent database. Analysis of clinical outcome was by intention to treat and included all patients who underwent randomization. Patient and limb survival were estimated with the Kaplan-Meier method and compared using log-rank tests. In the analysis of limb survival, patients were censored at death. Cox proportional hazards model was used 1) for analysis with prognostic factors and 2) for analysis of interactions between prognostic factors and treatment. Hazard ratios (HRs) were estimated to quantify the effect of prognostic factors. When the HR was greater than 1, the risk of amputation was higher with the prognostic factor present than without this factor. In multivariable analyses, we selected prognostic factors with a p-value < 0.20 and the variable indicating SCS-treatment. For all hypothesis tests, p<0.05 was considered statistically significant.

Results

A total of 120 patients were included in the study. Sixty patients were randomized to SCS-treatment and sixty patients received standard treatment. The median follow-up was 2 years (range 244-1710 days). Table 2 shows the demographic, clinical and circulatory characteristics. The mean age was 72.6 year, nearly 40% of the patients were diabetic, and over 60% had

Characteristics	n = 120	n = 60 SCS	n = 60 Standard
Male/female	70/50	33/27	37/23
Age (years)*	73 ± 10	73 ± 10	72 ± 11
Diabetes	45	22	23
Insulin-dependent	19	10	9
Current smoking	44	18	26
Hypertension	61	35	26
CVA or TIA	29	13	16
Myocardial infarction	45	23	22
Angina pectoris	27	12	15
Ischemic skin lesions	79	38	41
Gangrene	47	24	23
Vascular reconstructions			
°Nil	26	15	11
°1 or 2	55	26	29
°>3	39	19	20
Ankle systolic pressure (mmHg)[a]	38 ± 24	35 ± 25	41 ± 22
Ankle–brachial index[a]	0.25 ± 0.15	0.23 ± 0.16	0.28 ± 0.13
Radiological arterial score[a]	10.3 ± 2.7	10.1 ± 2.9	10.4 ± 2.6

CVA, cerebrovascular accidents; TIA, transient ischemic attacks.
[a]Data given as numbers or mean ± SD.

Table 2: Baseline characteristics of study group.

Characteristics	HR amputation	*P*-value
Male/female	1.02	0.94
Age (years)[a]	0.99	0.93
Diabetes	1.03	0.97
Current smoking	1.27	0.12
Hypertension	0.98	0.86
CVA or TIA	1.45	0.22
Myocardial infarction	0.97	0.91
Angina pectoris	1.38	0.29
Ischemic skin lesions	2.20	0.016
Gangrene	2.48	0.001
Vascular reconstructions		
°Nil		
°1 or 2	1.10 / intervention	0.18
°>3		
Ankle systolic pressure (mmHg)	0.92 / 10 mmHg	0.25
Ankle–pressure index	0.87 / 10%	0.87
Radiological arterial score	1.11 / point	0.05

CVA, cerebrovascular accidents; TIA, transient ischemic attacks.

Table 3: Univariate analysis of amputation risk

ulcerations or gangrene in addition to rest pain. There was extensive comorbidity and many patients had (multiple) vascular reconstructions on the affected limb. Mean Doppler ankle pressure was 38 mmHg, mean ABI was 0.25. The mean radiological arterial disease score was 10.3.

(Limb) survival data have been presented before[20]. Mortality was comparable in both treatment groups: at six months 17% in both groups, and at two years 36% in the SCS-group vs 37% in the standard treatment group (log rank, p=0.96). Limb survival was similar in both treatment groups: at six months 66% vs 68%, at two years 52% in the SCS-group vs 46% in the standard treatment group (log-rank, p=0.47). The general trend in both the SCS and standard treatment groups was toward some improvement of quality of life, with no significant differences between the groups[20].

The prognostic significance of the studied variables for the risk of amputation is summarized in Table 3. The analysis did not show a significant prognostic influence for age, sex, diabetes, hypertension, history of myocardial infarction or cerebrovascular symptoms, ankle pressure or ABI. Most of the patients (n=94) had previous revascularizations. The amputation outcome between those who had (multiple) previous revascularizations and those who did not was not statistically significant (HR 1.1 per previous revascularization procedure, p=0.18). The hazard ratio for smoking was 1.27 (p=0.12). Patients with ischemic skin lesions (ulcerations or gangrene) had a significantly worse prognosis, i.e. higher risk of amputation (HR 2.30, p=0.01). For the pooled cohort of patients, limb survival at six months was 76% in patients with rest pain and 62% in patients with ischemic skin lesions, at two years 65% and 40% respectively (log-rank, p<0.01). Angiographic abnormality as scored by the radiological arterial disease score was also associated with worse prognosis (HR 1.11 per point increase of the score, p=0.05). Based on the distribution of the radiological arterial disease score in this cohort of patients, three groups were formed: low score ≤ 8, intermediate score 9-12 and high score >12. Limb survival at six months in these groups was 75%, 59% and 53% and at two years 65%, 36% and 33% respectively (trend p=0.03).

A multivariable analysis was performed to estimate the effect of relevant prognostic factors on treatment (predictive effect). The results are summarized in Table 4. Relevant factors

Factor	HR amputation	*P*-value	HR mortality	*P*-value
Presence of gangrene	2.30	0.036	1.41	0.37
Presence of ulcerations	2.38	0.018	1.38	0.43
Radiological arterial disease score	1.17	0.003	1.10	0.14
Current smoking	1.23	0.19	1.03	0.84
Previous vascular reconstructions	1.05	0.52	1.92	0.28
SCS-treatment	0.92	0.86	1.00	0.99

SCS, spinal cord stimulation.

Table 4: The impact of prognostic factors and treatment effect in the multivariable analysis.

were selected from the risk factor analysis combined with the available literature[4,18,27-32]. Risk factors included were smoking, ischemic skin lesions, the number of previous vascular interventions and radiological arterial disease score. Adjusted for these factors, SCS was no more effective than standard treatment; the hazard ratio for the treatment effect (the amputation risk in SCS *vs.* standard treatment) was estimated at 0.92 (p=0.86). We could not identify a subgroup of patients who might specifically be helped by SCS.

Ischemic skin lesions	Radiological arterial disease score		
	4–8	9–12	>12
No	15%	25%	40%
Yes	25%	50%	80%

Table 5: Global estimated risk of major amputation within 6 months in patients categorized according to radiological arterial disease score and absence or presence of ischemic skin lesions.

Independent risk factors for amputation were: the presence of ischemic skin lesions (HR 2.30, p=0.036 for gangrene; HR 2.38, p=0.018 for ulcerations) and the radiological arterial disease score (HR 1.17 per point increase of the score, p=0.003). Global probabilities of amputation within six months were estimated for several categories of patients as is shown in Table 5.

The same factors (i.e., presence of tissue loss, smoking, the number of previous vascular interventions and radiological arterial disease score) were used in a multivariable analysis to estimate the influence on mortality risk. This analysis did not show significant associations of these factors with mortality (Table 4).

Discussion

In this cohort of patients with non-reconstructable CLI, the presence of ischemic skin lesions and a higher radiological arterial disease score, which can be easily calculated for each patient undergoing angiography, were significantly associated with amputation risk. Baseline risk estimation is important for evaluation of treatment outcome in patients with peripheral arterial disease[33,34].

Definition of the patient populations in studies assessing the efficacy of therapies of peripheral arterial disease is often complex and previously defined criteria and estimation of baseline risk have been disputed[27,26]. Comparison of studies is therefore difficult. Uniform reporting information remains the best method for allowing comparisons of studies involving differing revascularization techniques or medical management. Such data would provide more information on decisions about treatment in relation to base line risk probabilities.

Limb threatening ischemia as characterized by rest pain or ischemic skin lesions usually signals the need for evaluation of revascularization options and therefore location and severity of stenoses and patency of runoff vessels must be precisely assessed. Several imaging techniques are available to visualize the macroscopic vessels (digital subtraction angiography, MR angiography, ultrasonography)[35,36]. Runoff scores for segments of the arterial system have been specifically used to describe changes in peripheral circulatory patency after revascularization techniques. The original intention was to use these scores for research and not for clinical purposes[24]. However, imaging scores can also be used as a baseline characteristic for evaluation of conservative treatments. In CLI, it is often very difficult to decide for amputation. Although statistics can never replace clinical judgment, quantification of the burden of lower extremity atherosclerosis may be a valuable objective factor in this decision analysis.

If meaningful revascularization strategies are lacking, therapeutic options are limited.

The evaluation of non-surgical management as in spinal cord stimulation, vasoactive drugs or angiogenesis therapies underscores the need to develop and validate methods of assessing the severity or extent of PVD. In this study, we tested a simple scoring system that uses angiography to estimate the extent of macroscopic arterial disease. To be useful, such a scoring system must be reproducible. High correlation coefficients for inter- and intraobserver variability were reported by Crawford[37].

Limitations of the current analysis include interpretation issues and the studied patient group. The interpretation of angiograms remains subjective. The reader visually estimated the degree of stenosis using the pre-randomization angiography series from the participating hospitals. The interpretation of the transition point from the SFA to popliteal artery, collaterals, bypass grafts or variant anatomy remains rather arbitrary. In the calculation of the radiological arterial disease score, as presented in Table 1, only the metatarsal arch is scored in the foot. The assessment may be refined if the lateral and medial plantar branch and the dorsalis pedis branch were added to this score. The classification and generalization performance of the scoring system may be improved by better rules for scoring or by the use of computer-aided learning systems. The conversion factors used to translate angiographic findings into the score estimates (especially in multilevel disease) can be revised in such systems as well.

