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Spinal cord stimulation in sympathetically maintained complex regional pain syndrome type I with severe disability. A prospective clinical study

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Abstract

Background and purpose: In this prospective trial we assessed the long-term effect of spinal cord stimulation (SCS) on the improvement of functional status in complex regional pain syndrome type I (CRPS I).

Methods: A prerequisite for eligibility to SCS treatment was the responsiveness of patients to sympathetic nerve block. In 29 patients with chronic sympathetically maintained CRPS I, the efficacy of SCS on deep pain, allodynia and functional disability was determined. Pain intensity was estimated during SCS free intervals of 45 min (inactivation test) every 3 months and compared with that under SCS treatment.

Results: On SCS treatment, both deep pain and allodynia could be permanently reduced from 10 to 0–2 on a 10 cm visual analogue scale (VAS) ($p < 0.01$). During the inactivation tests, reoccurrence of pain up to 8 VAS (quartiles 6–8) was measured. Considerable impairments in daily living activities, objectified by the pain disability index, were also restored ($p < 0.01$). After a follow-up period of 35.6 ± 21 months, 12 of 16 patients with affected upper limb showed significant increase of the fist grip strength from 0 to 0.35 (quartiles 0.1–0.5) kg compared with 0.9 (quartiles 0.7–1.1) kg on the unaffected side ($p < 0.01$). Eight of ten patients with lower limb disability resumed walking without crutches. Previous pain medication could be significantly reduced ($p < 0.01$).

Conclusions: As a result of permanent pain relief under long-term SCS combined with physiotherapy, the functional status and the quality of life could be significantly improved in sympathetically maintained CRPS I.

Keywords: Complex regional pain syndrome type I (CRPS I); Long-term limb disability; Spinal cord stimulation; Sympathetic block; Back-to-work rate

1. Introduction

Complex regional pain syndrome type I (CRPS I), formerly known as "reflex sympathetic dystrophy", is a neuropathic pain syndrome (Merskey and Bogduk, 1994). There is widespread acceptance that a dysfunction of the sympathetic nervous system is crucially involved in the pathogenesis of this syndrome (Baron et al., 1999). In fact, the precipitating factors may be accidental or surgical trauma, most commonly minor. In rare cases it may also develop after one of various disease states, such as myocardial or cerebral infarction (Baron et al., 1999; Riedl et al., 2001). Patients with CRPS I share a number of clinical features including continuous burning pain

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associated with allodynia, hyperalgesia and sympathetic disturbances with skin colour changes, swelling, trophic changes and loss of function (Scadding, 1999). The painful state, which seems to be disproportional to the inciting event, may be explained by central and peripheral mechanisms (Jänig and Baron, 2004).

First, tissue damage and inflammation leads to a constant drive of input from abnormally hyperactive primary afferent nociceptors resulting in central sensitization with marked allodynia. Second, supraspinal stimulation of the periaqueductal gray (PAG) by inescapable stress, e.g. pain, may induce cutaneous vasodilatation presumably by inhibiting sympathetic vasoconstrictor neurons (Zhang et al., 1997), which might enhance peripheral inflammatory processes. Third, loss of sympathetic supply provokes an increased expression of mRNAs in dorsal root ganglia coding for upregulation of α_1-adrenoreceptors in affected nociceptive afferents (Cho et al., 1997; Wasner et al., 2001). Fourth, evidence of abnormal coupling between the affected sensory afferents and the accompanying efferent sympathetic fibers within the skin or deep somatic tissues may in turn encourage the sensitized state as a framework for pain in the absence of any cutaneous stimulation and enhances allodynia as well as vaso- and sudomotor disorders (Baron et al., 1999; Jänig et al., 1996; Riedl et al., 2001).

The upper limb is twice as commonly affected as the lower one. An explanation is that upper limb nerves contain a larger number of sympathetic fibers (Schmalbruch, 1986).

Mild cases recover spontaneously or after physical therapy, while moderate cases may require analgesics such as antidepressants and/or anticonvulsants additionally. Only a minority of patients with severe chronic pain and/or sympathetic dysfunction may require long-term multidisciplinary treatment including physical therapy, analgesics, sympathetic blockade or spinal cord stimulation (SCS) (Ahmed, 2003; Sandroni et al., 2003).

Clinical experience in the treatment of CRPS I is based on a few controlled trials with limited success for tricyclic antidepressants and corticosteroids (Braus et al., 1994; Christensen et al., 1982; Kingery, 1997). Initial remarkable results reporting temporary pain relief with local sympathetic blocks were published in 1946 by Evans (1946). However, strong evidence for long-term effects of sympathetic blocks in CRPS is not yet available (Baron et al., 1999).

A promising approach in the treatment of severely disabled CRPS seems to be the use of SCS initiating a marked inhibition of sympathetic activity in affected tissue (Kumar and Nath, 1997; Stanton-Hicks, 1999). Our previous experiences with SCS demonstrated excellent clinical long-term results in those cases, where sympathetically maintained pain (SMP) could be verified (Harke et al., 2002).

