NEUROAUGMENTATION IN THE TREATMENT OF COMPLEX REGIONAL PAIN SYNDROME OF THE UPPER EXTREMITY

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The authors report their results on 36 patients with advanced stages of complex regional pain syndrome. They were treated with either spinal cord stimulation, or peripheral nerve stimulation, and in some cases with both modalities. Thirty six months after implantation the reported pain measured on visual analogue scales was an average of 53% better, this change was statistically significant. Analgesic consumption decreased by about 50% or was reportedly more effective. The authors conclude that in late stages of complex regional pain syndrome, neuroaugmentation is a reasonable option when alternative therapies have failed.

Keywords : neuroaugmentation ; spinal cord stimulation ; peripheral nerve stimulation ; pain ; complex regional pain syndrome.
Mots clés : neuroaugmentation ; stimulation de la moelle épinière ; stimulation nerveuse périphérique ; douleur ; syndrome complexe régional douloureux.

INTRODUCTION

Injuries to the upper extremities often lead to painful syndromes characterized by burning pain, allodynia, and hyperalgesia (28). These symptoms are sometimes mediated by the sympathetic nervous system. The term "Reflex Sympathetic Dystrophy" (RSD) has been traditionally applied to describe this condition (4). The International Association for the Study of Pain introduced the term "Complex Regional Pain Syndrome" (CRPS) in an attempt to provide a common taxonomy and nomenclature in the classification of these syndromes (Table I). The entity was further subdivided into CRPS Type 1 to replace "Reflex Sympathetic Dystrophy" (RSD), and CRPS Type 2 corresponding to causalgia (22).

CRPS can occur after a variety of conditions such as : automated laser discectomy (27), fractures (5), electrical burns (29), nerve injuries (28), and a variety of other causes (26).

The management of pain in these patients is controversial and usually represents a dilemma. Both spinal cord stimulation (1) and peripheral nerve stimulation (29) have been reported to be of benefit in CRPS. We are reporting longitudinal pain ratings in a group of patients in advanced stages of CRPS that were managed with either spinal cord stimulation (SCS) and/or peripheral nerve stimulation (PNS).

MATERIALS AND METHODS

Patients

Thirty-six patients were included in this report. Twenty-eight were females (77.78%) ranging in age from 20 to 61 years, and 8 were males (22.22%) ranging in age from 23 to 55 years (Table II). Patients were referred to the Center for Pain Medicine with a presumptive diagnosis of CRPS of either upper extremity. History and physical examination revealed that the signs and symptoms had been present for at least two years in all cases (range from two to three years). Each patient was asked to rate his/her pain prior to implantation, and then every three months for 36 months. The mean score was 8.19 in the female group and 8.24 in males (Table II). All patients had received multiple

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Table I. — Complex Regional Pain Syndrome

Type 1 (RSD)	Type 2 (Causalgia)
Not limited to the distribution of a nerve	In the distribution of a nerve
Burning pain	Burning pain
Allodynia	Allodynia
Hyperesthesia	Hyperpathia
Pain may be sympathetically maintained	Pain may be sympathetically maintained

Table II. — Patient Data

Females 28 (77.8%)	Males 8 (22.2%)
Mean Age 51.4 years	Mean age 42.5 years
(range 20-61 years)	(range 22-55 years)
Mean VAS score 8.2 (SD 1.1)	Mean VAS score 8.2 (SD 0.74)

treatments such as psychiatric and psychological support, physical therapy, stellate ganglion blockade, sympatholytics, tricyclic antidepressants, calcium channel blockers, and narcotic analgesics.

Inclusion Criteria

As indicated in table III, in this study we included patients with objective basis for pain. They were considered for inclusion if they had pain localized to one upper extremity, if alternative therapies to relieve the pain had failed. If stellate ganglion blockade at C7 failed to provided pain relief, the patient was included in the study. Patients were screened psychologically, and only those without drug habituation and abnormal psychological profiles were selected for implantation.

Table III. — Inclusion Criteria

Pain localized to one upper extremity
There is objective basis for pain
Alternative therapies have failed
Failure of sympathectomy to provide long term pain relief
Psychological clearance
No drug habituation

Preimplantation Work-up

Patients were subjected to a complete history and physical examination. It became evident that patients had cold and mechanical allodynia, hyperesthesia, hyperalgesia, burning pain, atrophic skin, and sudomotor changes. Thermography with liquid crystal technology was used to measure temperature changes prior to and after implantation.