Despite these limitations, the radiological arterial disease score can be easily calculated for each patient with CLI undergoing angiography. Further evaluation in other prospectively followed cohorts should refine its prognostic value for the broader group of patients with occlusive peripheral vascular disease.

Calculation of the radiological arterial disease score combined with the presence or absence of ischemic skin lesions can be used to estimate the probability of amputation in patients with critical lower limb ischemia. This may be relevant to management of patients with multi-level disease and poor outflow in order to opt for risky revascularization, primary amputation or medical therapy. Moreover, estimation of baseline amputation risk is important for evaluation of (medical) treatments.

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Chapter IX

Management of critical limb ischemia in patients ineligible for vascular reconstruction

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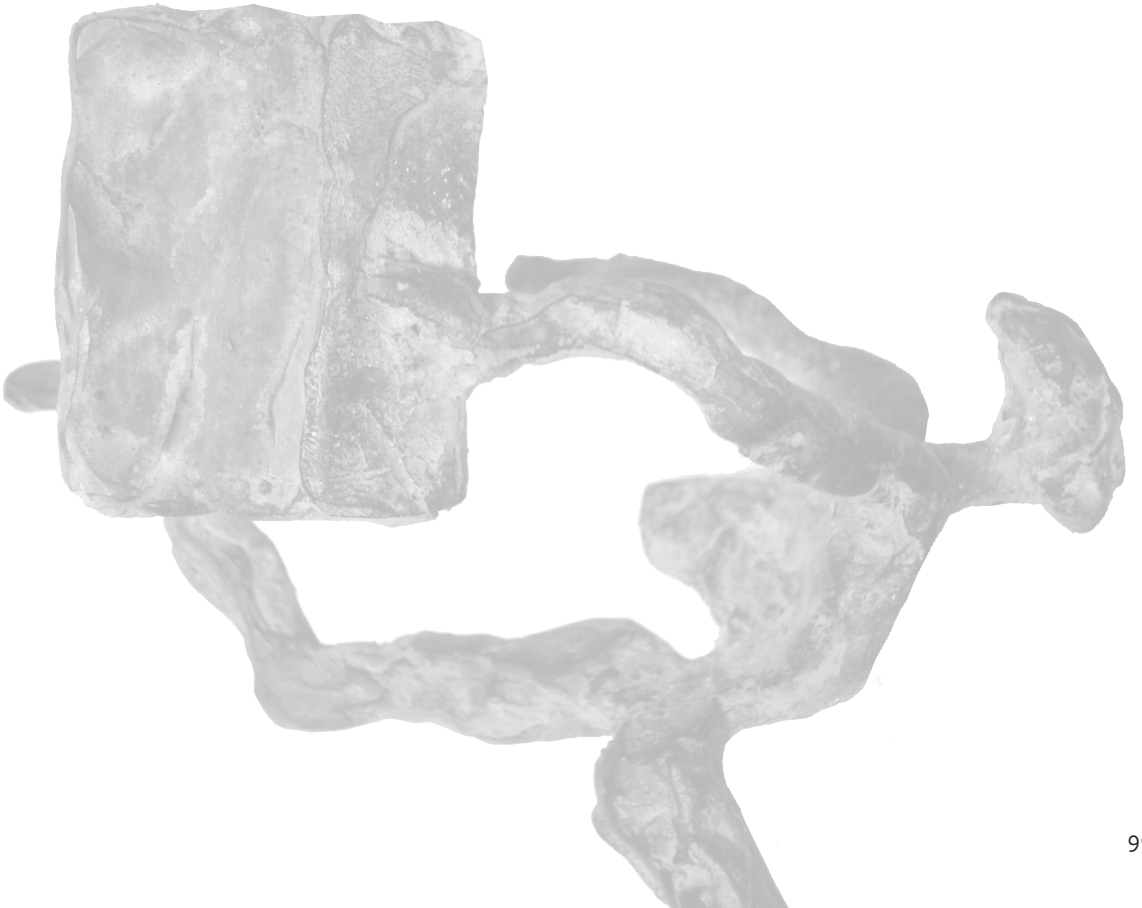
Eur J Vasc Endovasc Surg (accepted)



Abstract

Background

The objective was to propose a clinical management strategy for patients with critical limb ischemia (CLI), if revascularization is not possible.

Methods

After randomization to spinal cord stimulation or optimal conservative management, 120 patients with non-reconstructable CLI were followed >2 years or until death. The Nottingham Health Profile and EuroQol were used to assess quality-of-life. Potential risk factors for amputation were evaluated and a simple prognostic model was constructed.

Results

Major amputation occurred in 54 patients and 41 patients had died after median follow-up of 2 years. Mortality and amputation rate were particularly high during the first months (12% and 28% at 3 months respectively) and outcomes were similar in both treatment groups. Well-being following amputation was lower, although improvement was evident after 3-6 months up to levels reported by non-amputated patients. A simple prognostic model was created using the presence of ischemic skin lesions and a radiological score which could differentiate patients with low (17%), intermediate (36%) and high (92%) amputation risk.

Conclusion

An algorithm is presented with treatment choices and outcomes in patients with CLI. The presence of ischemic lesions in combination with multilevel disease and poor ambulatory ability or dementia may be factors to decide for primary amputation.

Introduction

With an aging population, more patients with atherosclerotic disease are presenting with critical limb ischemia (CLI)[1]. Despite marked advances in the technical ability to perform lower extremity revascularization, a number of patients have end stage peripheral vascular disease (PAD) that is not suitable for either primary surgical or endovascular (re)intervention[2]. It is widely accepted by those who routinely treat patients for CLI that there is only a minority of patients who cannot undergo at least some type of revascularization. Although best medical care may have improved and newer endovascular techniques have been developed, morbidity and mortality continues to be significant. Technically, revascularization procedures even to tibial and pedal arteries may be possible for the majority of patients with CLI, but not all patients will benefit from it[3]. In spite of all technical advances the incidence of major lower limb extremity amputation has not markedly diminished[4].

The decision whether and when to perform a risky revascularization is still a major issue in modern vascular care[2,3]. Spinal cord stimulation (SCS) has been proposed as treatment option, but in randomized trials SCS was no more effective than a conservative policy with adequate pain and wound treatment[5,6]. Along with the lack of a generally agreed upon definition of non-reconstructability within the vascular community, no uniform treatment algorithms exist for non-reconstructable CLI. In this article we will discuss this issue based on outcome data from a national multicentre trial in patients with CLI. This randomized trial did not show better (limb) survival with the addition of spinal cord stimulation to best medical treatment. However, the data yield much relevant information on mortality, morbidity, quality-of-life and costs in a patient population with non-reconstructable CLI.

The objective was to analyze the risk and impact of amputation, to develop a simple prognostic model and propose a clinical management strategy for this population of patients.

Methods

Study design of the randomized trial.

The detailed trial design and procedures of the study are available from previous publications[5]. Eligible patients had CLI and a meaningful vascular reconstruction was not possible. Inclusion criteria were, according to the European Consensus Document[7], persistent rest pain for more than 2 weeks or ischemic skin lesions, ankle pressure below 50 mm Hg or, in patients with diabetes and incompressible vessels, toe pressure below 30 mm Hg or absent palpable ankle pulses. Exclusion criteria were: synchronous CLI of both legs, non-vascular comorbidity (e.g. cancer) with a life expectancy < 1 year and psychosocial inability to complete follow-up (e.g. dementia). The arterial anatomy of the lower extremities was assessed by digital subtraction angiography with use of either stepping techniques with a single contrast material bolus or multiple contrast material injections. Many patients underwent (multiple) revascularizations of the affected limb before intake in this study. Most participating hospitals used similar criteria to refrain from (further) surgical or endovascular interventions. These were unavailable autologous veins (either saphenous or arm veins) for distal bypass surgery or the absence of all three crural arteries on a selective angiography. Distal crural PTA or crural or pedal synthetic bypass surgery were not commonly used in the study period 1991-1996. Calculating with 1500 amputations per year in the Netherlands and 10% of hospitals participating, the number of patients to be screened

for inclusion was estimated at around 150-200, and the number of eligible patients at 80 per year. The accrual rate turned out to be lower than expected, but approximated 25% of the target population. From 17 hospitals, 120 patients were enrolled until May 1994. The ethical committees at each center approved the study protocol, and patients gave written informed consent. The treatment strategies SCS in addition to best medical treatment ('SCS-treatment') and best medical treatment alone ('standard treatment') were allocated at random to eligible patients.

Treatment

Standard treatment included analgesics, antithrombotic drugs (aspirin, coumarins), hemorrheologic drugs (such as pentoxifylline, buflomedil, ketanserin), local wound care and antibiotics, if indicated. There was a list of recommended medication, but no fixed treatment regimen. Chemical lumbar sympathectomy and prostanoids were not excluded, but were used in three patients only. The patients allocated to SCS treatment additionally received an implantable neurostimulation system. A quadripolar lead (Medtronic, Minneapolis, MN, USA) was placed in the epidural space and connected to an Itrell II pulse generator (Medtronic). Both treatment regimens aimed at adequate pain suppression. During follow-up the treatment effect was optimized by altering medication, stimulation settings or both.