In a prospective, randomized, controlled trial success rates of SCS in CRPS I patients up to 58% were reported but without any functional improvement after 6 months (Kemler et al., 2000a). We hypothesize, that functional impairment of CRPS patients, especially those with SMP, can be reduced gradually: Under long-term stimulation over a period of 12 months or longer, the expected pain relief facilitates the acceptance of consequent physiotherapy and enhances back-to-work rate.

2. Methods

2.1. Patient selection

Twenty-nine CRPS I patients with SMP were referred to our pain clinic during 1995–2001 for SCS because of ineffective pain medication and physical therapy or increasing pain that had lasted for at least >1 year.

Patients were enrolled in the study if they were older than 18 years and met the diagnostic criteria for CRPS I established by the International Association for the Study of Pain (Merskey and Bogduk, 1994).

Since there is a close correlation between initial success of sympathicolysis in CRPS and later efficacy of SCS (Kumar and Nath, 1997) a temporary positive response to sympathetic block was a prerequisite and main selection criteria for the referring physicians. Although two cases (case 2 and 4) did not meet all of these criteria, they were included because they responded excellently to sympathicolysis (Table 1).

Exclusion criteria were: untreatable coagulation disorders, current or previous neurological or personality abnormalities unrelated to CRPS I objectified by the assessment of the individual personality profile of the Minnesota multiphasic personality inventory (MMPI) (Hathaway and Mc Kinley, 1943.) Normative MMPI–T scores were considered to be 50 ± 10 for all scales except hypochondriasis and hysteria scale, which are commonly elevated in chronic pain patients at about 70.

Sixteen patients reported pain in the upper limb, 10 in the lower limb and three in the chest. Pain began soon after trauma or injury. The initiating causes were: sprain/strains in 10 patients, surgery in nine, fracture in five, crush injuries in four and a neurological disease in one patient. All patients showed signs of sympathetic dysfunction including edema, sudomotor and/or vasomotor disturbances, atrophic changes as well as motor weakness and sensitivity to cold. The baseline characteristics of the patients are summarized in Table 1.

In accordance with the declaration of Helsinki, the objectives of the study were explained, and all patients gave their informed consent. The study was approved by the Ethical Committee of the Medical Association of Nordrhein, Düsseldorf, Germany.

Table 1
Baseline characteristics of 29 complex regional pain syndrome I (CRPS I) patients

Personal data			Cause of CRPS I	Disability degree	Duration (year)	Pain character		Concomit. symptoms		Sympathetic blockade > 8 h		
ID	Age (year)	Gender	Trauma – location			Deep pain (VAS) baseline	Allodynia (VAS) baseline	Edema	Affected area (°C)	Method	Deep pain (VAS)	Allodynia (VAS)
1	54	m	Severe shoulder trauma, r	++	2	9	10	+		1	0	0
2	28	f	spine fracture T2, l	++	4	9	0			1	0	0
3	66	f	Leg trauma after knee arthroplasty, l	++	11	8	0			2	2	0
4	40	m	Sternum fracture, l	++	24	10	10	+		1	0	0
5	77	f	Stroke, hemiparesis (hand)	++	4	10	0	+		1	0	0
6	52	f	Fract. of os naviculare, arthrodesis, r, l	++	1	10	10	+	29.8	n.r.	n.r.	n.r.
7	86	m	Repeated knee operation (OP)	++	2	10	10	+		2	5	0
8	50	f	Bagatelle trauma (hand), r	++	2	10	8	+		1	1	0
9	40	f	Hand distortion, r	+	13	10	10	+	32.1	1	0	0
10	79	m	OP CTS, l	++	1	7	7	+		3	0	0
11	42	m	Contusion of lower leg, r	++	3	10	10	+	28.8	2	5	0
12	56	m	toe fracture, l	++	5	10	10	+	31.7	2	4	0
13	27	f	Tendon avulsion D4, D5, r	+	2	10	10	+	29.0	1	5	0
14	48	f	Bagatelle trauma elbow joint, l	++	3	10	10	+	33.3	n.r.	n.r.	n.r.
15	39	f	Clavicula fracture, plexus lesion r	++	4	10	10	+	33.1	1	2	0
16	46	f	Tendovaginitis (hand), r	++	18	10	10	+	31.7	1	5	0
17	50	m	Fibula fracture, r	++	18	10	10	+		2	4	0
18	33	f	Tendon rupture hand, repeated OP, r	++	1	10	8	+		1	1	0
19	42	f	Tendon rupture D5, r	++	3	10	10	+	26.0	1	0	0
20	39	f	Bagatelle trauma hand, l	++	5	10	10	+	29.0	3	2	0
21	52	m	Bruising of middle finger, r	++	1	10	10	+	31.3	1	0	0
22	41	f	Upper arm fracture, repeated OP, l	++	2	6	0			1	0	0
23	39	f	OP discus triangularis, r	++	2	9	10	+	27.0	1	0	0
24	44	f	Distortion hand, l	++	1	10	10	+	31.0	1	0	0
25	74	m	Leg trauma after knee arthroplasty, r	+	7	10	0	+	32.1	3	2	0
26	50	m	OP for gout tophi (knee), r, l	++	10	8	0	+		2	0	0
27	47	m	OP cervical spine C6/7, r	++	2	8	5	+	31.4	1	1	0
28	61	m	OP following hematoma upper leg, l	++	3	8	0			2	0	0
29	42	m	rupture of talocalcanean ligament, r	++	3	10	10	+	28.7	2	2	0
Mean	49.7				5.4	9.4	7.2		30.38		1.5	0.0
SD	15				6	1	4		2.1		2	0
Median	47				3	10	10		31.1		0	0
Q25	40.1				2.0	9.0	5.0		29		0.0	0.0
Q75	53.5				5.0	10.0	10.0		31.8		2.0	0.0

