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Hyperuricemia Obstructs the Effect of Spinal Cord Stimulation on Peripheral Arterial Occlusive Diseases: The Retrospective Analysis of Eleven Cases

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Abstract

Objective: The indication of spinal cord stimulation (SCS), a treatment for intractable pain, has been expanded to include pain due to peripheral arterial occlusive disease (PAOD). However, its effectiveness may be influenced by the presence of some medical backgrounds. Then, the influences were analyzed in the current study, which identifyed an obstacle for effectiveness of SCS on PAOD.

Methods: Eleven patients with PAOD underwent implantation of a SCS device. The Fontaine's stages (FSs) of all patients before the implantation (pre-FS) were III (4 cases) or IV (7 cases). The relationship between FS 6 months post implantation (post-FS) and the patients' background, including age, duration of SCS introduction, chronic renal failure (CRF), diabetes mellitus (DM), hypertension, hyperuricemia (HU), hypercholesterolemia (HC), height, and body weight were retrospectively assessed.

Results: The effect of SCS on PAOD varied among the 11 patients and was not significant. However, a significant Spearman correlation (r=0.7144, p=0.0182) between post-FS and the serum value of uric acid (UA) was demonstrated. Furthermore, the effectiveness of SCS was significant (p=0.0313) in the 6 patients with normouricemia (NU) when comparing the pre- vs. post-FS, and both post-FSs differed significantly (p=0.0065) when comparing NU vs. HU patients. In contrast, the improvement was null in the other 5 patients with HU. There were neither significant changes nor correlations between post-FS and all of the other background characteristics that were assessed.

Conclusion: Considering that SCS improved FS, both pain scores and tissue blood flow were improved. SCS is an effective treatment for patients with PAOD; however, the results differed depending on the presence of NU or HU. Thus, UA is suggested to be a marker of PAOD or a predictor of its prognosis.

Keywords: Pain management, Spinal cord stimulation, Peripheral arterial occlusive disease, Uric acid, Hyperuricemia, Fontaine's stage

Introduction

Spinal cord stimulation (SCS) for treatment of pain was first attempted by two physician colleagues. Shealy et al. [1] surgically implanted electrodes by laminectomy in patients with cancer pain (1967). Shimoji et al. [2] inserted electrodes percutaneously into the epidural space by means of a cannulation technique for epidural anesthesia (1971). Both colleagues found that SCS was beneficial for pain relief or pain control. Today, SCS via the epidural space is a popular treatment for intractable pain, because the procedure is less invasive [3,4].

The indication of SCS has recently expanded to include the treatment for peripheral arterial occlusive diseases (PAOD) [5-8]. SCS has been found not only to control pain but also to salvage the extremities from amputation due to an increase in tissue blood flow [8-12]. The pain relief attributed to SCS results from reduced sympathetic tonus, because SCS itself inhibits sympathetic activity. In addition, the antidromic nerve impulses from SCS induce the secretion of vasodilators including calcitonin-gene-related peptide (CGRP), prostaglandins, and substance P [12-14].

On the other hand, patients with PAOD often have medical backgrounds that include chronic renal failure(CRF), diabetes mellitus(DM), hypertension, hyperuricemia(HU), or hypercholesterolemia(HC). These conditions with SCS may reflect the effectiveness of SCS in PAOD. In the current study, the influences of patients' backgrounds on the effectiveness of SCS for PAOD were analyzed.

Materials and Methods

The current retrospective study was performed with the approval of the Institutional Review Board, and informed consent was obtained

from each patient. In 2004 and 2005, eleven patients (10 males and 1 female) at our hospital were implanted with a SCS device for the treatment of PAOD of the extremities. The signs and symptoms of these patients were intractable, even after treatments including a vasodilator and an anticoagulant, an epidural block, and/or a bicarbonate bath.

Assessment and measurement

The severity of PAOD was assessed using the Fontaine's stage (FS) classification in 4 steps (I, asymptomatic; II, intermittent claudication; III, daily rest pain; IV, tissue necrosis). FS was assessed twice before (pre-FS) and 6 months after (post-FS) the introduction of SCS. The pre-FSs of all patients were III (4 cases) or IV (7 cases). Uric acid (UA), total cholesterol, glycohemoglobin A1c (measured in DM patients only), height, and body weight were measured simultaneously during assessment of the post-FS (Table 1).