Follow-up

All patients were assessed at 1, 3, 6, 12, 18 months after randomization and at the end of the study. Between follow-up visits patients came to the hospital as often as necessary. Treatment decisions and the decision to amputate were left to the treating vascular surgeon together with the patient. The primary endpoint was limb survival, defined as absence of major amputation. Types of amputation as well as the grounds for amputation were recorded. Major amputations were those above the level of the foot[8,9]. Amputations occurring within 3 months from randomization were classified as "early amputations", while amputations after 3 months were labeled as "late amputations".

Prognostic factors

Besides demographic parameters as age and sex, comorbidity variables were recorded: diabetes, smoking, hypertension, history of myocardial infarctions, cerebrovascular accidents (CVA) and transient ischemic attacks (TIA). Previous vascular reconstructions were summarized as the number of vascular and endovascular reconstructions at the affected limb. Presence of ischemic skin lesions was categorized to ulcerations and gangrene. Some patients had ulceration(s) as well as gangrene. Circulatory measurements were the angiographic score, ankle pressure, ankle-brachial index (ABI). Angiographies were reexamined by an independent observer (blinded for outcome) to calculate the radiological arterial disease score, constructed similar to the runoff score of the Ad Hoc Committee on Reporting Standards of the SVS/ISCVS. A total score was calculated from 1 (full integrity of circulation) to 20 (maximally compromised state) as explained in Table 1[8,10]. High agreement for inter- and intraobserver variability were reported[11].

Quality-of-life.

The Nottingham Health Profile (NHP) and EuroQol were used to assess quality-of-life. The NHP, a generic measure of health-related quality-of-life, is a self-administered questionnaire

	Arterial segment	artery	value	x	weight	subscore	
A.	*Suprainguinal*	common iliac	[0-4]	x	3	(a1)	
		external iliac	[0-4]	x	2	(a2	
		internal iliac	[0-4]	x	1	(a3)	
		common femoral	[0-4]	x	3	(a4) +	
						(a1+a2+a3+a4) /9	A [0-4]
B.	*Infrainguinal*	superficial femoral	[0-4]	x	2	(b1)	
		deep femoral	[0-4]	x	1	(b2)+	
						(b1+b2) /3	B [0-4]
C.	*Popliteal*	popliteal	[0-4]			(c)	C [0-4]
D.	*Infrapopliteal*	anterior tibial	[0-4]	x	1	(d1)	
		posterior tibial	[0-4]	x	1	(d2)	
		peroneal	[0-4]	x	1	(d3) +	
						(d1+d2+d3) /3	D [0-4]
E.	*Pedal arch*	arch	[0-3]			(e)	E [0-3]
	"base resistance"						+
	TOTAL RADIOLOGICAL ARTERIAL DISEASE SCORE						A+B+C+D+E+1 [1-20]

For 4 segments (A-D) angiographic disease was scored by weighting of the degree of occlusion in the main arteries. Points assigned: 0 = no evidence of disease, 1 = mild disease (stenosis<20%), 2 = stenosed (20-50%), 3 = severely stenosed (51-99%), 4 = occluded. For the pedal arch (E) points were assigned: 0 = completely patent arch, 2 = partially occluded arch, 3 = completely occluded arch. A "base resistance" of 1 is added as arbitrary intrinsic resistance of the normal vascular bed, leading to a "radiological arterial disease score" ranging from 1 to 20.

Table 1: Calculation of "radiological arterial disease score".

that consists of 38 items in six domains, including physical mobility, pain, sleep, social isolation, emotional reactions, and energy. The scores in each domain range from 0 (best health) to 100 (worst health). The EuroQol list is a self-administered, generic health questionnaire with five dimensions: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. The scores range from 0 (best health) to 100 (worst health). For assessment of pain, we used the pain-rating index (PRI) and Visual Analogue Scale (VAS) of the McGill Pain Questionnaire. For additional assessment of mobility the Sickness Impact Profile (mobility dimension) was used.

Statistical analysis

All data were recorded on standardized forms and entered in a concurrent database. Analysis of clinical outcome among treatment groups was by intention to treat and included all patients who underwent randomization. Mortality and time to amputation were estimated with the Kaplan-Meier method and groups were compared using log-rank tests. In the analysis of limb survival, patients were censored at death. Cox regression analysis was used 1) for analysis of time to

amputation in relation to prognostic factors and 2) for analysis of interactions between prognostic factors and treatment. Hazard ratios (HRs) were estimated to quantify the effect of prognostic factors. When the HR was greater than 1, the risk of amputation or mortality was higher with the prognostic factor present than without this factor. For multivariable analyses, we used prognostic factors considered important in the literature and or with a *p*-value < 0.20 in the univariable analysis. For practical application in a prognostic model, risk scores were constructed based on rounding of the regression coefficients from the Cox model[12]. The discriminatory performance was quantified by a concordance statistic ('c')[13]. It ranges between 0.5 (a noise model) and 1.0 (a perfect prediction model). Prognostic models may provide predictions that are too optimistic for future patients. We used a bootstrap resampling procedure to correct the model performance for such statistical optimism[13]. For all hypothesis tests, $p<0.05$ was considered statistically significant. Analyses were performed with SPSS (v 15.0, SPSS Inc, Chicago, Ill), and R (v 2.5.1, R Foundation for Statistical Computing, Vienna, Austria). Pain and quality-of-life measurements were assessed by covariance analysis and adjusted for baseline differences. Effects of amputation were fitted in a linear mixed model using the statistical package S-Plus.

Characteristic		N	amp.	Incidence % 6m	24m	HR [95% CI]	*p*-value
Sex	Male	70	32	31%	51%	1.0	0.94
	Female	50	22	37%	50%	1.02 [0.59 – 1.76]	
Age	<70	40	21	38%	66%	1.0	0.42
	>=70	80	33	30%	49%	0.80 [0.46 – 1.38]	
Diabetes	No	75	34	32%	52%	1.0	0.96
	Yes	45	20	35%	49%	0.99 [0.57 – 1.72]	
Smoking	No/past	75	30	30%	47%	1.0	0.22
	Current	44	24	39%	59%	1.41 [0.82 – 2.41]	
Hypertension	No	57	29	38%	57%	1.0	0.86
	Yes	61	24	30%	46%	0.98 [0.80 – 1.21]	
CVA/TIA	No	91	39	31%	49%	1.0	0.24
	Yes	29	15	41%	58%	1.45 [0.80 – 2.63]	
Ischemic ulceration	No	50	16	23%	37%	1.0	0.006
	Yes	70	38	41%	61%	2.20 [1.22 – 3.95]	
Gangrene	No	73	24	26%	37%	1.0	0.001
	Yes	47	30	41%	67%	2.48 [1.42 – 4.33]	
Vasc reconstructions	<=1	54	21	31%	45%	1.0	0.52
	>=2	65	32	36%	55%	1.20 [0.69 – 2.07]	
Ankle syst pressure	>40mm Hg	40	18	27%	52%	1.0	0.81
	<=40	28	13	42%	51%	1.09 [0.54 – 2.23]	
Ankle-brachial index	>0.25	40	16	22%	48%	1.0	0.26
	<=0.25	28	15	48%	57%	1.50 [0.74 – 3.04]	
Radiological dis. score	<8	22	3	5%	14%	1.0	<0.001
	8-11	42	21	44%	55%	6.22 [1.85-21]	
	>=11	50	29	42%	70%	7.24 [2.33 – 23]	
Treatment	standard	60	29	32%	54%	1.0	0.47
	SCS	60	25	34%	48%	0.82 [0.48-1.40]	

Table 2: Baseline characteristics and results in 120 patients with CLI of a lower limb.

Results

Characteristics of 120 enrolled patients are summarized in Table 2. After median follow-up of 2 years, 41 patients had died and 54 patients underwent major amputation. Comparative data on the randomized groups were reported before[5]. In summary, 60 patients were randomly assigned to receive SCS-treatment and 60 to receive standard treatment. Mortality and amputation rate were similar in the two treatment arms. As a combined illustration, amputation-free survival is shown in Figure 1.

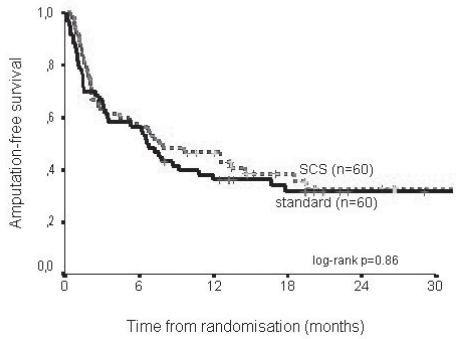


Figure 1: Amputation-free survival

Overall, major amputations occurred more frequently during the first three months (*n*=32/120, cumulative amputation rate 28% at 3 months). The amputation risk in patients with ulceration or gangrene (33% at 3 months) was higher than in patients without ischemic skin lesions (18%, *p*=0.01).