m, male; f, female; r, right; l, left.
n.r., not registered.
Sympathetic nerve block: 1, stellate ganglion; 2, lumbar chain; 3, guanethidine.

2.2. Diagnostic sympathetic blockage

Before SCS-implantation all patients underwent selective sympathetic block procedures once again.

The responsiveness to selective sympathetic nerve block was confirmed in 24 patients by local injection of lidocaine 1%, 10 ml for the stellate ganglion (via catheter) or 5 ml for the lumbar chain (L1–L2) ganglion (via 25 G needle). All blocks were placebo-controlled by injection of sodium chloride solution in the same session: after an unchanged temperature pattern and recording the amount of partial pain relief (approximately 30 min after injection of saline), another 10 or 5 ml of lidocaine 1% were injected, respectively (Price et al., 1998). For the three chest pain patients, spreading of local anesthetic solution to upper thoracic levels was proven by contrast solution imaging.

Intravenous regional block with guanethidine, reducing noradrenaline concentration in the post-ganglionic axon, was used in three patients in a dosage of 0.05–0.1 mg/kg BW again without placebo injection. In two cases the procedure was not documented. Sympathetic block was classified as complete when the skin surface temperature – in average 30.4 °C – exceeded 34 °C (Baron et al., 2002; Malmqvist et al., 1992; Treede et al., 1992) and the patients' visual analogue scale (VAS) rating showed a nearly complete decrease for more than 8 h (Maier and Gleim, 1998; Price et al., 1998). Temperature elevations were measured simultaneously in the affected zones and the contralateral parts using an infra-red thermometer (Thermo-Hunter PT-3S, Opted Kyoto, Japan).

2.3. Assessment of pain and functional impairment

All patients underwent identical pain and sensory assessment. The overall pain intensity was recorded by the patients in a diary four times a day, using a VAS ranging between 0 (no pain) and 10 cm (unbearable pain). The VAS was carefully introduced and clearly explained to the patients in order to achieve the most realistic data.

The sensory function was rated by focal tactile stimulation while dynamic mechanical allodynia was determined with a foam paintbrush by striking from normal skin toward the painful area. The diagnosis and each follow-up examination were confirmed by neurologists as an independent third party.

Patients' functional impairment was rated by applying the pain disability index (PDI), using scores between 0 (no disability) and 10 (total disability) to objectify the interfering influences on family activities, recreation, social activities, occupation, sexual behavior, self-care and life support activity (Tait et al., 1990).

The functional status of the upper limbs was examined by using a hand-held vigorimeter (Martin GmbH, Tuttlingen, Germany) in order to measure grip strength of both hands simultaneously; normal values 0.8–1.3 kg weight. The criteria for the functional status of the lower limb was assessed as the patients' ability to walk without crutches.

Furthermore, the consumption of strong and weak opioids, peripheral analgesics and antidepressants was recorded in the patients' diaries.

2.4. Implantation of the SCS system

The implantation of the SCS devices was performed in a two stage procedure under in-patient conditions until the end of wound healing. The first stage involved the percutaneous placement of a quadripolar lead into the epidural space (Medtronic, Model 3487 A) using a paraspinous needle insertion. Paresthesias topographically related to the affected region were elicitated with alternating electrical fields between the four electrode contacts. For the cervical spine, we preferred a lateral electrode position for dorsal root stimulation (generally C4–C6), while for the lumbar segments dorsal column stimulation was achieved with a medial electrode position (generally Th9 - Th12), X-ray controlled. To obtain a complete coverage of shoulder, arm and hand, a lateral placement was preferred because the affected low threshold dorsal roots and root entry zones could be precisely stimulated with low power. In contrast, a midline electrode placed in the cervical or thoracic area provided paresthesia predominantly in distal areas such as legs or feet and would require a higher output (Barolat, 1995). Therefore, in the cervical spine the lateralization is more comfortable, effective and without undesirable paresthesiae. The final positioning for optimal paresthesia coverage was realized by the individual patient's response rather than by topographical landmarks. The lead was secured surgically by anchoring it to the supraspinous ligament and exteriorising the system to a temporary transmitter (Medtronic Screener 3625, Medtronic Minneapolis, MN) for a 5–7 day trial stimulation period. If necessary, the electrode position was corrected in a second attempt.

