Abstract

Objective: Spinal cord stimulation (SCS) was proposed many years ago for pain treatment but healing of ischemic ulcers opened a new treatment indication. The aim of this review was to assess the efficacy of SCS. Methods: studies regarding ischemic pain, limb ischemia and SCS reported on Pubmed have been reviewed, including randomized controlled trials (RCTs), clinical trials, Cochrane library review, neurophysiological studies and microcirculatory evaluations. Results: Five RCTs, three multicenter studies and many clinical trials and reports of series have documented the clinical efficacy of SCS in the treatment of ischemic pain, particularly in patients with post-implantation increased blood flow. Pain relief, ulcer healing and limb salvage seems to be greater in non-diabetic patients, in diabetic without autonomic neuropathy, and in patients with rest pain or ulcer more than in patients with gangrene. A pain reduction of 75% was reported in the 3 RCTs; pain relief was significantly greater than in control group. Another study reported a lower use of analgesic in the SCS group. Moreover, pain relief obtained with SCS is maintained at follow-up while relief after medical treatment disappears quickly. The three multicenter studies showed a total pain relief between 41% and 43% and a cumulative pain reduction of 75% in 64.8% of cases. The clinical trials reported a pain reduction in up to 91% of patients. Based on six studies, the Cochrane reviewers found evidence to favor SCS over standard conservative treatment to improve limb salvage and clinical situation in patients with non-reconstructable critical limb ischemia (CLI). The mechanism of action of SCS is not completely clarified. Discussion and conclusions: the endovascular approach reduced the number of patients unsuitable for revascularization, however, some patients cannot be treated by angioplasty or open surgery; moreover, some are unfit for surgery, and others have persistent distal ischemia and pain with a functioning revascularization. In these cases SCS (alone or associated with prostanoids) can be indicated on the basis of the more recent evidences. A trial period with external stimulator, associated with a microcirculatory evaluation, is currently utilized to select patients that can derive benefit from this treatment, reducing costs.

Keywords: Spinal cord stimulation; Peripheral vascular disease; Critical limb ischemia; Vascular surgery; Electric stimulation therapy; Diabetic foot

1. Introduction

Critical limb ischemia (CLI) should be treated with surgical or endovascular technique to restore a pulsatile blood flow as distal as possible, in particular in patients with ischemic ulcers or gangrene. However, some patients cannot be revascularized or they do not reach a complete resolution of rest pain, so they need other treatment to improve their quality of life.

Spinal cord stimulation (SCS) has been first proposed in the clinical practice for treatment of intractable pain by Shealy in 1967. It was based on the gate-control theory, but further studies showed other pathophysiological changes related with electric stimulation of the spinal cord. A pain resolution in 94% and healing of ischemic ulcers in about half of 38 patients enrolled in a non-controlled study by Augustinsson [1] changed the interest of researchers from pain to vascular modifications.

The purpose of this review was to determine the efficacy of SCS in the treatment of pain in patients with untreatable CLI.

2. Materials and methods

The reference list was obtained searching on Pubmed with the following key words or features ‘spinal cord stimulation’ associated with ‘ischemic pain’ and ‘limb ischemia’, without any limits. Moreover, the Cochrane library and other relevant articles regarding animal studies, neurophysiologic and microcirculatory changes induced by SCS were obtained. Cochrane review, meta-analysis, review and many clinical trials were retrieved and utilized for discussion.