Mortality was also strikingly high during the first three months (*n*=14/120, cumulative mortality 12% at 3 months), and was similar in patients with and without ischemic skin lesions (13 and 11%, *p*=0.50). The initial (30-day postoperative) mortality rate of major amputation was considerable (9%), thereafter 2% per month, similar to the overall mortality risk in this cohort of patients with CLI. However, excess mortality during the first three months of the study was only to a small extent explained by amputations, since only 5 deaths were linked to preceding amputations.

During follow-up (at 1, 3, 6, 12 and 18 months), over 90% of the quality-of-life questionnaires were adequately completed by patients in study using reminding letters if required. The general trend for quality-of-life as measured by EuroQol or Nottingham Health Profile in the SCS and standard treatment groups was toward some improvement of self-reported well-being, with no significant differences between the randomized treatment groups (Figure 2a). Mobility as measured by the NHP and SIP questionnaires was impaired in both treatment groups with negligible changes over time (Figure 2b). Pain improved significantly ($p<0.005$) during the first months of the study equally in both treatment groups, using either the Mc Gill pain rating index, visual analogue scales or the NHP (Figure 2c). There was a trend toward some improvement of sleeping in both treatment groups over time, whereas social isolation, emotional reactions, and energy were almost constant.

Fifty-four patients underwent major amputation, 32 during the first three months of the study, 51 during the first year. Three patients had conversions to above knee amputation. A total of 89 minor and major amputations were recorded and reasons for amputation are shown in table 3.

For all patients, quality-of-life measurements were available before and after major amputation and these were used to model quality-of-life effects of amputation (linear mixed model). We estimated these effects both for patients who were amputated within three months (early amputation) and for those who had their major amputation later (late amputation).

The impact of major amputation on quality-of-life was prominently present in the first three months after amputation, with a –22 to –26% decrease in self-reported well-being ($p<0.02$) on NHP or EuroQol scales. After 3-6 months, amputees reported improvement in well-being to levels comparable to the non-amputated cohort (Figure 3a). Pain scores were worse in the

AMPUTATION	n	progressive tissue loss		intractable pain		infection	
toe	19	11	58%	13	68%	4	21%
metatarsal	7	6	86%	5	71%	1	14%
foot	6	4	67%	5	83%	0	0%
below knee	44	29	66%	29	66%	7	16%
above knee	13	13	100%	8	62%	1	8%
	89	63	71%	60	67%	13	15%

Table 3: Reasons for amputation

period around and immediately after amputation by –15 to –28% (p<0.01) on NHP and McGill scales, but improved considerably after 3 months to levels above +50% (p<0.0001), as shown in Figure 3c. In contrast, mobility scores progressively decreased following amputation from –18 to –30% (p<0.01) after 6 months on NHP and SIP scales (Figure 3b). Amputees reported gradually improved sleeping (p<0.05), whereas changes were insignificant in other dimensions (energy, social isolation and emotional reaction). For all dimensions of self-reported well-being, late amputation was associated with changes in quality-of-life analogous to early amputation.

A multivariable analysis was performed to estimate the effect of prognostic factors on the risk of amputation. We found no significant influence for age, sex, smoking, diabetes, hypertension, history of myocardial infarction or cerebrovascular incidents, previous vascular reconstructions, ankle pressure or ABI. Independent risk factors for amputation were: the presence of ischemic skin lesions (HR 2.2, p=0.010 for gangrene; HR 2.3, p=0.013 for ischemic ulcerations) and the radiological arterial disease score (HR 8.2 for scores 8-11 and HR 11.3 for scores ≥ 11, p=0.001). The results are summarized in Table 4a. The link of the multivariable analysis to a prediction model is created by a weighted score of 0 to 4 points for the major risk factors. Patients with a score of 0 or 1 had a relatively low risk of amputation (17% at 2 years), those with score of 2 had an average risk (36% at 2 years), but those with a score of 3 or more had very high risks (60% at 6 months, and 92% at 2 years, as shown in table 4b). The predictive performance was satisfactory, with a concordance statistic of 0.71 [95% CI 0.64 - 0.78]. Bootstrap validation indicated a minor reduction of the expected performance for future patients (0.71 to 0.68).

Discussion

Although many believe(d) that medical treatment for CLI generally leads to amputation[7,14-16], a surprisingly high number of patients can (temporarily) be stable or improve with conservative methods[17]. To devise a treatment algorithm for this patient group, we propose to consider the following points.

Baseline mortality in CLI was high at approximately 2% per month, even higher in the first months of the study. Postoperative mortality of major amputation was 9%. In most series and reviews mortality within 1 month after major amputation is even higher (9-18%)[18]. Well-being following amputation was lower, although improvement may be expected after 3-6 months up to levels of well-being reported by non-amputated patients. Although extrapolation to the broader group of patients with unreconstructable CLI is unrealistic, in most cases primary amputation will not be a preferential treatment option.

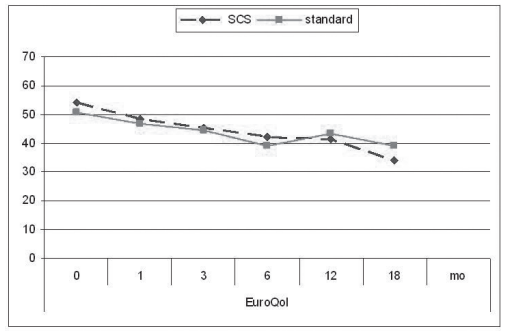


Figure 2a: **Q**uality-of-life: EuroQol from 0 (best health) to 100 (worst health

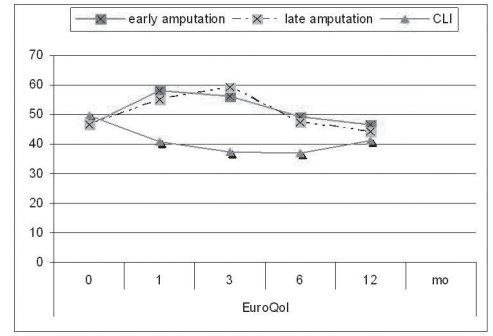


Figure 3a: Quality-of-life: EuroQol from 0 (best health) to 100 (worst health)

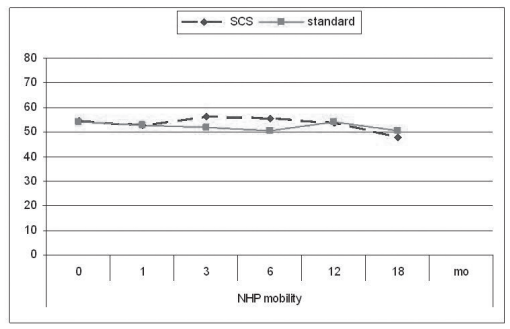


Figure 2b: Mobility: NHP from 0 (best) to 100 (worst)

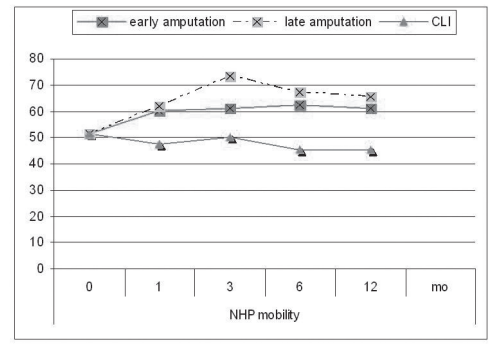


Figure 3b: Mobility: NHP from 0(best) to 100(worst)

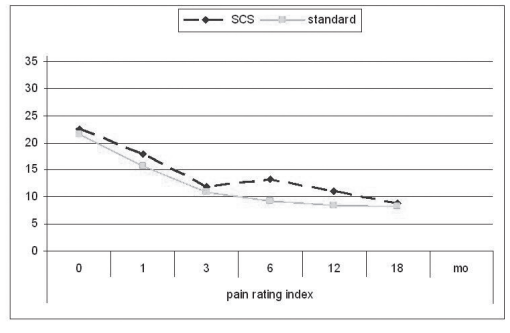


Figure 2c: Expressed pain: McGill pain rating index from 0 (no pain) to 36 (worst imaginable pain)

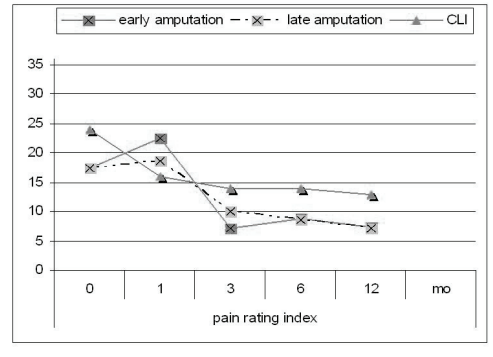


Figure 3c: Expressed pain: McGill pain rating index from 0 (no pain) to 36 (worst imaginable pain)

Figure 2: Health-related quality-of-life in the randomized treatment groups (left graphs)

Figure 3: Influence of amputation on health related quality-of-life. Effects are shown for patients who underwent amputation within three months (early amputation), for those who had late amputation, and for those patients without major amputation (CLI).

Patients at the highest risk of amputation are those with ischemic skin lesions and multi-level (angiographic) disease. Amputation incidence was extremely high during the first three months, suggesting that the definition of chronic CLI (rest pain for at least two weeks) may not be adequate. About 30% of patients with "chronic" CLI have rapidly progressive disease. Only after a few months, patients can be identified with relatively stable disease.