Following successful trial stimulation, the second stage required connecting the extension lead to the pulse generator, pocketed subcutaneously in the abdominal wall. All patients were supplied with Medtronic ITREL II or III devices (Medtronic, Minneapolis, MN) for ongoing stimulation. According to the patients' response, the following stimulation ranges were used: pulse width 50–450 ms, frequency 50–130 Hz, current 1–6 V. Continuous stimulation with cycling modes −15 s on and 15 s off, 24 h per day – as well as lowest possible parameter settings were used thus allowing prolonged battery life for the programable pulse generators.

2.5. Data collection and follow-up

Assessments were performed one week before and during hospitalization as well every 3 months after implantation of the SCS devices. All patients were asked to score pain intensity four times a day over a period of seven days prior to each check-up using a VAS. Mean VAS values as well allodynia, PDI scores, functional status of the limbs and complications were objectified and documented in the study protocol at the day of follow-up examination. In the majority of patients, the last follow-up was done after a mean period of 35.6 ± 21 months.

To assess the efficacy of treatment, SCS inactivation tests were performed every 3 months during the whole observation period as well. The patients switched off the devices after 30 min of acclimatization in a temperature controlled room between 21 and 23 °C to exclude temperature induced sympathetic vasoconstriction on pain (Wasner et al., 2001). The reactivation of SCS was allowed after 45 min. Surface temperature of both corresponding limbs was measured immediately before and after the inactivation test.

Physical therapy, administered daily for 30 min at home, consisted of a standardized program of graded exercises designed to improve the strength, mobility and function of the affected hand, leg or foot. In addition, all patients with disabilities of the upper extremities used a foam plastic ball for continued training of the hand.

There were seven categories of outcome measures: pain intensity, allodynia, PDI, drug consumption, functional status of the limbs, back-to-work rate, technically status of the devices including the accurate placement of the lead.

Statistical analysis was performed using SPSS for Windows software. For the clinical outcome measures – except drug consumption – the mean values before treatment, at 12 months and at last follow-up were calculated and compared using the paired samples Wilcoxon test. Differences in drug therapy were analyzed by χ^2 test. Two-tailed $p < 0.05$ was regarded as significant. Spearman's correlation coefficient by rank was calculated to determine associations between all outcome variables.

3. Results

The 29 patients enrolled in the study experienced ongoing pain for a median of 3 years (quartiles 2.0–5.0 years) after fractures, operations or trauma. All patients except two, who were regarded as CRPS-like syndrome, showed typical symptoms of CRPS I according to the IASP criteria. A median pain intensity level of 10.0 VAS (quartiles 9–10 VAS) was reported by these patients. The quality of pain was described as unbearable, burning or as a deep ache. In addition, allodynia was diagnosed in 22 patients with median VAS ratings of 10.0 (quartiles 5–10) as well. All patients had functional impairment of limbs that made them unable to work. The patients did not show abnormalities in clinical MMPI scales except of slightly elevated hypochondriasis and hysteria scales (T-values HY 65; HS 69) on average, which are typical for chronic pain patients (Table 1).

Analysis of preceeding therapy showed medications with strong opiods in ten, weak opioids in eight, antidepressants in one, peripheral analgesics or no medication in five cases. The medications had been taken up to five years (quartiles 2–5 years) on an as-needed basis. Many of these patients were reluctant to adopt a systematic time–contingent medication schedule and preferred an invasive approach.

On sympathicolytic interventions, pain and allodynia decreased temporarily in contrast to placebo from 10 to 0 (quartiles 0–2) VAS for more than 8 h. Block induced pain reduction was accompanied by objective signs of sympathicolysis, i.e. an increase of skin temperature over 34 °C so that the pain characteristic could be confirmed as sympathetically maintained (Table 1).

Immediately after the beginning of SCS treatment, an optimal paresthesia coverage of the entire painful area was achieved, so that deep burning pain and allodynia could be permanently reduced from 10 to 2 (quartiles 0–3) and 10 to 0 VAS, respectively, during the test phase ($p < 0.01$) (Fig. 1). No patient discontinued the trial and all received permanent SCS devices. Since the results at 3, 6 and 9 months were similar to those at 12 months, only the results at 12 months were considered: Under continuous SCS the patients were permanently pain free (Table 2, Fig. 1).