S. No	Age (yr)	Gen	Diag	Region	Dur (mon)	CRF	DM	BP	UA (mg/L)	TC (mg/L)	A1c (%)	Ht (m)	BW (kg)
1	72	m	ASO	lt. heal	8			i	34	2150	7.1	1.67	58
2	64	m	ASO	rt. toe	6			i	89	1670	8.2	1.61	57
3	48	f	SLE	bl. toe	21			s	22	2220	6.2	1.43	52
4	57	m	Burger	bl. toe	18			i	45	2370	…	1.57	58
5	76	m	ASO	rt. toe	8			i	49	1710	…	1.55	49
6	64	m	ASO	lt. toe	6			s	89	1830	7.7	1.6	59
7	60	m	ASO	lt. finger	6			s	84	1590	…	1.83	61
8	58	m	ASO	bil. toe	6			i	85	1340	6	1.57	58
9	81	m	ASO	rt. toe	14			i	41	2220	…	1.68	54
10	75	m	ASO	bil. toe	24			i	42	1460	6.5	1.64	80
11	67	m	ASO	bil. toe	11			i	81	1830	…	1.52	55
Mean	66	11	60	1854	7	1.61	58						
SD	10	7		25	342	0.9	0.1	8					

Measurement and assessment of post-FS was done simultaneously 6 months after implantation of a SCS device. Abbreviations; Gen: Gender; Diag: Diagnosis; Dur: Duration of SCS Introduction; mon: Months; CRF: Chronic Renal Failure; DM: Diabetes Mellitus; BP: Blood Pressure; UA: Uric Acid; TC: Total Cholesterol; A1c: Glycohemoglobin A1c (measured in patients with DM only); Ht: Height; BW: Body Weight; m: Male; f: Female; ASO: Arteriosclerosis Obliterans; SLE: Systemic Lupus Erythematosus; Burger: Burger's Disease; lt: Left; rt: Right; bl: Bilateral; i: Insufficient Control of BP; s: Sufficient Control of BP; SD: Standard Deviation

Table 1: Backgrounds of patients with peripheral arterial occlusive disease (PAOD).

SCS Device and Implantation

A SCS device (Itrel 3®, Medtronic Inc, and Minneapolis, Minnesota, USA) was implanted in each patient under regional infiltration anesthesia. An electrode was inserted into the posterior side of the epidural space at the T11–L1 spinal segment for PAOD involving one or both feet, or at C5–C6 for PAOD involving one or both hands. The position of the electrode was adjusted manually under perspective radiogram in order to ensure that the stimulated area corresponded exactly to the PAOD site with a trial stimulator generating a repetitive square-pulse. After adjustment, the electrode was fastened subcutaneously with knotted threads. A stimulation generator was then implanted into the subcutaneous tissue of the abdominal or chest wall.

Bipolar electric stimulation with square pulses produced by the implanted generator was delivered continuously throughout the day to patients via the electrode. Patients could adjust the pulse pattern by themselves within a frequency of 2.1–130 Hz, a voltage of 0–10.5 V, and a width of 60–450 μs to achieve an optimal level of pain reduction.

Grouping, background disorders, and medication

Patients were divided into 2 groups in several patterns according to their medical backgrounds (with/without CRF, DM, sufficient control of hypertension, HU, NU, and HC). HU and HC were defined as serum values of uric acid (UA) >70 mg/L and serum values of total cholesterol >1900 mg/L, respectively. DM or hypertension was diagnosed in accordance with the 1999 and 2004 World Health Organization (WHO) criteria. All patients with CRF underwent hemodialysis. Patients with DM, HU, and/or HC were medicated with the respective appropriate drugs. All 11 patients were medicated with one or more hypotensive drugs: control of hypertension in 8 patients was insufficient, while that in 3 patients was sufficient.

