Clinical Note

A Randomized, Double-Blind, Crossover Study of the Use of Transcutaneous Spinal Electroanalgesia in Patients with Pain from Chronic Critical Limb Ischemia

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Abstract
Transcutaneous spinal electroanalgesia (TSE) uses two electrodes placed over the skin of the dorsal spine to deliver pulses of short wavelength, high frequency, and relatively high voltage to the spinal cord without causing paresthesia. TSE has been used to treat pain and may improve limb blood flow. This randomized, double-blind, crossover study assessed the effect of TSE on microcirculation, pain, and activity in 8 patients (3 men, 5 women, median age 66.5 years, range 62–76 years) with chronic critical limb ischemia (CLI). After a one-week baseline period, patients used an active or inactive TSE machine for one hour daily for one week. Following a week of no stimulation, patients repeated the week of treatment with an identical matched machine. Daily use of TSE for one week did not improve microcirculatory perfusion (transcutaneous oxygenation), pain (verbal rating scale, McGill Pain Questionnaire), physical function (Functional Limitations Profile), mood (Beck Depression Inventory, Beck Anxiety Inventory), or sleep. There was no patient preference for the active TSE machines. This study showed that TSE administered daily for one week did not improve microcirculation, pain, or activity in patients with chronic CLI. J Pain Symptom Manage 2004;28:511–516.

Key Words
Transcutaneous spinal electroanalgesia, critical limb ischemia, pain

Introduction

Chronic critical limb ischemia (CLI) is common; 5% of men over 50 years of age have symptomatic vascular leg disease.[1] Progressive deterioration of claudication to rest pain and ulcers occurs in about 25% of cases and affects 500–1,000 patients per million population.[2] Chronic CLI produces significant morbidity, and patients are often disabled by pain that adversely affects their quality of life and limits their activity. Approximately 80% of patients undergo either surgical reconstruction or amputation. For the remainder, there is no surgical option, either because of the nature of the

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vascular problem or co-existing illness.[3] Much of the management of these patients could be regarded as palliative, the emphasis being on pain and symptom control. Chronic CLI carries a high mortality, 20% at one year and between 50% and 70% at 5 years after amputation.[3]

Patients with CLI should be referred to specialist centers where full evaluation of limb ischemia is possible. This may include assessment of the macrocirculation (by segmental blood pressure, systolic toe pressure measurement, Doppler analysis, Duplex scanning, and angiography) and the microcirculation (by transcutaneous oxygenation [$TcPO_2$], capillaroscopy, and laser-Doppler fluximetry). The first treatment options are endovascular procedures and vascular reconstructions. In patients with non-reconstructable disease, other treatment options include pharmacotherapy such as prostaglandin infusion, or sympathectomy. Spinal cord stimulation (SCS) has been shown to improve limb blood flow, reduce pain, heal ulcers and increase activity, but it is invasive and expensive.[4–6] Transcutaneous electrical nerve stimulation (TENS) has also been reported to improve lower limb blood flow.[7,8] Although it is simple, non-invasive, and cheap, double-blind studies of TENS are difficult to conduct as its effect depends on producing paresthesia.[9]

Transcutaneous spinal electroanalgesia (TSE) is a method of electrical stimulation that uses two electrodes placed over the skin of the dorsal spine to deliver pulses of short wavelength (pulse width 4 μsec ± 1 μsec), high frequency (1800–2500 Hz ± 10%) and relatively high voltage (100–300 V) to the spinal cord.[10] Such pulses do not cause action potentials in peripheral nerves, and so there is no sensation of paresthesia. It is, therefore, possible to undertake a blind assessment of the technique. TSE has been used to treat pain[10] and it has been suggested to increase blood flow to the limbs of animals (unpublished data). However, there have been no studies of using TSE in patients with vascular pain. This study was, therefore, the first to assess the effect of TSE on microcirculation, pain or activity in patients with chronic CLI.

Methods

Study Design and Recruitment

This study employed a double-blind, crossover design where active and placebo TSE was used in outpatients with chronic CLI. All those recruited were under the care of consultants in the Departments of Pain Management and Vascular Surgery at St. James's University Hospital, Leeds, United Kingdom. The St. James's University Hospital Ethics Committee approved the study.