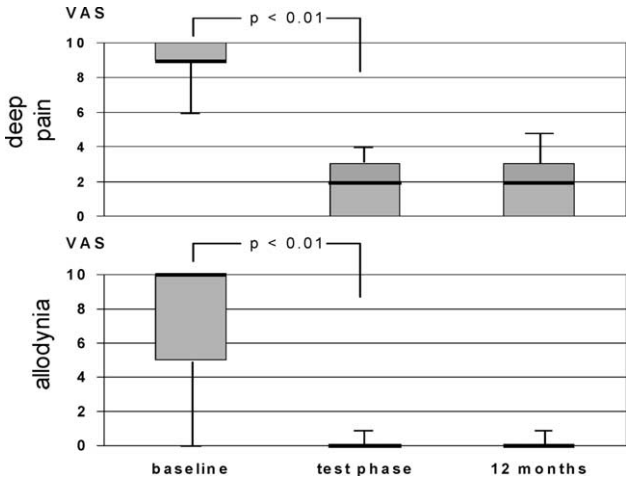

Fig. 1. Pain character and intensity (VAS) in 29 patients with complex regional pain syndrome type I (CRPS I) at baseline and on spinal cord stimulation (SCS) during a follow-up period of 12 months. The temporary pain increase during the inactivation test is not presented in the diagram.

Table 2
Response to SCS treatment in 29 complex regional pain syndrome I (CRPS I) patients

Personal data	Outcome at 12 months		Response during the SCS inactivation test			SCS outcome at a mean follow-up of 35.6 ± 21 months				Maintenance of SCS devices		
ID	Deep pain (VAS)	Allodynia (VAS)	Deep pain (VAS)	Allodynia (VAS)	Skin temp. affected vs. unaffected area (°C)	Stimulation period (mo)	Deep pain (VAS) last follow up	Allodynia (VAS) last follow up	Back-to-work	Frequency of generator exchange	Lead replacement	Explantation
1	2	0				96	2	0	no	1		+
2	0	0				85	2	0	yes			
3	0	0				69	0	0	(yes)			
4	2	0	10	0	(Both sides affected)	65	2	0	yes			
5[a]	4	0				30	4	0	no			
6	1	0	8	0	0	38	4	0	no			
7[a]	2	0				36	3	0	(yes)	1		
8[a]	4	0				36	3	0	yes			
9	3	0	2	8	−0.1	34	2	0	yes			
10[a]	5	0	7	7	n.r.	20	3	0	no			
11	4	0	8	8	0	26	4	0	no	2		
12	3	0	6	0	2.2	50	2	0	(yes)	3	3	
13	0	0	8	8	2.2	13	0	0	yes			
14	1	0	7	0	1	17	3	0	yes			
15	2	0	6	0	1.9	42	2	0	yes	2	3	
16	2	0	8	8	0.1	39	5	0	yes			
17	3	0				50	2	0	(yes)	3	2	
18	0	0				12	0	0	(yes)			+
19	3	1	10	10	2.5	37	2	0	yes	1	1	
20	3	0	10	10	4	35	5	0	no	1		
21	0	0	4	0	2.1	34	0	0	yes		1	
22	2	0				17	3	0	yes			
23	0	0	10	10	4.1	30	0	0	no			
24	2	0	3	0	1.1	23	2	0	no			
25	2	0	8	0	0.2	20	4	0	(yes)	2	2	
26	0	0				18	0	0	yes			
27	0	0	8	0	0.9	20	0	0	yes			
28	0	0				12	0	0	no			
29	0	0	4	0	1.4	25	2	0	yes			
Mean	1.7	0.03	7.1	4.0	1.5	35.6	2.1	0.0				
SD	1.5	0.18	2	4	1.3	21	2	0				
Median	2	0	8	0	1	34	2	0				
Q25	0	0	6.0	0.0	0.2	20.0	0.0	0.0				
Q75	3	0	8.0	8.0	2.2	38.6	3.0	0.0				

n.r., not registered; (yes), homework.
[a] Non-survivor.

Severe impairments and strong functional limitations in daily living activities of more than 60–90% were significantly reduced, indicated by decreasing PDI scores of more than 50% ($p < 0.01$) (Fig. 2). During the inactivation tests, a painful state of 8 VAS (quartiles 6.0–8.0) occurred within a period of 45 min. Due to the increasing pain intensity the spinal cord stimulator was reactivated immediately at the end of the test period. Furthermore, after acclimatization for 30 min in warm environment and during SCS treatment, the mean skin temperature in the affected areas was initially 0.38 °C higher than the contralateral side. However, 45 min after SCS inactivation, the affected zones showed a mean skin temperature decline of 1.5 °C, compared to the contralateral areas (Table 2).The temperature decline was always combined with a livid discoloration of the extremity.

During a mean follow-up period of 35.6 ± 21 months a long-term pain relief was observed under continuous SCS; the patients still reported a median level of 2.0 (quartiles 0–3.0) VAS for deep pain whereas allodynia was completely abolished (Table 2). At the same time, 12 of 16 patients (75%) with impaired hand and finger function regained the ability to almost normal movements. The significantly increased grip strength reached nearly 50% of the normal values ($p < 0.01$) (Fig. 3). Eight of ten patients (80%) with an affected leg resumed walking without crutches. Altogether, a back-to-work rate of 70% could be observed (Table 2).

According to Spearman's rank correlation, the severity of pain significantly correlated with the grade of disability assigned on PDI ($r = 0.601$; $p = 0.005$). The increase in grip strength significantly correlated with the back-to-work rate ($r = 0.672$; $p = 0.017$).