Implantation Data

In 24 patients spinal cord stimulators (SCS) were implanted, 7 patients received both SCS and peripheral nerve stimulators (PNS) (SCS-PNS), and 5 PNS only (Table IV).

Table IV. — Implantation Data

Females	Males
SCS only n = 18	SCS only n = 6
SCS and PNS n = 6	SCS and PNS n = 1
PNS only n = 4	PNS only n = 1

Stimulation trial

Under local anesthesia and intravenous sedation, strict sterile technique and fluoroscopic guidance, the epidural space was entered with a modified Touhy needle. A stimulating lead (Piscis II Medtronics) was advanced in the vicinity of the cervical spinal cord. The cervical spinal cord was stimulated electrically. When paresthesiae covered the painful area and the patient reported some degree of pain relief, the electrode was stitched to the skin and connected to an external pulse generator. The patient was discharged home after a 24 hour hospital stay. On the fifth to seventh day, the electrode was removed. Patients were given antibiotics for the duration of the trial and five days thereafter.

Patients reporting 50% or greater pain relief during the trial period had stimulators surgically implanted. This was achieved under local anesthesia and IV sedation four weeks later applying the trial parameters.

Seven patients with SCS were additionally implanted with peripheral nerve stimulators, three at the median nerve, one at the radial nerve, and three at the ulnar nerve (see reference 29 for details of surgical implantation). The electrode was attached to an external impulse generator. Patients underwent a trial of stimulation for five to seven days, and if further pain relief was reported, the internal pulse generator was permanently implanted.

In five patients, only peripheral nerve stimulators were implanted, three of them at the median nerve, one at the ulnar nerve, and one at the radial nerve. The technique has been described above (Table IV).

Statistical Analysis

In order to test the statistical significance of our data, we conducted three repeated analyses of variance. For each one of the three groups in our study, we compared the VAS (visual analog scale) prior to implantation and 36 months later.

RESULTS

Stellate ganglion blockade produced pain relief (mean VAS post block 6.61) in 16 patients (38.9%). Evidence of sympathetic blockade was obtained by temperature elevation, decreased sweating, and vasodilatation, the duration of pain relief varied from four hours to three days. Immediately after the permanent system was implanted, the patients with PNS only, reported 75.7% pain relief, the patients with SCS only, reported 63.5% reduction in their pain and the patients with both SCS and PNS reported 78.1% pain relief (fig. 1).

Our data analysis indicated that 35 months after implantation, patients in the SCS group reported the pain was about 45.3% better, this was statistically significant ($F = 334.94$, $df = 7/161$, $p < .0001$), in the PNS group the pain level was about 51.3% better ($F = 187.29$, $df = 7/42$, $p < .0001$), and the SCS-PNS group reported 63.5% pain reduction ($F = 225.44$, $df = 7/28$, $p < .0001$). There was no apparent difference in the mean VAS for the three groups prior to implantation ($F = .02$, $df = .44/14$, $p < .97$) or at 36 months ($F = 1.49$, $df = .18/6$, $p < .24$).

Two patients developed infection at the generator implant site on the anterior chest wall; despite aggressive antibiotic therapy, the infection persisted and the generators were removed. Another patient developed a psychosis, therefore the SCS was removed. Two patients with SCS were re-operated on because of electrode migration and increase in pain level, adequate pain relief was reported postoperatively.

Narcotic intake decreased by about 50% in 44.4% of the patients. In the rest, we did not observe a significant reduction in analgesic consumption; however, the analgesic was about 80% more effective in relieving pain.

Quality of life has improved as reported by most patients, 41% of patients have returned to work on a modified duty.

DISCUSSION

Patients with CRPS referred to pain centers for evaluation and treatment often are in advanced stages of the disease. There is no consensus on the ideal treatment of these patients, the management being rather controversial. For this reason, they present a significant therapeutic challenge. A reasonable approach to this problem is from a multi-disciplinary point of view, involving behavioral medicine, physical therapy modalities, and the participation of the pain medicine specialist to perform invasive procedures.

