An investigation into the 'carry over' effect of neurostimulation in the treatment of angina pectoris

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SUMMARY

Neurostimulation, by way of transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation, improves signs and symptoms of myocardial ischaemia, with evidence (from non-randomised studies) that this effect extends beyond the period of stimulation itself ('carry-over' effect). In this randomised controlled trial, 10 patients underwent baseline treadmill-exercise-testing (TET), followed by two further tests at fortnightly intervals. TENS was compared to placebo in a randomised fashion. TENS produced a significant increase in total exercise time (399.3 vs. 364.5 s, $p < 0.05$) and time to maximum ST depression (374 vs. 324 s, $p = 0.01$) without a significant difference in the maximum degree of ST depression (2.0 vs. 2.1 mm, p = NS). Rate-pressure product at peak exercise was not significantly different (197 vs. 193, p = NS). TENS produced a non-significant change in time to onset of angina (352 vs. 325 s, $p = 0.07$). Pre-treatment with TENS produces a significant improvement in exercise tolerance and measures of ischaemia but not significant improvement in symptoms.

Keywords: Neurostimulation; TENS; SCS; carry-over effect

INTRODUCTION

Neurostimulation, in the form of spinal cord stimulation (SCS) and transcutaneous electrical nerve stimulation (TENS), has anti-ischaemic properties in refractory angina pectoris (1–10). Curiously, this anti-ischaemic effect extends beyond the period of active stimulation itself, a phenomenon termed the 'carry-over effect'. The carry-over effect has been exploited in clinical practice; typically, patients use their neurostimulators for 1 h, three times per day as prophylaxis to ischaemia as well as during acute angina episodes. This strategy was examined by DeJongste and colleagues (8) using 48 h ambulatory ECG (AECG) assessments. Their study confirmed that regular prophylactic SCS use reduced the total ischaemic burden on AECG as well as improving symptoms and glyceryl tri nitrate (GTN) consumption, as measured using patient diaries. However, this was a non-randomised study, with patients being studied before and after SCS implantation. The patients were all in functional class III and IV (Canadian classification of angina severity) and deemed unsuitable for any other form of treatment, already being on maximally tolerated medications. Thus, it is possible that by selecting patients with extreme symptoms in the first place, the decrease in ischaemia was actually a reflection of the 'regression to the mean' phenomenon (a scenario which has been shown to occur when using AECG assessments of ischaemia) (11).

The carry-over effect has caused problems in the field of neurostimulation research. Many experimental studies have employed non-randomised study protocols, in order to avoid confounding results with the carry-over effect. However, this approach could allow other confounding factors to occur. Ischaemic pre-conditioning, for example, has been invoked as a possible confounding factor in the SCS study of Mannheimer and colleagues (12).

Neurostimulation has proved difficult to study for other reasons: first, there is no good placebo due to the characteristic paraesthesia produced during stimulation. Second, the stimulation itself produces a characteristic artefact upon ECG tracings, making blinding impossible for those involved in ECG interpretation. Finally, the carry-over effect has not been studied or measured, but rather it remains a reported phenomenon. There is no information available on its magnitude and duration, or indeed, whether it actually exists, at least in the context of refractory angina research, as it could be simply other confounding factors as discussed previously.

This study aimed at testing and quantifying the effect of the carry-over phenomenon in a randomised placebo-controlled trial. In doing so, we will avoid many of the pitfalls discussed above as well as investigating the carry-over effect of TENS.

METHODS

Ten patients with chronic stable angina pectoris were recruited. Baseline characteristics are summarised in Table 1. All patients studied gave written consent, and the study was

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Table 1 Baseline characteristics

Patient number	*Age*	*Sex*	*Angiogram result*	*LV function*
1	54	M	3VD	Normal
2	64	F	Unknown	Normal
3	74	M	LAD disease	Mild impairment
4	72	M	3VD	Normal
5	63	M	LAD disease	Moderate impairment
6	54	M	Unknown	Normal
7	66	M	2VD	Normal
8	61	M	3VD	Normal
9	80	M	Unknown	Normal
10	53	F	3VD	Normal

M, male; F, female; VD, vessel disease; LAD, left anterior descending artery.

approved by the local ethics committee. All patients were naive to TENS. All patients were left on their current medications, with no changes made during the duration of the study.

The study consisted of three consecutive treadmill exercise tests (TET), performed at the same time of day, each at 2-week intervals (symptom-limited full-Bruce exercise protocol) (Figure 1). The first TET was a baseline study, with the other tests performed after 2 weeks of either TENS or placebo in a randomised order. Baseline tests were used to generate at patient-assessed difficulty rating or Borg score to aid with reproducibility. Randomisation was carried out using the sealed envelope method.