As a result of the overall improvement, previously used pain medications could be significantly reduced

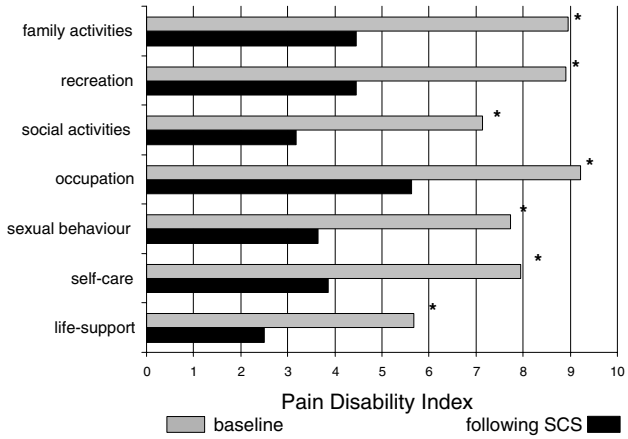

Fig. 2. Pain disability index (PDI) in 29 patients with complex regional pain syndrome type I (CRPS I) at baseline and on spinal cord stimulation (SCS) during a follow-up period of 12 months ($^{*}p < 0.01$).

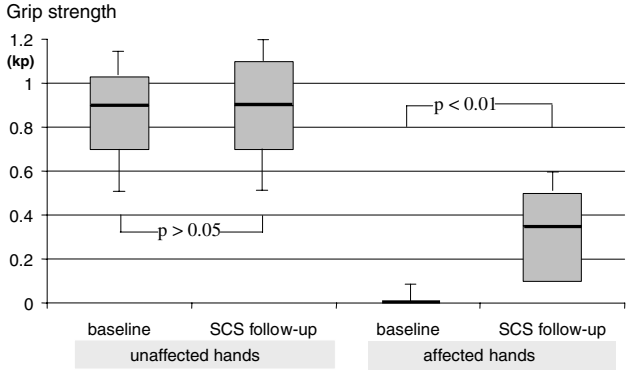

Fig. 3. Grip strength of both hands in 12 patients with complex regional pain syndrome type I (CRPS I) presenting hand and finger disorders at baseline and on spinal cord stimulation (SCS) after a mean follow-up period of 35.6 months. Median and 25–75th quartiles.

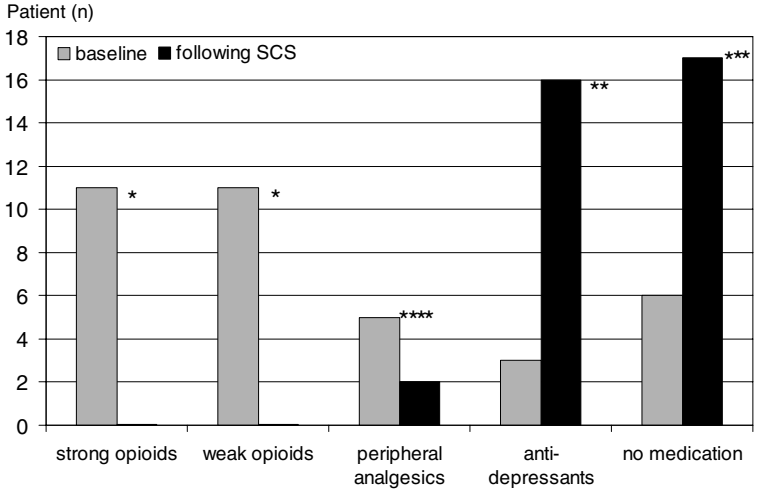

Fig. 4. Analgesic and other drug consumption in 29 patients with complex regional pain syndrome type I (CRPS I) at baseline and on spinal cord stimulation (SCS) during a follow-up period of 12 months ($^{*}p = 0.0018$; $^{**}p = 0.0077$; $^{***}p = 0.0035$; $^{****}p = 0.0063$).

or completely cancelled: prescription of opioid analgesics was no longer necessary. Seventeen of twenty-nine patients did not require any pain medication during SCS therapy. Low dose tricyclic antidepressants seemed to be the appropriate comedication in 16 cases to optimize activities of daily living (Fig. 4). In two cases spontaneous improvement occurred. Four patients died of different diseases after more than 12 months of follow-up (Table 2).

The generator unit was exchanged in 16 patients because of battery exhaustion after more different time intervals (Table 2) depending on stimulation characteristics. In 12 cases, the paresthesia coverage of the painful areas was unsatisfactory requiring surgical revision of the lead.

The average costs for each implantation procedure including hospital charges for 12 d/patient were 11.844,59€. Average aftercare costs including follow-up, correction of lead dislocation, device reimplantation and hospitalization make a total of 1.335,23€/patient/year. Thus, the cumulative costs/patient after a three year treatment period were 15.850,58€ or 18.230$/patient.