Analysis and statistics

Changes in non-parametric values were analyzed using the Wilcoxon's signed rank test for paired values and the Mann–Whitney U test for non-paired values in combination with the Dunn's multiple

comparison tests. For parametric values, the paired and Student's t-tests in combination with a two-way analysis of variance (ANOVA) were used. Correlations were analyzed using the Spearman's rank correlation for non-parametric data and the Pearson product-moment correlation coefficient for parametric data (GraphPad Prism 6, GraphPad Software, Inc., La Jolla, CA, USA). Values are expressed as medians with quartiles and ranges and means with standard deviations (SD). A p value of <0.05 was considered to indicate statistical significance.

Results

The effectiveness of SCS varied among the 11 patients. Although FS did not improve significantly (Figure 1), a significant correlation (Spearman r=0.7144, p=0.0182) between the post-FS and serum UA values was demonstrated (Figure 2). This result differed on the basis of two aspects of patients' medical backgrounds. All 6 patients with NU improved, whereas the improvement was null in all 5 patients with HU. Each decrease in FS was to stage I, II, or III, and the improvement was significant (p=0.0313) in a comparison between the pre- vs. post-FS within the NU patients. Also, both post-FSs differed significantly (p=0.0065) when comparing the NU vs. HU patients (Figure 3). size, the difference seems to be significant. If so, however, this result may be of pseudo-significance (see also text). The statistics are the same as that in (Figure 1).

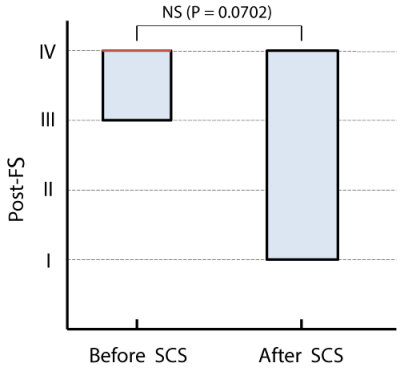

Figure 1: The change in the Fontaine's stage before (pre-FS) and after (post-FS) spinal cord stimulation (SCS) in all eleven patients. A significant change was not noted. This may have been attributable to the small sample size. The Wilcoxon's signed rank test in combination with the Dunn's multiple comparison test was used. Red bars, shadowed boxes, and black bars represent medians, quartiles, and ranges, respectively. NS, not significant.

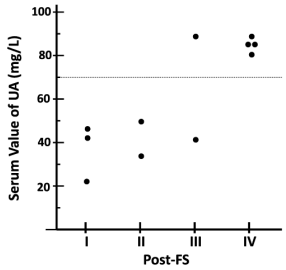

Figure 2: The correlation between the serum value of uric acid (UA) and Fontaine's stage after spinal cord stimulation (SCS). A significant (Spearman's r=0.7144, p=0.0182) correlation was demonstrated by Spearman's rank correlation.

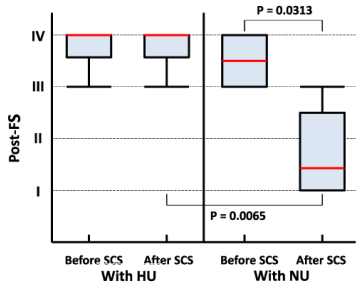

Figure 3: The changes in the Fontaine's stage before (pre-FS) and after (post-FS) spinal cord stimulation (SCS) in patients with hyperuricemia (HU) and normouricemia (NU). A significant (p=0.0313) change in the pre- vs. post-FS within patients with NU, and a significant (p=0.0065) difference in the post-FSs of NU vs. HU patients. The statistics are the same as that in Figure 1.

Statistically insignificant trends towards improvement were detected on comparison of the pre- vs. post-FS in the NU patients (p=0.125) and on comparison of both post-FSs in the CRF vs. non-CRF patients (p=0.167; Figure 4).