Patients were eligible for inclusion if they had arteriosclerotic, chronic, stable CLI in one or both legs and were able to use a TSE machine after instruction. Chronic CLI was defined as either 1) persistent ischemic pain at rest in patients who have needed regular analgesia for over 2 weeks, and who have a systolic arterial ankle pressure of ≤50 mm Hg and/or toe systolic pressure of ≤30mmHg; or 2) ulceration or gangrene of the foot or toes in patients with a systolic arterial ankle pressure of ≤50 mm Hg and/or toe systolic pressure of ≤30 mm H; or 3) $TcPO_2 \leq 50$mm Hg.[11]

Patients were deemed ineligible if they were under 16 years of age, had previously had an amputation of the target limb, were suitable for immediate reconstructive surgery, had a likely life expectancy of less than two months, had a contra-indication to TSE use (e.g., pacemaker) or were unable to complete the assessment process. In all patients, other treatments had to remain stable during the study period. All patients gave written informed consent to participate in the study after they had received verbal and written information.

Intervention

The TSE machine manufacturer (Advanced Pain Management) provided five pairs of identical machines; one machine in each pair was active and the other inactive. The only way to differentiate between the active and inactive machines was by their code number, which was held securely until the end of the study. Both active and inactive machines displayed a colored light when switched on. Patients were randomized according to a computer-generated random number chart to receive either an active or inactive machine first. None of the clinicians or investigators directly involved with the patients knew whether an active or inactive machine was in use. Patients were also blind to treatment, as active TSE does not cause any sensation. After a one-week baseline assessment, patients were shown how to use the TSE machine. This was supplemented with written

Table 1
TcPO2 Measurements at Baseline, Following Placebo TSE, at the End of the Washout Period, and Following Active TSE

	Right Leg Supine				Right Leg Dependent				Left Leg Supine				Left Leg Dependent			
Patient	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
1	25	58	54	41	26	68	65	47	41	49	55	48	43	56	59	60
2	47	35	52	44	54	41	57	58	5	4	4	39	24	3	7	43
3	45	49	19	57	58	58	54	68	45	29	35	52	61	48	62	67
4	51	42	56	53	54	52	58	51	24	45	49	40	47	50	52	46
5	23	27	13	27	36	44	31	50	31	34	22	18	41	44	42	30
6	21	25	30	26	31	40	48	39	1	18	35	31	59	29	46	55
7	49	53	49	51	52	56	44	46	54	37	34	46	53	36	32	44
8	20	10	18	10	34	2	19	8	35	9	21	19	53	4	23	8
Median	35	39	40	43	44	48	51	49	33	32	35	40	50	40	44	45
SD	14	16	18	16	13	20	15	18	19	16	16	13	12	20	19	19

A = Baseline; B = Following placebo TSE; C = Washout; D = Following active TSE.

instructions. At each follow-up visit, their use of the machine was checked. Patients were asked to apply the machine daily for one hour, at the same time of day, for one week. During the second week of the study patients had no stimulation to allow any effects of the TSE to wear off. During the third week, patients received the matching TSE machine from the code randomization and used it as instructed during the first week. Thus, each patient had a baseline week followed by two periods of one week of active and one week of inactive TSE separated by a washout period of one week.

Outcome Measures

The primary outcome measure was a change in transcutaneous oxygenation. A rise in $TcPO_2$ of at least 20 mmHg was judged to be clinically significant.[3] As this is the first study of TSE with chronic CLI, the aim was to recruit 8 patients. At the end of the baseline week, and at the end of weeks 1, 2, and 3, assessments included: 1) $TcPO_2$ in both legs, in the supine position and with legs dependent. Measurement involved attaching a small electrode to the skin; this heated the underlying skin slightly to induce a hyperemia, and then recorded any increase in oxygen delivery;[11] 2) McGill Pain Questionnaire;[12] 3) Beck Depression Inventory;[13] 4) Beck Anxiety Inventory;[14] and 5) Functional Limitations Profile of the Sickness Impact Profile.[15]

Patients also completed a daily diary during the two weeks when using the TSE machine. The diary contained a four-point Verbal Pain Rating Scale (none, mild, moderate, and severe) for pain at best, at worst, and overall. Patients recorded the total number of hours slept (to the nearest half-hour) and rated the overall quality of their sleep on a numerical rating scale (5–extremely poor to 0–extremely good). Any changes in analgesia or adverse events were recorded. At the end of the study, patients were asked which machine they preferred.