4. Discussion

Previous observations showed success rates of 70–100% in terms of pain reduction following SCS in CRPS I patients (Kumar and Nath, 1997; Stanton-Hicks, 1999). Functional improvement could not be proved in a randomized trial after 6 months (Kemler et al., 2000a).

Our study was restricted to CRPS I patients with extraordinary high pain intensity and severe functional impairment in an advanced stage of the disease refractory to conventional treatment for at least one year.

Since long-term effects of sympathetic block series regained an improvement in about 90% of CRPS I patients, this response could be considered as a predictor for successful SCS treatment (Kumar et al. 1997; Wang et al., 1985). As in all our cases the temperature increase of about 3 °C confirmed the onset of sympathetic block and pain relief thereafter persisted longer than the expected duration of local anaesthetics, the diagnosis of SMP could be confirmed (Maier and Gleim, 1998; Price et al., 1998).

Several lines of clinical evidence support the hypothesis that SMP is associated with abnormal sympathetic function. Normally, peripheral nerves accompanied by sympathetic nerves are bathed in a solution of norepinephrine under sympathetic activity (Bonica, 1990). In contrast, long-standing CRPS I is associated with a loss of sympathetic noradrenergic outflow, which leads to denervation supersensitivity (Drummond, 2001): Large-diameter mechanoreceptors, nociceptors and sensory afferents acquire an adrenergic responsiveness in association with an increased mRNA expression of α_1-adrenoreceptors on sensory and autonomic fibers (Wasner et al., 2001). Therefore the density of adrenoreceptors is higher in CRPS I patients than in controls (Birklein and Handwerker, 2001; Drummond, 2001). Although reduced venous concentrations of noradrenaline are proven, the vasculature develops an increased vasoconstrictor activity: Traces of noradrenaline or local cold temperature stimuli may lead to an impairment of nutritive-capillary blood flow. Hypoxia and acidosis will develop so that protons, the most important nociceptor stimulants, cause an increase of pain (Birklein and Handwerker, 2001). Injection of smallest amounts of norepinephrine into the skin rekindles hyperalgesia in patients with SMP rendered pain-free by sympathetic block (Ali et al., 2000; Torebjork et al., 1995). The mentioned vasomotor disturbances should be discussed in all of our patients.

The autonomic nervous dysfunction might respond favorably to SCS in CRPS patients with SMP, whenever there is abnormal sympathetic function with disturbed circulation (Harke et al., 2001; Kumar et al. 1997): The dominating mechanisms are most likely suppression of cutaneous sympathetic vasoconstrictor activity exerted mainly via the α_1-adrenoreceptors as well as an antidromic vasodilatation mediated by a calcitonin gene-related peptide release by peripheral terminals (Linderoth et al., 1994). Thus, SCS may counteract these autonomic disturbances, normalize the impaired microcirculation and effectively abolish both continuous and evoked pain (Meyerson and Linderoth, 2000).

The effect of SCS on efferent vasomotor activity could be indirectly demonstrated in our patients after acclimatization in warm environment. During the SCS inactivation test the skin temperature declined to an average of 1.5 °C on the affected side. However, vasoconstriction and reduced blood flow objectified by cold limbs could be reversed by continuing SCS.

In contrast, in CRPS patients with sympathetically independent pain, sympathetic inhibition by SCS has no significant influence on the microcirculation (Kemler et al., 2000b). In these patients, pain relief is not associated with an improvement of microcirculation. In consequence further mechanisms underlying pain alleviation with SCS in CRPS patients still remain to be discussed. Several neurophysiologic mechanisms have been proposed, for example: inhibitory effects on central sympathetic systems as well as an activation of descending inhibitory pathways by supraspinal orthodromic SCS stimulation of the PAG (Roberts and Rees, 1994; Stiller and Linderoth, 1995). Additionally, microdialysis studies demonstrated that the release of γ-amino butyric acid (GABA) by SCS may actually inhibit the release of excitatory amino acids in the dorsal horn, thus suppressing neuronal pain transmission and sympathetic outflow (Linderoth and Foreman, 1999). Moreover, GABA

inhibits the motor neurons of the spinal cord so that continuous stimulation may decrease the dystonic posturing of arms, hands and legs and support the reestablishment of the functional status in the majority of patients (van Hilten, 2000). The amelioration of spasticity with SCS may be attributed to enhancement of glycine release, thus inhibiting γ-motor neurons and tonicity (Simpson et al., 1991).

The significant improvement of the functional status after a pain history of 3 years in 12 of 16 patients with affected hands and a back-to-work rate of overall 70% is impressive compared to published epidemiological data: According to the data base established by the Reflex Sympathetic Dystrophy Syndrome Association of America in 1997, 58% of 789 RSD long-term sufferers are unable to work and 17% have had to change their jobs (Schaffer, 1997).