An algorithm as in Figure 5 represents treatment choices and possible outcomes in CLI. Nowadays technically, the majority of patients can undergo at least some type of revascularization, although not all patients will benefit from it[3]. If a meaningful vascular reconstruction is not considered possible, patients should receive adequate medical care including adequate pain medication, dedicated wound care and cardiovascular risk factor reduction. Other treatment options have not shown to be more (cost-)effective[19,20]. About one third of these patients will die or lose their limb within 3 months. However the majority of patients can be stable or improve with adequate pain medication and dedicated wound care[17]. When patients improve, treatment advice as for intermittent claudication remains appropriate: optimal control and treatment of all cardiovascular risk factors, low dose aspirin and statins, recommendation to stop smoking, and walking exercise to stimulate collateral blood flow.

Increasing pain and progressive tissue loss are the common reasons for amputation. Observing the condition of the patient and the ischemic limb during optimal medical management may be more informative and reliable than available (micro)circulatory measurements[21-23]. Controversies on interpretation of critical levels and cut-off points in studies estimating amputation risk or level and insufficient specificity could well be associated with the variability of the parameters[24-26]. Although the study was not designed for this purpose, we found no evidence that delayed amputation was associated with inferior well-being or mobility as compared to early amputation.

Characteristic		HR [95% CI]	*p*-value	Points in amputation risk model
Ischemic ulceration	No Yes	2.3 [2.0 – 2.7]	0.013	0 1
Gangrene	No Yes	2.2 [1.7 – 2.9]	0.010	0 1
Radiological dis. score	<=8 8-11 =11	1.0 8.2 [2.4 - 28] 11.3 [3.6 – 36]	<0.001	0 1 2

a. Multivariable analysis

Amputation risk model (total points)	N	Amp.	Incidence % 6 m	[95% CI] 24 m
0 – 1	23	4	17 [7 – 40]	17 [7 – 40]
2	43	14	19 [10 – 35]	36 [23 – 53]
3 – 4	48	35	60 [45 – 75]	92 [79 – 98]

b. Estimated risk of major amputation at 6 and 24 months in patients categorized according to the prognostic model and Kaplan-Meier limb survival curves

Table 4: Prognostic modeling

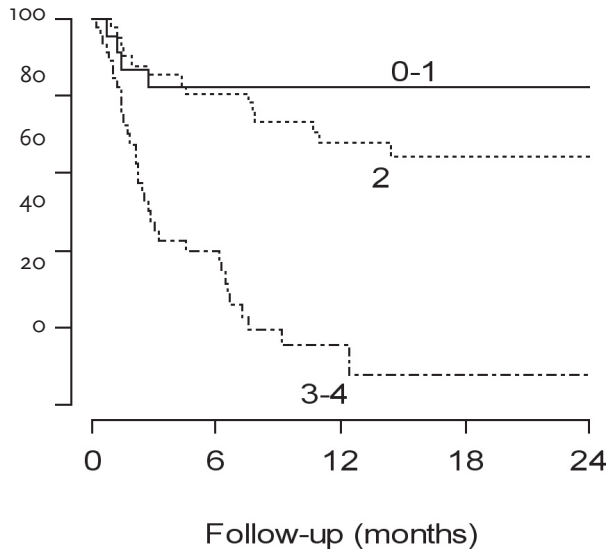


Figure 4: Kaplan-Meier limb survival curves in patients classified according to the prognostic model.

In the last decades, the debate regarding treatment for CLI has shifted from technical feasibility to patient-oriented functional outcomes. Standard endpoints of procedural success, graft patency, and limb salvage have been found to be a poor predictors of both patient palliation and functional success[2]. The drive to limb salvage has shifted towards efforts to decrease patient morbidity while maintaining as much function as possible. As noted in the guidelines of the TransAtlantic Inter-Society Consensus Working Group[9,27], there are patients who will be better served by primary amputation, but how can they be identified?

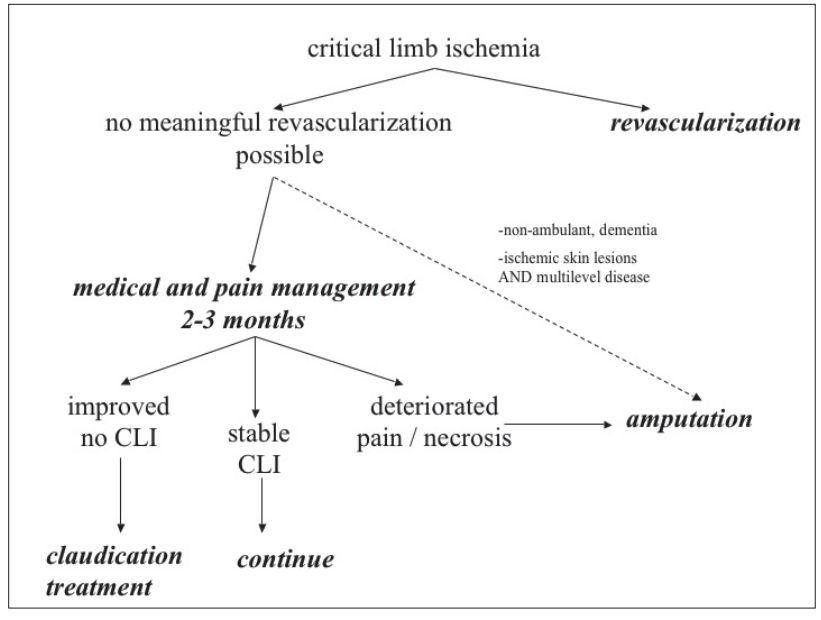


Figure 5: Treatment algorithm

Primary amputation is associated with considerable mortality. Furthermore, less than 50% of the elderly vascular population of patients with below-knee amputations ambulate outdoors and patients with above-knee amputations are almost universally non ambulatory[28-30]. In this study, this phenomenon was illustrated by inferior mobility scores in amputees. However pain scores greatly improve. Poor ambulatory ability at the time of presentation, dementia and depression have been described as highly important predictors of poor functional outcome in the treatment of CLI[30,31]. Combined with the very high risk of amputation in CLI patients with ischemic skin lesions and multilevel disease, these may be factors to decide for primary amputation rather than prolonged medical management for intractable ischemia and pain. The decision to amputate is of course ultimately up to the patient. The proposed prediction model (Figure 4) and algorithm (Figure 5) may aid in that difficult decision.

CLI patients often have extensive comorbidity, which contributes to limb loss and poor patient survival. Treatment of CLI needs to be viewed as palliative rather than curative, and the limited benefits of invasive and expensive therapy must be considered against life expectancy. Patients presenting with CLI for whom meaningful revascularization is not an option, represent a heterogeneous group with very diverse prognoses. Selection of patients will have major impact on outcome in the selected group. Therefore, (retrospective or prospective) evaluation of any treatment without comparable control groups is risky and results may be more attributable to selection than to the treatment effect.

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Chapter X

Summary and discussion

Summary

There has been a long history of interest in the effects of spinal cord stimulation (SCS) for critical limb ischemia (CLI), especially if a meaningful revascularisation is not possible[1,2]. Although multiple journal articles have reported "positive" results of this treatment[3-19], controlled trials were set up merely in the nineties of last century[20-22].

In the largest randomized trial (ESES-trial) up to date, we compared two treatment regimens (best medical treatment and best medical treatment plus SCS), and aimed at answering the question which mode of therapy works best—rather than how it works. We did not find that spinal-cord stimulation was of benefit above that of best medical treatment. Amputation-free survival was not improved (p=0.86). The rates of amputation were similar in both groups (p=0.47) and were particularly high during the first 3 months.

The EuroQol and Nottingham Health Profile showed poor quality-of-life compared with matched reference values of the general population at baseline, but the general trend was toward some improvement of self-reported well-being, with no significant differences between the randomized treatment groups. Patients with a spinal-cord stimulator used significantly less pain medication, which suggests substantial pain relief from this treatment. Pain relief was reported using visual analogue scales (VAS), the pain rating index of the McGill pain questionnaire and the pain weighted scores of the Nottingham Health Profile. Similar pain reduction was seen in the standard and SCS-treatment groups. Although spinal cord stimulation may be beneficial for ischemic pain, the effect is not stronger than adequate conservative pain treatment.

Other available data on pain relief from SCS in critical limb ischemia are from uncontrolled series. The authors reported "remarkable" or "substantial" pain relief in 73-85% of patients[5,8,11,23,24]. Excellent pain relief after a trial period of stimulation (of a few weeks) was considered a predictive factor for long-term success[25]. However, no comparative data were available confirming this hypothesis. A trial stimulation period was therefore not incorporated in the study design of our randomized trial. Careful analysis of the pain scores indicated that only a small percentage of patients (15–20%) had 'excellent' (>75%) pain relief. The data of the trial were used to evaluate data on pain relief between intake and 1 month follow-up and outcome. Simulation of a trial stimulation with our data proved to be negative. Although the amputation incidence was lower in patients with good pain relief, there was no difference in limb survival between patients with pain reduction during SCS-treatment or patients with pain reduction during medical treatment.