Use of an Oral Placebo

Patients were invited to take part in a study comparing new treatments for angina, in order to avoid expectation and biasing towards neurostimulation. They were told in the consent form that the oral treatment would be either a standard anti-anginal tablet or a placebo, and an active or inactive TENS; however, all patients received oral placebo and active TENS. In this way, we hoped to achieve an effective form of placebo treatment. An oral placebo was chosen above 'sham-TENS' (which is an inactive TENS unit), as patients would obviously distinguish between the placebo and active treatments. Active TENS produces a characteristic paraesthesia, and patients are told to increase the strength of this paraesthesia to a maximally tolerated level.

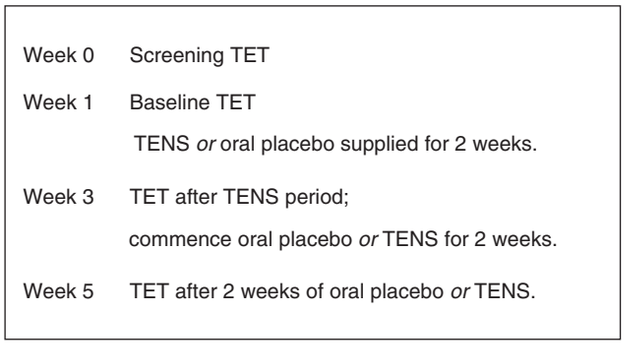

Figure 1 Summary of study protocol

Stimulation Protocol

Stimulation was achieved using a TENS unit (Cefar, Lund, Sweden) with the electrodes positioned so as to cover the area of the precordium, where angina was perceived. Stimulation was at a frequency of 70 Hz and a pulse width of 0.2 ms in continuous mode. Patients used TENS for 1 h, three time per day as well as 1 h before carrying out the TET. The unit was completely removed before entering the treadmill room.

Exercise ECG Analysis

A horizontal line was taken through the mid-point of the PR interval to represent the iso-electric line. The vertical distance from this line to the ST segment was measured at the reference point upon a specially prepared ECG ruler (made by the Bristol university medical physics department), corresponding to 60 ms after the J point of the QRS complex.

This process was repeated for three consecutive traces in the same lead. At least two leads were measured, and the two appeared to demonstrate the largest ST depression on simple inspection of the ECG. The three measurements were averaged and subtracted from the average of ST level measured from a resting, standing ECG taken just prior to the start of the test.

Statistical Analysis

Statistical analysis was performed using the Wilcoxon-matched pairs-signed rank sum test, with p values < 0.05 being regarded as statistically significant.

RESULTS

TENS vs. Placebo

TENS was found to produce a significant increase in total exercise time (399.3 vs. 364.5 s, $p < 0.05$) and increased time to maximum ST depression (374 vs. 334 s, $p = 0.01$) as compared to placebo; this was achieved without a significant difference in the maximum degree of ST depression (2.0 vs. 2.1 mm, p = NS), indicating a shift in ischaemic threshold, i.e. the patients achieved a similar level of ischaemia as measured by ST depression but at a higher workload, as measured by exercise time (Figure 2–4). This is reflected by an improvement in the standardised measure of ST depression at a fixed time interval (180 s); this was reduced from 1.1 mm to 0.7 mm ($p < 0.05$). Rate-pressure product at peak exercise was not significantly different (197 vs. 193, p = NS), and all patients were aware of symptoms, which led them to terminate the test, i.e. there was no masking of angina by TENS. When time to onset of angina was analysed, however, TENS did not produce a significant difference over placebo (355 vs. 325 s, $p = 0.07$), although there was a trend towards an increase until angina onset (Table 2).

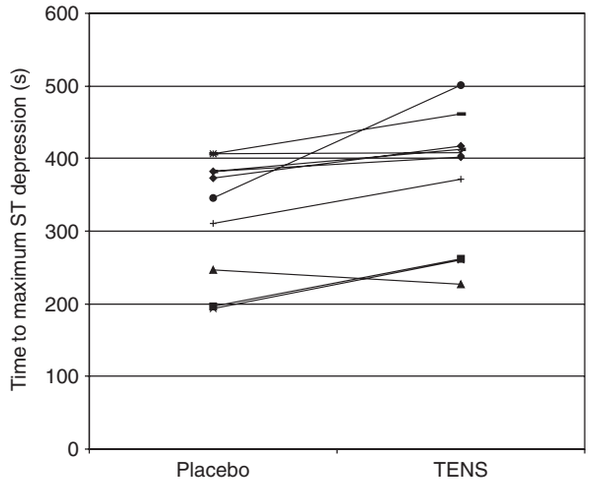

Figure 2 Individual results showing a significant increase in the time taken to achieve maximum ST segment depression ($p = 0.01$)

Placebo vs. Baseline and TENS vs. Baseline

The placebo treatment did not produce any significant improvement in any of the measures, including time to symptoms. TENS, when compared to baseline, demonstrated a significant improvement in all parameters.