Selection criteria: (1) paper written in English, French, Italian; (2) conducted to examine the effectiveness of SCS as treatment of ischemic pain of the limbs; (3) in patients with angiographic exclusion of revascularization; (4) reporting methods of evaluation of pain; (5) with complete report of means, percentages, or statistics about pain; and (6) with 6-month follow-up.
Table 1
Results of reported RCT and multicenter studies

<table>
<thead>
<tr>
<th>Author – treatment</th>
<th>Publication type</th>
<th>Mean follow-up (m)</th>
<th>n treatment – Fontaine stage</th>
<th>Pain relief at follow-up of treated group</th>
<th>n control – Fontaine stage</th>
<th>Pain relief at follow-up of control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suy et al. [6]</td>
<td>Medical treatment vs. SCS + medical treatment RCT</td>
<td>20</td>
<td>20 stage IV</td>
<td>14 (70%) painless</td>
<td>18 stage IV</td>
<td>5 (28%) painless</td>
</tr>
<tr>
<td>Jivegard et al. [7]</td>
<td>Peroral analgesic vs. SCS + peroral analgesic RCT</td>
<td>18</td>
<td>25 stage IV</td>
<td>Significant reduction of VAS at 6–12 months (P=0.0014)</td>
<td>26 stage IV</td>
<td>Significant reduction of VAS at two months but not at 6–12 months</td>
</tr>
<tr>
<td>Claesys and Horsch [8]</td>
<td>PGE1 vs. SCS + PGE1 RCT</td>
<td>12</td>
<td>45 stage IV</td>
<td>18 stage II (P=0.0014) 13 stage III (P=0.0013)</td>
<td>41 stage IV</td>
<td>41 stage IV 3 (7%) stage III</td>
</tr>
<tr>
<td>Klomp et al. [9]</td>
<td>Best medical treatment (analgesic, ASA, coumarins, vasoactive) vs. SCS + best medical treatment RCT</td>
<td>18</td>
<td>60 stage IV</td>
<td>Significant pain reduction Difference of pain reduction between treatment and control not significant Significant less pain medication</td>
<td>60 stage IV</td>
<td>Significant pain reduction</td>
</tr>
<tr>
<td>Broseta et al. [2]</td>
<td>SCS MulticSt</td>
<td>25</td>
<td>41 stage III, 14 stage IV</td>
<td>17 (41.5%) total pain relief 12 (29.3%) pain relief 75% 1 (2.4%) pain relief 50%</td>
<td>25 stage IV</td>
<td></td>
</tr>
<tr>
<td>Galley et al. [3]</td>
<td>SCS Retrospective MulticSt</td>
<td>23</td>
<td>244 stage III, 139 stage IV</td>
<td>In stage III pain relief &gt; 75% in 75% of patients In stage IV 57% of success (healing or stabilization of ulcers) Global success in 62% of 199 patients followed</td>
<td>207 definitive SCS in 212 p.</td>
<td></td>
</tr>
<tr>
<td>Amann et al. [4]</td>
<td>SCS MulticSt</td>
<td>41</td>
<td>At 12 months 43% had improved from Fontaine stage III–IV to stage I–II</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Randomized controlled trials (RCTs) of SCS vs. other form of treatment, multicenter trials and clinical trials (CT), have been analyzed. When more papers by the same authors with the same or similar number of patients were reported, the most complete one was selected.

As our purpose was not to do a meta-analysis, we included even papers that reported results only in percent.

Exclusion criteria: mixed diagnosis of Buerger and Raynaud disease (when possible we excluded only this subgroup from the report), case reports, clinical trials with <20 cases treated.

3. Results

Five RCTs were identified; one of Guarnera G et al. (Minerva Cardioangiol 1994), comparing SCS to surgery, was excluded because it was a study in progress in a small sample. Moreover, we found three multicenter studies [2–4] and many reports about the ESES study, that was considered as a single trial.

The multicenter study reported by Rickman S et al. (J Vasc Nurs 1994) and the CT of Visconti (Minerva Cardioangiol 1996) were not considered because of a limited follow-up and in only 60% of cases.

In the clinical trial of Gersbach et al. [5] the 15 patients of the non-atherosclerotic group were not analyzed because they were inhomogeneous.