Spinal-cord stimulation was associated with a substantial number of complications. Initial positioning of the SCS system was not optimal in 6 patients and 3 patients needed lead repositioning within 30 days. During further follow-up, 13 lead displacements occurred, and 11 reposition procedures and one re-implantation were performed. Infection was reported in three patients. Three batteries failed within 18 months. Because of these difficulties eight patients (13%) had suboptimum stimulation. If only patients with adequate stimulation were analysed, limb survival was not superior (p=0.39).

In the standard treatment group side-effects were reported in ten patients: upper gastro-intestinal bleeding (3), nausea (7), and dizziness (2). In the spinal cord stimulation group side effects occurred in four patients: duodenal perforation (1), nausea (2), and pruritus (1).

Over two years, the costs of SCS-treatment were about €7,900 (28%) higher as compared to best medical treatment alone (€36,600 *vs.* €28,700, *p*=0.009). Most of these costs were attributable to hospitalisation and rehabilitation. Initial costs in SCS-treatment were high due to implantation. Since all other costs evolved similarly in both treatment groups, SCS-treatment remained the more expensive therapy during follow-up. Survival and amputation-free survival were similar in the two treatment groups of patients with CLI; therefore cost-effectiveness is reduced to cost-minimisation analysis. Based on limb survival (HR=0.82), the "number needed to treat" (NNT) to save one limb was estimated at 14, resulting in €110,000 per limb saved.

The presence of ischemic skin lesions (ulcerations or gangrene) and a radiological arterial disease score were significantly associated with amputation risk. The risk factors were combined in a simple prognostic model, which can be used to estimate the individualized probability of amputation in patients with CLI. No effect was found for SCS-treatment at multivariable analysis, and no subgroup effects were identified.

From earlier studies it was implied that SCS might be a beneficial therapeutic alternative particularly in those patients without established gangrene[5-7,26]. This idea was born from the observation, that the amputation rate was highest in patients with gangrene, suggesting that SCS had no limb-saving effect in those patients. However, retrospective data collection and lack of a well-defined control group limits differentiation of prognostic factors and factors that modify treatment effects (predictive factors).

Discussion

The conclusion of our randomized trial was that SCS was no more effective than best medical treatment alone in preventing amputations and costs more. Even so, a debate emerged whether a subset of patients might in fact be helped by SCS. It was stated "that the best candidates for the procedure are those with ischemic rest pain without tissue loss" or that "SCS treatment appears beneficial to a subgroup of CLI patients"[25-27]. A systematic review[28] suggested improvement of limb survival in patients treated with SCS and expansion of the indication in CLI. This review included 6 studies[13,20-22,29,30]. Major flaws of this review were the inclusion of a non-randomized study[13] in which patients with CLI did or did not receive treatment based on a transcutaneous pO2 classification and trial stimulation, and exclusion of some patients from the smallest study, which is questionable and compromises objectivity. Therefore, the main conclusion of this review, that SCS is significantly better than conservative treatment alone in achieving a reduction in amputation risk, was not justified. Meta-analysis of the five available randomized studies yields a relative risk reduction of –0.07 (*p*=0.15).

Although many believe(d) that medical treatment for critical limb ischemia generally leads to amputation[13,16,31,32], a surprisingly high number of patients can (temporarily) be stable or improve with conservative methods[33]. A treatment algorithm was proposed that considers the heterogeneity of this patient group.

Baseline mortality was high at approximately 2% per month, even higher in the first months of the study. Postoperative mortality of major amputation was 9%. In most series and reviews, mortality within 1 month after major amputation was even higher (9-18%)[34]. Well-being following amputation was lower, although improvement may be expected after 3-6 months up to levels of well-being reported by non-amputated patients. Together with the increased death

risk following amputation, this means that primary amputation will not be a treatment option for the majority of patients. If a meaningful vascular reconstruction is not possible, patients should receive adequate medical care including pain medication and dedicated wound care. Other treatment options have not shown to be more (cost-)effective.

In the last decades, the debate regarding treatment for CLI has shifted from technical feasibility to patient-oriented functional outcomes. Standard endpoints of procedural success, graft patency, and limb salvage have been found to be poor predictors of both patient palliation and functional success[35-37]. The drive to limb salvage has shifted towards efforts to decrease patient morbidity while maintaining as much function as possible.

Adequate medical care including pain medication and dedicated wound care can provide pain relief up to that achieved with spinal cord stimulation treatment. Poor ambulatory ability at the time of presentation, dementia and depression have been described as the most important predictors of poor functional outcome in the treatment of CLI[38-40]. Combined with the very high risk of amputation in CLI patients with ischemic skin lesions and multilevel disease, these may be factors to decide for primary amputation. In all other patients, the effect of a conservative treatment strategy including cardiovascular risk factor reduction[41-43], adequate pain management and wound care can be evaluated within 2-3 months[33].

Patients presenting with CLI for whom meaningful revascularization is not an option, represent a heterogeneous group with very diverse prognoses. Selection of patients will have major impact on outcome in the selected group. Therefore, (retrospective or prospective) evaluation of any treatment without comparable control groups is risky and results may be more attributable to selection than to treatment effects. This largely explains the ongoing debate on the usefulness of SCS in CLI.

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Chapter XI

Samenvatting en discussie

Inleiding

Perifeer atherosclerotisch vaatlijden komt vaak voor in de Westerse wereld[1-4]. In Europa gebruikt men bij chronisch vaatlijden vaak de klinische classificatie volgens Fontaine om de mate van ernst van perifeer vaatlijden te beschrijven: asymptomatisch (I), claudicatio intermittens (II), ischemische pijn in rust (III) en ischemische ulceraties of gangreen (IV). De meeste patiënten hebben claudicatio intermittens (etalagebenen), van wie slechts een minderheid in ernstige mate, en het risico op amputatie is slechts zeer beperkt[2,5,6]. In een Rotterdams bevolkingsonderzoek, waarbij 7715 mensen werden onderzocht, kwam claudicatio intermittens voor bij ongeveer 1% van de onderzochte personen tussen 55 en 60 jaar, oplopend tot 5% in de groep tussen 80 en 85 jaar. De prevalentie van asymptomatisch perifeer vaatlijden, gedefinieerd als een enkel-arm-index lager dan 0.90, was 17% bij mannen en 20% bij vrouwen boven de leeftijd van 55 jaar[7].

Van de patiënten met claudicatio intermittens wordt circa 5-10% binnen 5 jaar behandeld met een revascularisatie (stent of bypass), hoewel er grote variatie is in het overgaan tot behandeling tussen landen en regio's. Hypertensie, roken en diabetes mellitus zijn belangrijke risicofactoren om kritieke ischemie te ontwikkelen[3]. Bij naar schatting 5% van patiënten met symptomatisch perifeer vaatlijden is er op enig moment sprake van kritieke ischemie, gepaard gaande met ischemische pijn in rust of niet genezende wonden of gangreen, waardoor uiteindelijk 1% tot 4% een amputatie ondergaat[2,6]. De kans op ernstige cardiovasculaire incidenten (hartinfarct, herseninfarct) en overlijden ten gevolge daarvan is echter veel groter dan het amputatierisico[6,8-15].

Bij kritiek vaatlijden staan pijn in het aangedane been (of zeldzaam in de aangedane arm) en ulceraties of gangreen op de voorgrond. Ischemische pijn is vaak intens en invaliderend. De behandeling van keuze is het verbeteren van de perifere circulatie door het weer doorgankelijk maken van een vernauwd traject via een chirurgische revascularisatie (bypass) of een endovasculaire ingreep (angioplastiek of stent)[16,17]. Ondanks grote technische vooruitgang is dit bij een aantal patiënten onmogelijk of zinloos, meestal omdat er geen geschikte autologe vene (meer) beschikbaar is als bypass of omdat het uitstroomtraject te slecht is[13,18,19].

Het beloop van chronische kritieke ischemie is voor een individuele patiënt moeilijk in te schatten[20,21]. Voor het natuurlijk beloop van kritieke ischemie (zonder revascularisatie) werd vaak gerefereerd aan oudere literatuur, waarin amputatiepercentages werden gemeld van 60-80% binnen een jaar[8,22,23].

Naast een algemene inleiding wordt in hoofdstuk I een literatuuroverzicht gegeven van de verschillende niet-chirurgische behandelingen die zijn toegepast bij patiënten met kritiek vaatlijden. In ieder geval is er aandacht vereist voor pijnbestrijding, wondverzorging en behandeling van risicofactoren[24]. De waarde van medicamenteuze therapie met bloedviscositeitsverlagende en reologische medicijnen om de (micro)circulatie te bevorderen is marginaal gebleken[25]. Van intermitterende intraveneuze infusie met prostacycline-analogen werd beschreven dat ischemische pijn verminderde en dat de wondgenezing verbeterde, hoewel de resultaten van de verschillende onderzoeken niet consistent waren[26-29]. Hoewel ilomedine in Nederland geregistreerd is voor ernstige ischemie (Fontaine stadium III-IV), is de klinische relevantie van het effect onduidelijk, aangezien niet aangetoond is dat amputaties voorkomen worden. Hyperbare zuurstofbehandeling is duur en verschillende onderzoeken toonden elkaar

tegensprekende resultaten[2,30]. Van intermitterende pneumatische compressie (IPC) therapie werd toename van de bloeddoorstroming en verbeterde wondgenezing beschreven, maar er is niet aangetoond dat amputaties voorkomen worden[31,32]. Recent is veel aandacht voor factoren die angiogenese, het vormen van collaterale arteriën, kunnen bevorderen. Klinische fase I en II studies met (gen)therapie om de angiogenese te stimuleren toonden redelijk gunstige resultaten, zodat verder onderzoek hiernaar zinvol lijkt[33-36].