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences Computer Program (SPSS Version 11).[16] Median values and quartile ranges were calculated and non-parametric tests of significance were used. All significance levels were set at $P = 0.05$.

Table 2
Median $TcPO_2$ Measurements at Baseline and Median Changes in $TcPO_2$ After One Week of Treatment with Placebo and Active TSE Machines

	Median Baseline $TcPO_2$ (mm Hg)	Median Change $TcPO_2$ (mm Hg) Placebo TSE	Median Change $TcPO_2$ (mm Hg) Active TSE	*P* value (Sign test)
Right leg supine	35	4.0	−3.5	0.727
Right leg dependent	44	2.0	−3.0	1.000
Left leg supine	33	1.0	−3.0	1.000
Left leg dependent	50	−15	−3.0	0.727

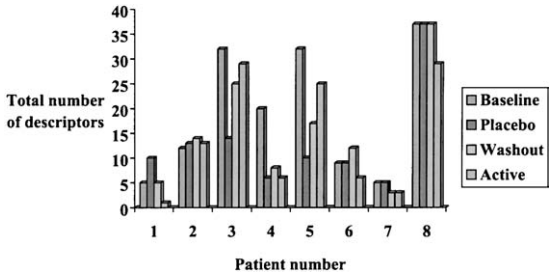

Fig. 1. Total number of descriptors chosen on the McGill Pain Questionnaire at baseline and after placebo, washout, and active treatment weeks.

Results

Eight patients (3 men and 5 women) were enrolled and all completed the study. The median age was 66.5 (range 62–76) years. Patient's analgesic drug regimens remained constant throughout the study. Four patients were receiving so-called "weak" opioids, three patients were receiving co-analgesic drugs, and one patient was receiving a nonsteroidal anti-inflammatory drug.

Primary Outcome

$TcPO_2$ measurements at baseline, after placebo TSE, after the washout period, and after active TSE are shown in Table 1. There were no differences in median $TcPO_2$ changes when the placebo and active TSE machines were compared (Table 2).

Secondary Outcomes

The total number of descriptors chosen on the McGill Pain Questionnaire by patients at baseline, and after the placebo, washout, and active treatment weeks are shown in Figure 1. There was no statistically significant difference between the median change in number of descriptors with placebo (0) and active treatment (–1.5) (sign test 1.000). The daily verbal rating scale showed no statistically significant differences between active and placebo TSE. Overall pain remained unchanged in five patients, and improved with the active machine in one patient and the placebo machine in one patient (sign test 1.0). Pain at its best improved in two patients with the active machine and two with the placebo machine and remained unchanged in the other four (sign test 1.0). Pain at its worst remained unchanged in six patients and improved in two with the active machine (sign test 1.0).

Patient's activity, as measured by the functional limitations profile, was no different between active and placebo TSE (Tables 3 and 4). There were no differences in the Beck Depression Inventory or the Beck Anxiety Inventory when active and placebo TSE were compared

Table 4
Median Functional Limitations Profile at Baseline and After One Week of Treatment with Placebo and Active TSE Machines

Functional Limitations Profile	Median Baseline Value	Median Change Placebo	Median Change Active	Sign Test
Physical	34.2	−0.4	−8.0	0.453
Psychological	32.0	−5.4	2.7	0.125
Overall score	26.8	−3.5	−4.8	1.000

Table 3
Functional Limitations Profile at Baseline, Following Placebo TSE, at the End of the Washout Period, and Following Active TSE