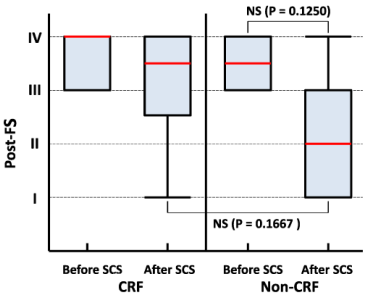

Figure 4: The influence of chronic renal failure (CRF) on the effectiveness of spinal cord stimulation (SCS). A positive but insignificant difference was noted. With a larger sample

There were neither significant changes nor correlations between post-FS and age, duration of SCS introduction, DM, control of hypertension, HC, height, or body weight.

Discussion

The effectiveness of SCS in patients with PAOD was varied. However, a significant correlation between post-FS and serum UA value was demonstrated. Interestingly, the result split completely between the patients with NU and HU such that the effectiveness was significantly evident in all patients with NU (54.5%) but null in all patients with HU (45.5%). Thus, HU was identified as an obstacle to the treatment of PAOD using SCS. It should be noted that the observed insignificant effectiveness in all 11 patients may have been attributable to the small sample size examined in the current study.

The results of previous studies have already shown that SCS produces vasodilatation and promotes peripheral circulation [8-12]. For the evaluation of PAOD severity, FS rather than pain score was utilized in the current study. Therefore, the observed decreases in FS indicated a pain relief effect as well as a circulation-promoting effect attributable to SCS. Although the findings are limited within the patients with NU only in the current study, these findings support results from previous studies indicating that SCS allowed for the salvage of necrotic extremities [8-14]. The safety and efficacy associated with SCS preceding surgical treatments should lead to its more frequent use as opposed to amputation or arterial grafts.

Chemical substances, such as UA, adenosine triphosphate (ATP), DNA, high mobility group–box chromosomal protein-1 (HMGB-1), and SAP130, have recently been implicated as important mediators in the pathologic state of tissue necrosis. In the process of necrosis due to ischemia, UA is released from necrotic tissue in order to signal danger and triggers an acute inflammatory response to sterile cell death [15]. Subsequently, macrophages, followed by neutrophils, infiltrate into necrotic tissues receiving the danger signal from these chemical substances [16]. In our current patients with HU, therefore, massive tissue necrosis had been advancing to more severe condition despite of the SCS treatment. Thus, the effect of SCS in the patients with HU was obstructed. As such, UA is suggested to be a marker of PAOD or a predictor of its prognosis.

CRF is associated with abnormal phosphorus metabolism, which induces secondary hyperthyroidism and promotes vessel calcification [17-19]. These metabolic changes may increase arterial stiffness and offset the positive effects of SCS. Then, the influence of CRF may be stronger than that of other medical backgrounds assessed in the current study. Consequently, CRF may boost the severity of PAOD, and at a glance seemed to be a risk factor for PAOD [20]. However, CRF does not usually induce HU; rather HU is a risk factor for CRF [21-23]. In a study that included a larger sample size, the offsetting effect seemed to be significant. If so, however, this result may be of pseudo-significance. Overall then, HU is ranked upstream [21,22].

In addition, UA has already been also demonstrated to be a risk factor for atherosclerosis [24-26], cardiovascular events [25,27], metabolic syndrome [23,28], and stroke [29]. Taking these findings into account, HC, DM, and body weight are likely to influence the effectiveness of SCS on PAOD. However, none of these medical backgrounds showed even minimal effects on the effectiveness, because UA is not released due to these medical backgrounds and HU is also ranked upstream. Furthermore, an increasing effect of these medical backgrounds on arterial stiffness appears still weaker than that of CRF. HU is usually caused by over-uptake or under-excretion of purine compounds, and acts as a risk factor for the aforementioned medical backgrounds. In PAOD, however, UA is released from the necrotic tissue and acts as a danger signal. Therefore, the clinical utility of assessing HU differs depending on the patient's medical background (with or without PAOD).

In the current study, most patients (90.9%) receiving SCS were males. This phenomenon may be worthy of note, and may be attributable to a gender difference [30], and/or a life-style gap between genders. In conclusion, SCS has been shown to improve pain and increase in the tissue blood flow due to PAOD. In the treatment of PAOD, the current study identified an obstacle, UA, which is suggested to be a marker of PAOD, or a predictor of its prognosis.

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