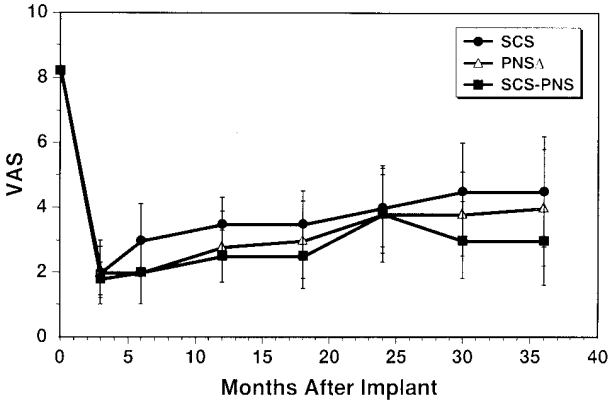

Fig. 1. — Visual analogue scores (VAS) after implantation in all patients in the study. We compared patients with SCS (•) SCS + PNS (■), and PNS (△) before implantation and 36 months after. VAS decreased an average of 78% immediately after implant. At 36 months the average VAS was 53% better with respect to preimplant values. This change in VAS is statistically significant in the three groups (see text for statistical analysis).

CRPS is a disorder of the upper or lower extremities that may develop after a number of initiating events (26). It is characterized by burning pain, allodynia, hyperesthesia, hyperpathia, and motor disorders (4). Also, the syndrome usually consists of vasomotor changes, suggestive of sympathetic nervous system involvement. It had been traditionally assumed that the pain in this syndrome was maintained by the sympathetic nervous system (4). It has become evident that, in a large number of patients, sympathetic maintained pain cannot be demonstrated (33). This observation is supported by the fact that in the series being reported here, stellate ganglion block resulted in pain relief only in about 40% of patients. This could be related to the fact that the patients in our study had been treated for a long time with stellate ganglion blocks, surgical sympathectomy, and sympatholytics. It is possible that, in early stages of CRPS, sympathectomy could yield a higher number of patients obtaining pain relief.

The response to either SCS or PNS is dramatic in the immediate post implant period (Fig. 1), the pain level in our observations decreased by about 76%. Thirty-six months after implantation the VAS score is greater, though statistically significant in all patients regardless of the type of implant. In cases of low back and lower extremity pain treated with neuroaugmentation, it has been reported that five years after implantation, only about 47% of patients continue to benefit from the procedure (24). It is possible that the patients in our series, with SCS, will have a similar failure rate at five years or longer. It is also possible that the PNS group will have a lower failure rate after five years, as has been suggested for patients with this type of implant (15).

Neuroaugmentation has been used in failed back surgery syndrome (25), urinary bladder dysfunction, pain (11), peripheral vascular disease (7), angina pectoris (12), reflex sympathetic dystrophy (1, 15, 29), and other painful conditions (17). The mechanism of analgesia of neuroaugmentation is not completely understood. Since the publication of a hypothesis invoking presynaptic gating mechanisms in the dorsal horn (21), it has been assumed that activation of large diameter afferents causes presynaptic inhibition of C fiber input to the spinal cord and therefore analgesia. The concept though attractive, was based on indirect evidence, there was no demonstration that C fiber input to the spinal cord was amenable to presynaptic control. Other studies have demonstrated that C fiber input to the spinal cord can in fact be modulated presynaptically (9). In as much as the gating hypothesis could be an interesting possibility to explain the analgesic effects of neuroaugmentation, it does not seem to fully explain its mechanism of action. If the clinical effects of neuroaugmentation were produced by such a mechanism of action, it would be expected to be particularly useful in acute nociceptive pain (e.g. postoperative pain), this has not proven to be the case. Furthermore, some studies have failed to demonstrate presynaptic inhibition of A delta driven dorsal horn neurons by large diameter fiber activation (36).

Studies, with single unit recording in the lumbar dorsal horn of cats with thoracic cord transection, have demonstrated that concomitant SCS induces activity in laminae II-III, possibly due to direct synaptic activation from dorsal column collaterals. Cells in deeper layers of the dorsal horn that were driven by peripherally applied noxious stimulation were inhibited. This effect was assumed to be due to interneuronal activation in, or near, the substantia gelatinosa, and since the thoracic spinal cord had been transected, it was concluded that SCS exerted its effect predominantly via spinal mechanisms (10). Experiments on spinothalamic tract cells have provided evidence that dorsal horn cells, activated by noxious peripheral stimulation, could be inhibited by SCS (13), thus supporting a spinal mechanism of action. It has been proposed that SCS might produce analgesia effect by modulating supraspinal structures (14, 30). Studies concerned with SCS-induced analgesia have provided some evidence on the possible role of supraspinal mechanisms. Transection of the dorsal columns, between a segment receiving nociceptive input and a more rostrally placed SCS electrode, did not abolish, in some experiments, the SCS-induced suppression to high threshold cutaneous stimulation, therefore, a supraspinal site of action was suggested (31).