	Functional Limitations Profile–Physical				Functional Limitations Profile–Psychological				Functional Limitations Profile–Overall			
Patient	A	B	C	D	A	B	C	D	A	B	C	D
1	27.2	12.1	14.4	13.7	24.4	9.2	9.8	12.5	24.4	12.7	13.9	14.6
2	27.7	44.4	43.4	49.3	26.6	41.6	26.3	36.7	22.3	35.7	29.1	35.7
3	44.2	33.1	37.3	29.7	47.6	41.0	44.2	39.1	37.5	32.1	33.4	28.6
4	42.6	63.2	51.2	66.5	38.0	19.0	8.3	53.9	54.2	35.1	25.9	52.9
5	31.4	30.6	33.5	18.6	37.4	34.2	19.0	17.8	28.5	27.0	22.6	15.3
6	14.0	14.6	33.9	14.4	9.9	5.7	5.5	12.2	10.2	8.5	17.7	10.9
7	44.7	35.8	44.8	27.4	14.8	5.7	8.0	6.2	25.1	17.8	22.6	14.3
8	36.9	36.9	36.9	—[a]	52.7	52.7	52.7	—[a]	36.4	36.4	37.2	—[a]
Median	34.1	34.5	37.3	27.4	32.0	26.6	14.4	17.8	26.8	29.5	24.3	15.3
SD	10.6	16.2	10.9	19.7	15.1	18.5	18.0	17.8	13.1	11.2	7.8	15.4

Lower score = more impaired.
A = Baseline; B = Following placebo treatment; C = Wash-out; D = Following active treatment.
[a]Data missing.

Table 5
Beck Depression and Anxiety Inventories at Baseline and After One Week of Treatment with Placebo and Active TSE Machines

	Median (Interquartile Range) Baseline Value	Median (Interquartile Range) Change Placebo	Median (Interquartile Range) Change Active	Sign Test
Beck Depression Inventory	11 (4.3, 21.5)	0 (−1.5, 1.0)	−2.5 (−3.0, 3.8)	0.727
Beck Anxiety Inventory	10 (4.8, 12.8)	−0.5 (−5.0, 0.0)	−0.5 (−2.8, 2.3)	1.000

(Table 5). The median number of hours of sleep was not significantly different between the placebo and active treatments (5.4 hours and 5.3 hours, respectively, sign test 0.625). A non-statistically significant improvement in the overall quality of sleep occurred (median value for placebo TSE 2.8, median value for active TSE 2.0, sign test 0.453).

No adverse events were reported. At the end of the study, five patients showed no preference for either the active or placebo TSE machine. Two patients preferred the placebo machine and one patient the active machine.

Discussion

This study confirmed that patients with chronic stable CLI have significant pain, with a median baseline score of moderate pain on a verbal rating scale and significant pain as recorded by the McGill Pain Questionnaire. The patients in this study also had reduced physical functioning on the Functional Limitations Profile. Daily use of TSE for one week, compared to placebo, did not improve the microcirculatory perfusion as measured by $TcPO_2$. There was no reduction in pain with active TSE compared to placebo. Although there was some improvement in physical functioning with a reduction in the Physical Component of the Functional Limitations Profile, this was not statistically significant. It may be difficult to detect changes in physical functioning in patients with chronic CLI because of other co-existing medical conditions.[11] There were no differences in mood or sleep with active TSE use.

There are several possible explanations for the observed lack of effect of TSE in patients with vascular limb pain. It is conceivable that patients did not comply with the treatment or applied the machines incorrectly. However, verbal and written instructions were provided and use of the machine was checked at each visit. Also, patients were keen to enter the study and try the treatment due to the severity of their symptoms and lack of other available treatments. Secondly, it is possible that the length of TSE stimulation (one hour per day for one week) was too short. However, TSE has previously been shown to have cumulative pain relief with long periods of post-stimulation relief when used for this length of time.[10] It is most likely that TSE was ineffective in this study because of the pathophysiology of chronic stable CLI. Although the precise pain mechanisms in CLI are not known, it has been postulated that TSE is ineffective "where inflammation continues to provide an ongoing source of input from peripheral nociceptors."[10]

This study was the first to examine the use of TSE in patients with pain due to chronic CLI. A double-blind design was possible because, unlike TENS, TSE does not cause any sensation. Although the study only recruited a small number of patients, the group was homogeneous and had identifiable pathology. There were no trends towards an improvement in symptoms.

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