4. Pain relief

The results of these trials are reported in detail in Tables 1 and 2; when described, the number of patients reaching pain relief have been reported. All the 4 RCTs [6–9] showed a significant pain reduction in the group of patients treated by SCS; and only the ESES study did not show difference between the treated and the control group. Nevertheless, in this study the SCS group utilized significantly less pain medication, which suggests substantial pain relief from this treatment. Augustinson et al. [1], Broseta et al. [2] and Jivegard et al. [10] classified pain by rank (Augustinson based ranks to 0–100 point scale results); Klomp et al. in the ESES study [9] utilized the pain-rating index (PRI) of the McGill Pain Questionnaire. The other Authors utilized the Visual Analogic Scale (VAS). The multicenter study reported by Galley et al. [3] analyzed the greatest number of patients but has the limits of a retrospective study.

Three RCTs (Table 1) showed significantly greater long-term pain reduction with SCS than with the best medical
## Table 2
Results of reported CT. (ATS atherosclerotic, Diab diabetic)

<table>
<thead>
<tr>
<th>Author – treatment</th>
<th>Publication type</th>
<th>Mean follow-up (m)</th>
<th>n treatment – Fontaine stage</th>
<th>Pain relief &gt;75%</th>
<th>Pain relief 50–75%</th>
<th>Pain relief at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augustinsson et al. [1] CT</td>
<td></td>
<td>15</td>
<td>34 p &lt;br&gt; 12 stage IV &lt;br&gt; 21 ATS &lt;br&gt; 5 Diab</td>
<td>52 (72.2%)</td>
<td>37 (62.8%)</td>
<td>Pain reduction in 91% &lt;br&gt; ATS: Excellent in 3 (14%) and good in 9 (43%) &lt;br&gt; Diab: Excellent in 1 (20%) and good in 2 (40%)</td>
</tr>
<tr>
<td>Bruni et al. [15] CT (series)</td>
<td></td>
<td>&gt; 8</td>
<td>72 stage III &lt;br&gt; 59 stage IV &lt;br&gt; 33 stage IV &lt;br&gt; with gangrene</td>
<td>47/72 = 65.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gersbach et al. [5] CT Selected group</td>
<td></td>
<td>46</td>
<td>72 atherosclerotic &lt;br&gt; 19 (26%) stage III &lt;br&gt; 53 (74%) stage IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guarnera et al. [20] CT</td>
<td></td>
<td>Up to 80</td>
<td>35</td>
<td></td>
<td></td>
<td>Pain relief in 77%</td>
</tr>
<tr>
<td>Horsch and Claeys [12] CT</td>
<td></td>
<td>35.6</td>
<td>177 &lt;br&gt; 114 stage III &lt;br&gt; 63 stage IV</td>
<td>93 (81.6%) stage III &lt;br&gt; 17 (43.6%) stage IV</td>
<td>9 (7.9%) stage III &lt;br&gt; 19 (30.2%) stage IV</td>
<td></td>
</tr>
<tr>
<td>Jacobs et al. [13] CT</td>
<td></td>
<td>Up to 36</td>
<td>20 &lt;br&gt; 6 stage III &lt;br&gt; 14 stage IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jivegard et al. [10] CT</td>
<td></td>
<td>27</td>
<td></td>
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<td></td>
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<tr>
<td>Kumar et al. [21] CT</td>
<td></td>
<td>Up to 36</td>
<td>39</td>
<td></td>
<td></td>
<td>Pain relief in 77%</td>
</tr>
<tr>
<td>Mingoli et al. [22] CT</td>
<td></td>
<td>Up to 76</td>
<td>76 &lt;br&gt; 10 stage III &lt;br&gt; 63 stage IV</td>
<td></td>
<td></td>
<td>Pain control in 80% at the one-year and 75% at the two-year follow-up</td>
</tr>
<tr>
<td>Neuhauser et al. [23] CT Retrospective</td>
<td></td>
<td>Up to 57</td>
<td>21 &lt;br&gt; 15 stage IV</td>
<td>15/21 (71%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petrakis and Sciacca [24] CT</td>
<td></td>
<td>58</td>
<td>64 diabetic &lt;br&gt; 14 stage III &lt;br&gt; 60 stage IV</td>
<td>Overall 59.38% &lt;br&gt; stage III 79% &lt;br&gt; Ulcers &lt; 3 cm² 68% &lt;br&gt; Ulcers &gt; 3 cm² 37%</td>
<td>Overall 14.06% &lt;br&gt; III stage 7% &lt;br&gt; Ulcers &lt; 3 cm² 14% &lt;br&gt; Ulcers &gt; 3 cm² 18%</td>
<td></td>
</tr>
<tr>
<td>Petrakis and Sciacca [25] CT Retrospective</td>
<td></td>
<td>71</td>
<td>150</td>
<td>85 (56.67%)</td>
<td>28 (18.67%)</td>
<td></td>
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</tbody>
</table>