Possible involvement of endogenous opioids in

SCS-induced analgesia has attracted the attention of some investigators ; however, no increase of these substances has been demonstrated in cerebrospinal fluid (16). Likewise, naloxone failed to reverse the effects of SCS in other experiments (23). Thus, this possibility though attractive, is unlikely to be the answer on the mechanism of action of SCS-induced analgesia. Serotonin was shown to increase in spinal tissue after SCS (6). This finding has been corroborated using microdialysis in the dorsal horn of the rat (18). Serotonin is present in the periaqueductal grey matter (PAG), and is probably one of the mediators of analgesia during PAG stimulation (2), therefore, it is likely that this substance might explain at least partly SCS-induced analgesia. Studies on the role of inhibitory aminoacid transmitters have addressed the role of GABA in SCS-induced analgesia (34). They have demonstrated that SCS induces a decrease in the extracellular concentration of GABA in PAG. The suggestion was that since GABA neurons in the PAG exert a tonic inhibitory effect on PAG output, a decreased GABA level here would result in a disinhibition of PAG, leading to a more powerful descending pain-suppressing effect in the spinal cord. At the spinal level SCS induces the release of GABA assayed by microdialysis, it was also found that the spontaneous release of GABA was significantly lower in rats with tactile allodynia compared with intact animals (20).

Other aminoacid inhibitory transmitters have been suggested as possible mediators of SCS-induced analgesia. The dominant inhibitory transmitter in the spinal cord is glycine (35), it has been investigated primarily for its actions on motor neuron function. Glycine is found in interneurons in the ventral horn of the spinal cord (3), in addition, pools of glycine are present in the dorsal horn grey matter (3), therefore it is likely that glycine may participate in spinal nociceptive processing. Glycine has been reported to be released during SCS in experimental animals and to modify pain-induced behavior suggestive of analgesia (32).

PNS probably operates through mechanisms similar to SCS in the central nervous system. In addition, peripheral mechanisms may also participate in PNS-induced analgesia, it has been shown experimentally that both SCS as well as stimulation of the distal end of severed dorsal roots are capable of inducing significant increases in skin and muscle blood flow in experimental animals, this change was thought to be due to inhibition of the sympathetic tone (19). CRPS is associated with vasoconstriction in skin and muscle ; therefore, it is not surprising that PNS could be particularly beneficial in patients with this syndrome.

There is surprisingly little information on the role of noradrenergic mechanisms in SCS-induced analgesia. There is, however evidence that C fiber input to the spinal cord can be modulated presynaptically by clonidine in a yohimbine antagonizable manner (8), suggesting that noradrenergic mechanisms may play a role in the mechanism of action of SCS.

The mechanisms underlying SCS-induced analgesia are complex, it probably is the result of interactions between monoamines, inhibitory aminoacid transmitters, cathecholamines, and possibly neuropeptides.

In conclusion, we are suggesting that in advanced cases of CRPS, SCS, PNS or a combination of both is an option when all other alternatives have failed. The long term results of this treatment modality remain to be defined.

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SAMENVATTING

O. CALVILLO, G. RACZ, J. DIDIE, K. SMITH. Neuroaugmentatie in de behandeling van complexe regionale pijn syndromen van het bovenste lidmaat.

De auteurs beschrijven 36 patiënten met complexe regionale pijn in een gevorderd stadium. Zij werden behandeld met ruggemergstimulatie, perifere zenuwstimulatie of beide. Zesendertig maand na de implantatie van de electroden was de pijn gemiddeld 53% beter. Het analgetica verbruik verminderde met 50% of was effectiever. Het gebruik van neuroaugmentatie bij complexe regionale pijn is een bruikbare optie wanneer andere therapiën faalden.

RÉSUMÉ

O. CALVILLO, G. RACZ, J. DIDIE, K. SMITH. La neuroaugmentation dans le traitement du syndrome douloureux régional complexe au membre supérieur.

Les auteurs rapportent une série de 36 patients, présentant un stade avancé de syndrome douloureux régional complexe. Les patients ont été traités soit par stimulation de la moelle épinière, soit par stimulation nerveuse périphérique, soit par les deux techniques associées. Trente-six mois après l'implantation du stimulateur, les auteurs observent une diminution significative de la douleur mesurée à l'aide de l'échelle visuelle analogique, en moyenne de 53%. La consommation d'analgésiques a diminué d'environ 50%, ou le traitement analgésique était plus efficace. Les auteurs concluent que la technique de neuroaugmentation constitue une alternative thérapeutique raisonnable pour les cas tardifs de syndrome douloureux régional complexe, lorsque les autres modalités thérapeutiques ont échoué.