The favorable results achieved in our study may be explained by restricting the SCS treatment to those patients responsive to sympathetic blocks. In addition, careful management during the test phase with the goal of an accurate lead positioning, may have added to optimize the outcome. In contrast to other investigators, who used a percutaneous temporary bipolar lead, we achieved a better performance by using quadripolar leads (Kemler et al., 2000a). These leads, allowing optimal combinations of contacts, have been found most effective for best paresthesia coverage and pain relief compared to percutaneous test electrodes with two contacts only (North and Guarino, 1999). As far as reliability and/or durability is concerned, quadripolar leads may promise higher position stability in the epidural space and accuracy of paresthesia allocation. As a consequence of the complete coverage of the affected areas with one quadripolar lead, the use of octopolar or double quadripolar electrodes seemed to be unnecessary. Revisions to improve paresthesia coverage could be promptly performed under in-patient treatment conditions in contrast to a home-testing practice done in other studies. In our trial, lead revisions due to unsatisfactory pain relief were necessary in four cases/year.In comparison to other clinical reports, our patients exemplified an optimal behavior with a low complication rate of 14%/year (Kemler et al., 2000a). The lack of relevant complications, i.e. wound infections, may be a consequence of our in-patient treatment. In addition, the fact that our technique with permanent leads prevents a second puncture of the epidural space may represents an advantage in contrast to the temporary leads which must be removed and replaced by permanent electrodes in a second intervention.

In cases of cervical stimulation a lateral electrode position enables the stimulation of low threshold root fibers with a low output voltage, so that extraordinary long physical life of the batteries was possible (Barolat, 1995). Continuous stimulation with cyclicing mode is an energy-saving technology. Battery longevity up to 85 months was observed in our study. The cumulative costs per patient are comparable with those reported elsewhere (Kemler and Furnée, 2002).

Since pain per se seems to be the most terrible and disabling disorder (Geertzen et al., 1998), pain relief by SCS may be an important prerequisite for performing a standardized physiotherapy regimen – offered regularly to in all our patients. Undoubtedly, physiotherapy was facilitated by SCS and may contribute to reduce the central sensorimotor mismatch in these patients (Moseley, 2004). Furthermore, there is clinical evidence that remobilization of the limbs can reverse CRPS-like abnormalities (Guo et al., 2004). This effect could not be achieved after 6 or 12 months but after a mean follow-up of 35 months. Finally, after complete recovery from limb immobility, SCS devices could be even removed in two cases.

However, there are interesting novel hypotheses that SCS may have an impact on the cortical network: Based on the idea of a sensorimotor mismatch in CRPS patients, published by Moseley (2004), we assume that the activation of supraspinal circuits by SCS may correct sensory disturbances of central origin (Roberts and Rees, 1986; Stiller and Linderoth, 1995). It can be observed that the pain relieving effect by dorsal column stimulation depends on a complete paresthesia coverage of the affected central area, and it can be assumed that the cortical network involving the affected sensory and motor representation is continuously modulated and may also abolish or decrease pain, motor changes and autonomic changes.

The absence of placebo control normally leads to an overestimation of the treatment results because the proportion of the placebo response would not be estimated objectively. Unfortunately, in the present trial an optimal study design was not easy to apply for some ethical reasons. Our patients were afraid of unbearable pain and were not ready – after having passed almost every non-invasive therapeutic option – to be part of a control group. To compensate for the weakness of the study design, we employed measurable functional criteria in addition to the subjective pain intensity. Insofar, the significant functional improvement may represent an objective sign for the beneficial effect of SCS treatment.

In fact, the beneficial results achieved on SCS cannot be attributed to a placebo effect or spontaneous improvement for two reasons: First, before SCS treatment, all patients suffered from a progressive course of CRPS I for many years, which was refractory to pharmacological pain medication. Furthermore, all patients had a long-term response to SCS that was ultimately stable. Second, the efficacy of SCS was controlled by applying the inactivation tests, thus comparing the patients' condition during stimulation-free intervals with that of SCS treatment. All patients experienced pain elevation

up to 8 VAS within a period of 45 min (Linderoth and Foreman, 1999; Linderoth et al., 1994). No patient wanted to prolong the stimulation break on his own free will. With the definition of the inactivation test interval, we referred to one of our previous studies, where neuropathic pain candidates tolerated a mean stimulation break of 145 min. It is remarkable, that, under different instructions, the same patients tolerated a mean switch-off time of 44 h, but with impairments (Harke et al., 2001). The high convenience of SCS seems to be based on the reliable protection against pain so that the patients themselves preferred in such a difficult-to-treat condition continuous stimulation.

5. Conclusions

We emphasize that our results are only valid for CRPS patient with SMP. Our assumption that long-term SCS combined with adequate physiotherapy may restore functional impairment, could be confirmed in patients with long history of disease and extraordinary degree of impairment. The highly impaired psychosocial and professional activities were frequently restored to a high degree (>50%) associated with significantly less drug consumption, thus optimizing the life quality of emotionally distressed chronic pain patients.

However, controlled studies are still necessary to prove long-term SCS combined with a standardized physical therapy program in highly impaired CRPS patients.

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