Sinds 1976 is er veel belangstelling geweest voor behandeling met epidurale ruggenmerg stimulatie bij patiënten met ernstig vaatlijden. Via een elektrode nabij het ruggenmerg en een pacemaker kunnen prikkels toegediend worden, waardoor de patiënt een tintelend gevoel waarneemt in een gebied overeenkomend met het gestimuleerde ruggenmergniveau. Pijnsensaties in dat gebied worden daardoor verminderd waargenomen. Het werkingsmechanisme is onduidelijk, beïnvloeding van sympathische activiteit en verbetering van de microcirculatie zouden een rol kunnen spelen[37-41].

In de literatuur zijn vele retrospectieve series van patiënten met ernstig perifeer vaatlijden beschreven, die met epidurale ruggenmergstimulatie behandeld zijn. Hierin werden veelal goede resultaten beschreven qua pijnvermindering, wondgenezing en "beenbehoud"[42-66]. Dit is echter geen bewijs dat de behandeling effectief is. De klachten die worden veroorzaakt door perifeer vaatlijden kunnen sterk variëren. Het is bekend dat sommige patiënten met afsluitingen van slagaderen naar de benen in de loop van de tijd collateralen ontwikkelen, zodat de doorstroming weer herstelt en klachten verminderen. Het ontwikkelen van collateralen kan gestimuleerd worden door looptraining en maatregelen om trombose en toenemende aderverkalking te voorkomen. Voor patiënten die veel pijn ervaren of slecht genezende wonden hebben, kan het echter onmogelijk zijn om activiteiten te ontwikkelen om de bloedsomloop te stimuleren. Omdat vermindering van klachten bij patiënten met perifeer vaatlijden dus afhankelijk kan zijn van meerdere factoren, kan het werkelijke effect van een behandeling alleen gekwantificeerd worden in een directe vergelijking van die behandeling met het tot dan toe best bekende alternatief. Pas rond de jaren '90 werden initiatieven ondernomen voor gerandomiseerd onderzoek naar epidurale ruggenmergstimulatie.

Samenvatting en discussie

De volgende hoofdstukken van dit proefschrift beschrijven het gerandomiseerde onderzoek naar de effectiviteit van epidurale ruggenmergstimulatie en de resultaten hiervan. Hoofdstuk II beschrijft de opzet van deze studie. Het was een pragmatische studie, waarbij het doel was om de vraag te beantwoorden welke behandeling (ofwel optimale medicamenteuze behandeling ofwel optimale medicamenteuze behandeling plus epidurale ruggenmergstimulatie) het beste resultaat had, en niet wat het werkingsmechanisme was. Zeventien ziekenhuizen in Nederland namen deel aan dit onderzoek. Patiënten met chronisch kritiek vaatlijden van een been kwamen in aanmerking voor deze studie, indien een bypass operatie of endovasculaire procedure onmogelijk of zinloos werd geacht. De patiënten hadden persisterende pijn in rust gedurende tenminste 2 weken en/of ischemische ulceraties of gangreen. Zij werden zowel mondeling als schriftelijk geïnformeerd over het onderzoek en gaven allen schriftelijke toestemming voor deelname. Toewijzing van de behandeling vond plaats via randomisatie door een onafhankelijk bureau. Patiënten werden in hun eigen ziekenhuis gecontroleerd na 1 maand, na 3, 6, 12 en 18 maanden en aan het einde van de studie. Daarnaast werden aan hen vragenlijsten toegestuurd.

Er werd niet alleen geregistreerd hoeveel van hen overleden of een amputatie ondergingen, maar ook hoe zij hun kwaliteit van leven waardeerden, hoeveel pijn zij hadden, hoeveel complicaties zich voordeden en hoeveel kosten er werden gemaakt. De geplande inclusie van 120 patiënten werd voltooid na een periode van ruim 2,5 jaar, 60 patiënten kregen de standaardbehandeling en 60 de ruggenmergstimulatie-behandeling.

Hoofdstuk III vermeldt de belangrijkste eindpunten van het gerandomiseerde onderzoek. Behandeling met ruggenmergstimulatie was niet beter dan behandeling met alleen optimale medicamenteuze behandeling. In beide behandelgroepen overleed een vergelijkbaar deel van de patiënten binnen twee jaar (36% *vs.* 37%, p=0,96). Ook de amputatievrije overleving was vergelijkbaar (33% *vs.* 34%, p=0,86). De kwaliteit van leven verbeterde enigszins in beide groepen in de loop van de tijd, maar er waren geen verschillen tussen de groepen. De kosten van behandeling met epidurale ruggenmergstimulatie waren echter aanzienlijk hoger dan behandeling met optimale medicamenteuze behandeling.

In hoofdstuk (III en) IV worden de technische problemen beschreven die optraden gedurende de behandeling met ruggenmergstimulatie. Bij 25 van de 60 patiënten werd een complicatie geregistreerd. Het goed positioneren van de epidurale elektroden was niet bij alle patiënten succesvol, bij 6 patiënten faalde de eerste implantatieprocedure, bij 13 patiënten trad dislocatie op van de elektrode tijdens de follow-up. Veertien maal werd een repositie verricht van elektroden en 3 maal een re-implantatie. Drie patiënten kregen een infectie en bij drie patiënten was de batterij leeg binnen anderhalf jaar. Ten gevolge van deze problemen was de ruggenmergstimulatie-behandeling suboptimaal bij 8 patiënten (13%). De amputatie incidentie was echter niet lager, indien alleen patiënten met adequate stimulatiebehandeling werden geanalyseerd (p=0,39).

Er werden ook andere complicaties geregistreerd: in de groep met standaardbehandeling kregen drie patiënten een maagbloeding, waren 7 patiënten misselijk en hadden er 2 last van duizeligheid. In de groep met epidurale ruggenmergstimulatie kreeg 1 patiënt een duodenumperforatie, waren 2 patiënten misselijk en had er één last van jeuk.

Hoofdstuk V gaat over de metingen van pijn en kwaliteit van leven. De hoeveelheid pijn werd gemeten met behulp van gestandaardiseerde vragenlijsten (visuele analoge schalen (VAS), McGill pijnvragenlijst en Nottingham Health Profile lijst), het verbruik van pijnmedicatie werd gekwantificeerd met de Medication Quantification Scale (MQS). In beide groepen hadden patiënten na verloop van tijd minder pijn. De pijnvermindering was echter vergelijkbaar in beide behandelgroepen. Patiënten die een epidurale ruggenmergstimulator hadden gekregen, gebruikten gemiddeld significant minder analgetica. Waarschijnlijk leidde de ruggenmergstimulatie dus wel tot een vermindering van de pijnklachten.

Retrospectieve series rapporteerden "opvallende" pijnvermindering door ruggenmergstimulatie bij het merendeel van behandelde patiënten[45,46,65,67,68]. Bovendien is gesuggereerd dat pijnvermindering tijdens een periode van proefstimulatie een predictieve factor zou zijn voor goede amputatievrije overleving[69]. In onze gerandomiseerde trial werd geen proefstimulatie verricht. Slechts een minderheid van de patiënten had goede pijnvermindering (>50% op de VAS-schaal). Met de gegevens van deze trial werd het effect van proefstimulatie gesimuleerd, door de uitkomsten te analyseren bij patiënten met en zonder pijnvermindering na een maand behandeling. Hoewel de amputatie incidentie lager was bij patiënten met minder

pijn na een maand behandeling, was er geen verschil tussen de groepen patiënten met minder pijn tijdens ruggenmergstimulatie-behandeling en patiënten met minder pijn tijdens standaardbehandeling.

In hoofdstuk VI worden de kosten van behandeling getoond, uitgesplitst naar operatieve verrichtingen, ziekenhuisopname, poliklinische zorg, revalidatie, opname in verpleeg- en verzorgingshuizen, thuiszorg, medicatie, en niet-medische kosten. De kosten van epidurale ruggenmergstimulatie waren aanzienlijk hoger dan die van de optimale medicamenteuze behandeling. Gemeten over twee jaar, kostte de behandeling per patiënt ongeveer 7.900 euro meer (€36.600 *vs.* €28.700). Onafhankelijk van de behandeling, werd het merendeel van de kosten veroorzaakt door ziekenhuisopname en revalidatie. Door implantatie van elektrode en pacemaker waren de initiële kosten van epidurale ruggenmergstimulatie hoog in vergelijking met standaardbehandeling. Aangezien alle andere kosten min of meer vergelijkbaar waren, blijft deze therapie duurder na follow-up van 2 jaar. Bij een gelijk veronderstelde effectiviteit van de behandelstrategieën qua (amputatievrije) overleving en kwaliteit van leven, waren de totale kosten van optimale medicamenteuze therapie dus lager (kosten-minimalisatie).