Treatment, that included analgesic [7], rheologic [6] and prostaglandin [8].

The ESES study did not report data regarding pain results, but only two figures; one shows a reduction of PRI from 22.6 (SCS group) and 21.6 (control) to about 11–12 after three months of treatment, the two curves almost being similar. Regarding analgesic use, they utilized the medication quantification scale (MQS) that, leaving from 7 (SCS) and 7.4 (control), increased to about nine for control and decreases to about 3.4 in the SCS group at one month follow-up. The two curves remain divergent and significantly different in the first six months of follow-up. The Authors attribute an average 40% reduction of pain to amputation, that have a life-table curve quite similar in
the two treatments; while the MQS is significantly lower in SCS group for all times considered at follow-up. Even these data confirm the superiority of SCS in pain control. In particular, in two RCTs 49.2% of treated patients were painless at follow-up compared with 15.2% of control group [6, 8].

The three multicenter studies showed a total pain relief between 41.5% [2] and 43% [4] and a cumulative pain reduction of 75% in 64.8% of cases.

The clinical trials reported in Table 2 show a pain reduction in up to 91% of patients, with a pain relief ranging from 14% in the atherosclerotic group of Augustinsson et al. [1], to 77% of Guarnera et al. [20].

In non-controlled studies reported in a review of Ubbink (Acta chir belg 2000), pain relief has been reported in more than 60% of patients. It cannot be excluded that the lower pain relief reported by Augustinsson et al. [1] was related with the lower quality of the devices and to the scarce experience.

Particularly interesting is pain reduction in patients with ulcers or small gangrene that avoid, in many cases, a major amputation; this is reported in 29% of the Claeys and Horsch study [8] (associated to healing), in 57% of the Galley et al. report [3], but even in 68% of diabetic patients with small ulcers [24].

Pain relief is well documented in all the publications; it is obtained in a higher rate than with prostanoid treatment, and it is not dependent on circulatory changes but it is more significant in patients with an impressive increase in their blood flow [11]. It can be noted immediately during test stimulation, particularly in Fontaine stage III patients, whereas in some patients pain relief is needed for more days. Patients without clinical improvement generally do not show a transcutaneous oxygen tension (TcPO₂) increase, and frequently require major amputation as in the sample of 177 patients with untreatable CLI, with a 66% cumulative limb salvage at four-year follow-up [12].

Pain relief [12] and TcPO₂ increase are the selection criteria generally used for the implantation of an internal device.

Very probably the anatomical microcirculatory changes observed following SCS implantation, as the increase in the number of perfused capillaries without an increase in their diameter, shown by capillaroscopy [13], or the increase in capillary density at three months [14] and the increase in the peak-rest erythrocyte velocity during reactive hyperemia (Ubbink DTh et al. J Vasc Surg 1999), are responsible for the improvement or healing of the ischemic lesions. Modifications by laser-Doppler have been documented by Ubbink in the same paper; they seem to be dependent on the electrode position; capillary blood flow and skin temperature tend to decrease when the stimulation is above T10 and tend to increase when it is at a lower level (T12) [11].

Results in patients with end-stage renal failure are discordant: Bruni et al. [15] did not show positive results, on the contrary for Brummer et al. [16] implantation of a SCS device in patients with end-stage renal disease with critical limb ischemia dramatically improves quality of life and pain relief.

5. Complications

The more frequent complications reported are: lead migration and lead breakage, infections (in the implantation site, at the level of the electrode connection and of the abdominal pocket), unwanted stimulations, hardware malfunction and allergy to metal.

The Cochrane review [17] reports a complication risk of 12% (95% CI: 5–20%). Infections of the lead or subcutaneous pulse generator pocket occurred less frequently; the pooled risk was only 3% (95% CI: 0–6%). Depletion of the battery within 18 months of follow-up also occurred: five times in the SCS-EPOS study, and three times in the ESES study. The overall complication risk was 0.18 (95% CI: 0.03–0.32), indicating a number needed to harm of 6 (95% CI: 3–33).

The incidence of complication is quite different in the studies examined in the Cochrane review: the incidence of infection ranges between 0 and 5 (8/210–mean 3.8%). As for other hospital-acquired infections, the incidence is related to many factors, the most important of which are équipe- and hospital-dependent.

The battery end-of-life cannot be considered a true complication; it is strictly dependent on the stimulation parameters and can be linked to the intensity of pain. It was reported in 10/210 patients (4.8%). Even other complications, as lead migration or dehiscence of the subcutaneous pocket can be surgeon-related more than device-related. However, new devices are now available to reduce some hardware ‘complications’ including rechargeable battery.

Conservative treatment has less reported complications, but gastric hemorrhage and renal failure associated with FANS and dependence on narcotics are well known. The study of Claeys and Horsch [8], that utilized PGE1, reported a 23.2% overall incidence of complications in the medical arm, even if no patient needed to stop therapy owing to adverse events. The complications or the adverse events reported during treatment with PGI2 and PGI1 for CLI often need stopping therapy, and for this reason medical treatment with prostanoïds is contraindicated in many patients.

6. Discussion and conclusions

The mechanism of action of SCS is not completely clarified; based on the gate theory, it was used two years later (this theory) for the treatment of pain by Shealy. Cook, in 1976, first reported its efficacy in the reduction or relief of ischemic pain associated with peripheral disease and of neuroischemic pain due to diabetic vasculopathy.

For Linderoth and Meyerson (Eur J Pain 2000;4:317–9), experimental studies on animals suggested mechanisms based on inhibition of sympathetic activity and/or antidromic release of vasoactive substances; other studies showed an alteration of myocyte oxygen demand. Other more recent experimental animal studies of Croom (Am J Physiol 1997) support the hypothesis that SCS (even at intensities far below the motor threshold), may activate antidromically afferent fibers in the dorsal roots, thus causing peripheral release of calcitonin gene-related peptide (CGRP), which produces cutaneous vasodilation.

Theoretically, sympathectomy should reduce the effects of SCS, but this experience is not confirmed in our series.
(unpublished data) and in the reported papers; Bruni et al. [15] reported positive results in 58.9% of 39 patients with previous sympathectomy. However, Petrakis (Surg Neurol 2000), reported a treatment failure or partial success in diabetic patients with autonomic neuropathy.

Soon after implantation of the temporary stimulator, an increase in TcPO2 can be observed, but many patients need some days to show this modification. Petrakis (Int Surg 1999) states that a significant TcPO2 increase within two weeks of temporary implantation is associated with clinical improvement and SCS success. An increase in TcPO2 ≥ 15%, associated with complete pain relief, is considered a suitable indication for implantation of a definitive stimulator [14].

TcPO2 and the ratio between foot and chest TcPO2 (RPI) did not change in patients who required major amputation in a sample of 177 patients with untreated CLI, with a 66% cumulative limb salvage at 4-year follow-up [12]. A TcPO2 increase of 50% within three months after SCS implantation was associated with success.