In hoofdstuk VII werden subgroepeffecten geanalyseerd. Door een aantal onderzoekers werd gesuggereerd, dat bepaalde patiëntengroepen meer baat zouden kunnen hebben bij epidurale ruggenmergstimulatie dan andere[46,47,69-73]. Het zou voornamelijk die patiënten betreffen zonder ischemische huidlaesies, zonder hypertensie, en die patiënten die nog een redelijke bloedcirculatie hebben, zoals gemeten met een transcutane zuurstofspannings-test.

Van een aantal factoren (leeftijd, geslacht, diabetes, hypertensie, cardiovasculaire comorbiditeit, eerdere vaatingrepen, ulceraties, gangreen, enkeldruk, enkel-arm-index) werd geanalyseerd of deze factoren prognostische invloed hadden. Alleen de aanwezigheid van ischemische huidlaesies was een belangrijke onafhankelijke prognostische factor, de hazard ratio voor amputatie was 2,3 (p=0,01). Het effect van behandeling met ruggenmergstimulatie was echter geenszins groter bij patiënten zonder ischemische huidlaesies. Er konden geen subgroepen van patiënten geïdentificeerd worden, bij wie een beter effect van ruggenmergstimulatie mag worden verwacht.

In vier andere, kleinere gerandomiseerde onderzoeken werden ook geen significant betere resultaten van ruggenmergstimulatie-behandeling aangetoond[71,74-76]. In een systematische review uit 2004, waarin resultaten bijeengevoegd werden van vijf gerandomiseerde studies, waaronder die van ons, en één niet-gerandomiseerde studie[59], werd gesuggereerd dat er een klein voordeel zou bestaan voor patiënten die behandeld waren met epidurale ruggenmergstimulatie[73,77]. Deze review heeft een aantal tekortkomingen, zoals het includeren van een niet-gerandomiseerde studie[59] en het excluderen van een aantal patiënten uit één van de gerandomiseerde studies, waardoor het de vraag is of dit voordeel reëel is of dat het te verklaren is uit de gebruikte methoden. Dit debat is nog niet gesloten. Wel is het zo dat het enthousiasme voor epidurale ruggenmergstimulatie bij ernstig vaatlijden getemperd is.

Hoofdstuk VIII beschrijft de ontwikkeling van een prognostisch model om de kans op amputatie te schatten. Op basis van het al of niet aanwezig zijn van ischemische huidlaesies (ulceraties of gangreen) en de uitgebreidheid van de afwijkingen bij angiografisch onderzoek, kon een individueel risicoprofiel gemaakt worden per patiënt. Dit profiel had een redelijk goede voorspellende waarde voor amputatie. Het risico op amputatie varieerde van 17% in de

gunstigste groep tot 92% in de ongunstigste groep.

In hoofdstuk (VIII en) IX komt de heterogeniteit aan de orde van de patiëntengroep met kritieke ischemie die in aanmerking kwam voor deelname aan ons onderzoek. Een deel van de patiënten werd beter door het geven van medicamenten, adequate wondbehandeling en adviezen. Andere patiënten echter hadden een veel slechtere prognose en ondergingen al na korte tijd amputatie of overleden.

Het gemiddelde overlijdensrisico was hoog, ongeveer 2% per maand. De postoperatieve mortaliteit na amputatie was nog hoger, namelijk 9%, hetgeen overeenkomt met getallen uit de literatuur[12,78,79]. De kwaliteit van leven na amputatie was gedurende 3-6 maanden slechter, waarna een verbetering optrad tot een niveau van welbevinden vergelijkbaar met niet-geamputeerde patiënten. Het hoge overlijdensrisico samen met de verslechtering van kwaliteit van leven impliceert dat primaire amputatie geen goed alternatief zou zijn voor de meerderheid van patiënten met kritiek vaatlijden. Als patiënten niet (meer) in aanmerking komen voor een vaatreconstructie of endovasculaire procedure, dan wordt een beleid van optimale medicamenteuze ondersteuning geadviseerd, inclusief adequate pijnmedicatie, wondverzorging en behandeling van risicofactoren[80-83]. Andere behandelingsopties zijn niet (kosten-) effectiever gebleken.

De laatste jaren is er in de vaatchirurgische literatuur veel aandacht geweest voor functionele uitkomsten na behandeling van kritiek vaatlijden[13,19,80,84]. Het voorkómen van amputatie is niet per definitie een positieve uitkomst voor een patiënt, indien lopen (om andere redenen) niet meer mogelijk is. Er werd een algoritme voor behandeling van deze patiëntengroep gepresenteerd, rekening houdend met de geïndividualiseerde kans op amputatie en het verwachte functionele resultaat[14,85]. Door de heterogeniteit van deze groep patiënten blijft het van groot belang om nieuwe behandeltechnieken, hoe veelbelovend ook, steeds te testen in vergelijking met een referentiegroep

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Dankwoord

Dankwoord

Dankwoord

"I was just guessing at numbers and figures
Pulling the puzzles apart
Questions of science, science and progress
Do not speak as loud as my heart"

Nobody said it was easy... (the Scientist, Coldplay)

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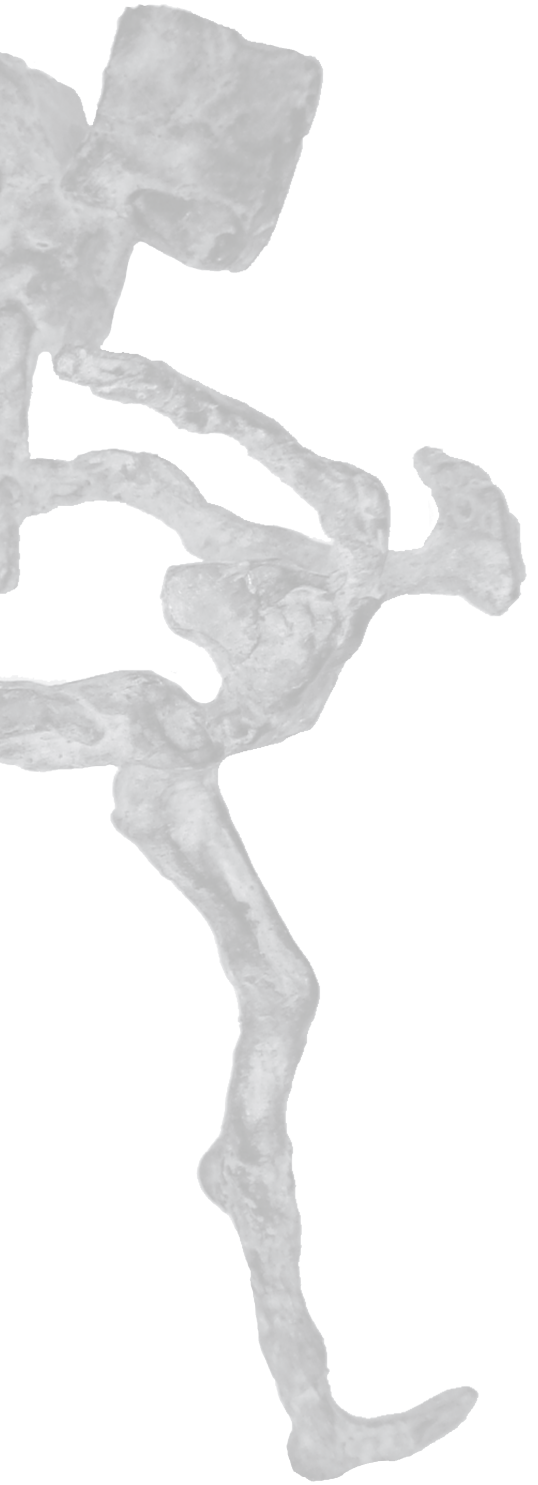
Curriculum vitae

and publication list



Curriculum Vitae

Curriculum vitae

Houke Marian Klomp werd op 10 juli 1965 geboren in Rotterdam. In juni 1983 behaalde zij het eindexamen Gymnasium ß aan het Erasmiaans Gymnasium te Rotterdam. Zij studeerde geneeskunde aan de Erasmus Universiteit Rotterdam, behaalde het doctoraal examen in oktober 1987 en het artsexamen in april 1990.
Na het artsexamen was zij kortdurend assistent-geneeskundige niet in opleiding in het Academisch Ziekenhuis Rotterdam-Dijkzigt, maar werd na een aantal maanden klinisch onderzoeker aldaar en schreef het protocol voor het onderzoek, waarop dit proefschrift is gebaseerd. Vanaf 1991 was zij trialcoördinator van deze multicentre trial.
In 1994 startte zij met de opleiding algemene heelkunde, in het Academisch Ziekenhuis der Vrije Universiteit (opleider prof.dr. R.I.C. Wesdorp, later prof.dr. H.J.Th.M. Haarman), en in het Medisch Centrum Alkmaar (opleider prof.dr. A.B. Bijnen). Van 1997 tot 2000 was zij bestuurslid van de landelijke Vereniging van Assistent-Geneeskundigen in de Heelkunde (VAGH).
Vanaf 2000 werkt zij als chirurg in het Nederlands Kanker Instituut - Antoni van Leeuwenhoek Ziekenhuis, vanaf 2001 als vast staflid met aandachtsgebied oncologische thoraxchirurgie.
Zij heeft twee zonen, Maurits (9 jaar) en Philip (7 jaar).

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