The TcPO2 increase in patients treated by SCS is maintained at 1-year follow-up evaluation, while the increase observed following PGE-1 treatment is temporary and generally not present after six months [8].

Switching off the SCS, TcPO2 levels decrease in a few hours, to improve rapidly switching on again the stimulation [3], but another clinical study reported that, after switching off the system, the clinical improvement persisted for 10 days and the neurohormonal pattern showed high plasma values of beta-endorphin and Met-enkephalin, normal dynorphin B, endothelin-1 and catecholamines, and low nitric oxide. Met-enkephalin levels were further increased (P < 0.01) immediately after switching on the electrical stimulation again. The persistence of high plasma opioid levels after switching off the spinal cord stimulation explains the absence of subjective complaints and suggests an involvement of opioids in the regulation and improvement of the microcirculation [18].

However, severe rest pain commonly recurs at the time of battery depletion, or because of accidental system dysfunction; it always disappears shortly after correction of the failure. This observation confirms that clinical improvement is due to SCS, and that the delivery of an adequate electrical current at the right spinal level is essential to keep its pain relieving effect [5].

The endovascular approach reduced the number of patients unsuitable for revascularization, and in many cases a PTA or other endovascular treatment allow even temporary improvement of peripheral circulation, that sometimes is enough for ulcer healing or to reduce rest pain. In clinical practice, however, some patients with CLI cannot be treated either by angioplasty, or by open surgery. Moreover, there are some patients that are unfit for surgery because of a very high operative risk, and patients with functioning but partial revascularization such as profundaplasty or bypass on a blind popliteal artery, with persistent distal ischemia.

Recently, a Cochrane review [17], evaluating the results of six studies comprising nearly 450 patients, found evidence to favor SCS over standard conservative treatment to improve limb salvage and the clinical situation in patients with non-reconstructable CLI, so now these cases can be treated even with SCS, prostanoids or both.

One of the problems reported by the Cochrane review [17] and by other studies is the high cost of this treatment. Smith highlighted the 26% increase in the overall cost of spinal cord stimulation over best medical treatment [19]; for Klomp, analyzing data of the ESIS Study Group (Eur J Vasc Endovasc Surg 2006), the cost of SCS-implantation and complications (£7950 per patient) exceeded by far the cost due to amputation procedures (£410 per patient). The total costs of treatment were £36,600 per patient over two years for the SCS-group vs. £28,700 for best medical treatment alone (28% higher for SCS-group, P = 0.009). Indeed, institutional and social amputation-related costs are much higher, moreover, recently some authors suggest to repeat prostanoid treatment in patients with CLI two to four times a year to improve the results; this approach reduces the difference of costs between the two kinds of treatment.

However, pain reduction is not the only target of this treatment; limb salvage is more ambitious, but until now results of SCS are not quite different from those obtained with the conservative treatment.

Many parameters not well studied can modify the outcomes: the extension of the vascular occlusion, the associated infections, the progression of the disease, the time between onset of symptoms and treatment. The general impression, reading many of the papers reported in literature, is that patients unsuitable for vascular reconstruction are proposed for SCS implantation when their microcirculation is particularly compromised, in other words ‘too late’, when repeated surgical and medical treatment have failed, with consequent poor outcomes.

Microcirculatory parameters seem to be the most important factors to foresee the outcome.

Patients unsuitable for vascular reconstruction, and patients already revascularized with a TcPO2 > 30 mmHg, but with persistent pain and/or ulcers that don’t heal for months with the best medical treatment, could be considered for SCS implantation to reduce rest pain and to improve ulcer healing.

In a selected number of patients, SCS can be a true alternative to limb amputation; the possibility of trying its efficacy at low risk and low costs, using a temporary device, should be considered even for ethical and pitiful reasons. In the future, SCS must be compared with the emerging treatment as gene therapy and cell implantation.

References