DISCUSSION

This study has confirmed the presence of the carry-over effect using a randomised, placebo-controlled study protocol. TENS was able to significantly increase exercise time without causing unrecognised ischaemia, as demonstrated by the similar levels of ST segment depression at peak exercise. However, despite there being a decrease in ischaemic parameters, the time to onset of angina was not significantly different.

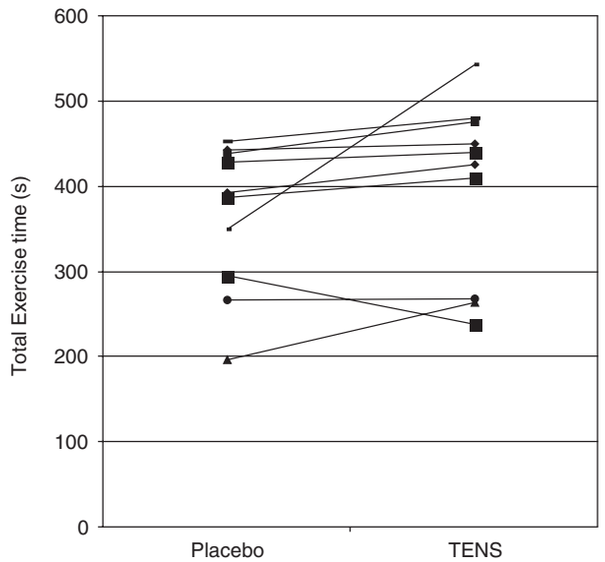

Figure 3 Individual results demonstrating a significant increase in total exercise time ($P < 0.05$)

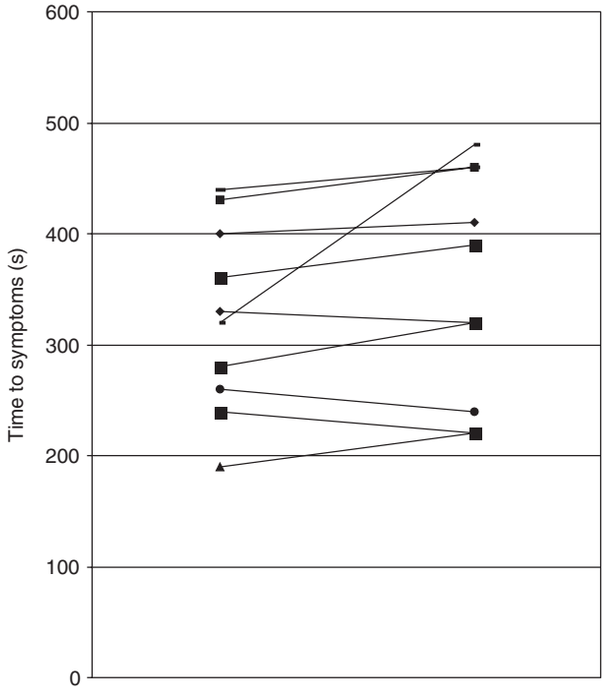

Figure 4 Individual results showing a non-significant trend to an increase in the time to symptoms (p value not significant)

This finding is perplexing, as angina is said to occur last during the so-called 'ischaemic cascade', and one would perhaps expect the whole cascade to be shifted by an anti-ischaemic effect.

It should be noted that the onset of angina was taken as the very first sensation of the patients' typical angina, and it occurred in all patients before ST segments reached maximum depression but not the first sign of ST depression. Thus, the time interval after first onset of symptoms until maximum ST depression was increased by TENS. Furthermore, there was no significant difference between maximum ST depression, and all patients exercised to their pre-specified Borg scores. Therefore, we may conclude that TENS appeared to ameliorate the patients' angina, i.e. eventhough the onset was not significantly different, the angina did not increase in severity at the same rate, allowing the patient to exercise longer. This may be represented diagrammatically:

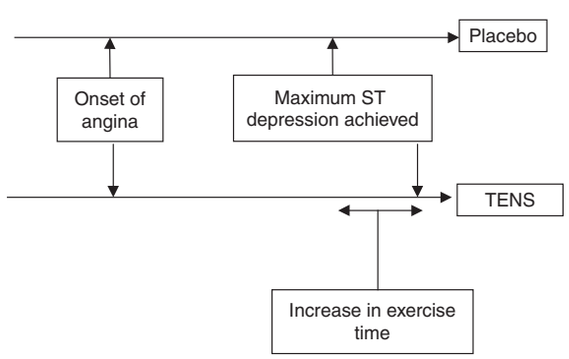

Table 2 Summary of results

Mean (SD)	*Baseline*	*Control*	*TENS*	*TENS vs. control*
Max ST ↓	2.2 mm (0.6)	2.1 mm (0.7)	2.0 mm (0.5)	p = NS
Total exercise time	367.7 (107.2) s	364.5 (86.5) s	399.3 (105.5) s	$p < 0.05$
Time to max ST ↓	338 s (106)	324 s (83)	374 s (93)	p = 0.01
ST↓ at 3 min	1.5 mm (0.5)	1.1 mm (0.7)	0.7 mm (0.5)	$p < 0.05$
Time to symptoms	312 (97.4) s	325 (83.6) s	352 (102.2) s	p = NS
RPP	209 (67)	193 (52)	197 (77)	p = NS

It should also be remembered that the patients did not receive stimulation during the actual treadmill test itself. However, time to symptoms represents the onset of the first awareness the patient has of their typical angina. At this point, the vast majority of patients were happy to continue exercising, recognising the onset of angina, but not currently at an intensity that would cause them to stop their exertion. Speaking to patients afterwards, it was clear that this would correlate to the point that they would start to slow down and reach for their GTN if they were exerting themselves in everyday life. It is for this reason that the time until onset of symptoms is perhaps not a useful reflection of clinical benefit, and that the extension in the time from onset of symptoms until peak exercise is more clinically relevant. If TENS had been active during the test itself, it could be possible for the early sensation of angina to be masked, and this could account for the fact that other researchers have found that the time to onset of angina has been consistently increased. However, this is only speculation, and previous studies have been keen to point out that neurostimulation does not mask ischaemic symptoms, and thus, putting the patient at risk. In this present study, the fact that total exercise time increased without an increase in the degree of ST depression demonstrates that TENS does not mask angina nor allow ischaemia to go unrecognised.

The Use of Tens in Clinical Practice

TENS has traditionally been reserved for the sufferers of refractory angina. This patient group have very little options open to them, and thus, anything which improves their quality of life by reducing symptoms is clinically useful. This present study has shown a modest increase in exercise tolerance, an effect which has been achieved on top of regular anti-anginal medications. Thus, it is now known that TENS can be successfully employed within this patient group.

That question is, however, is TENS a practical or necessary for therapy for use in this patient group? Certainly, whilst the device is small, it is cumbersome to wear if a patient is going about normal daily activities (again, this is less of an issue in refractory angina sufferers). The benefit provided by the device, as measured in this study, is relatively small, and thus, one could not recommend the use of TENS in this fashion. It has to be remembered that the unit was removed during the period of exercise itself, as this study aimed at looking at the carry-over effect in isolation. What is unknown is whether the effect of TENS is potentiated by receiving active stimulation during exertion, as well as regular prophylactic use. A study examining this question is under way.

The Findings in Relation to Previous Research

As discussed in the previous section, these findings are not in agreement with some of the other work reported in the field of neurostimulation; Mannheimer and colleagues demonstrated (in a non-randomised stimulation protocol) that TENS was very effective at increasing time to angina. In that study, TENS was used constantly throughout the stress test, and it is conceivable that the anti-nociceptive effect of TENS was acting upon symptoms, and the anti-ischaemic effect was secondary to another different process. Alternatively, it may be that the documented improvement in symptoms and ischaemia is due to a combination of ischaemic pre-conditioning and a TENS-mediated effect. As discussed earlier, in this study, the TENS machine was used immediately prior to the stress test but removed for the duration of the test itself.

The use of a randomised protocol is also in contrast to many of the other studies of neurostimulation. The reason why previous researchers used non-randomised protocols was due to the concern that the carry-over effect would confound results. Previously, there has been no information upon the duration of this effect. This study has demonstrated that there is little or no effect from carry-over after 2 weeks of 'wash-out'. This has been concluded by the fact that there are clear differences between the TENS and placebo arms of the study, and yet, when compared with baseline tests, the placebo phase did not yield any significant differences. The non-significant trends with placebo when compared with the baseline tests are likely to be a reflection of factors such as training effect and the placebo effect. This finding allows this protocol to be used in further randomised-controlled cross-over studies using TENS.

It should be stressed that these patients had used TENS for only 2 weeks prior to this study and were previously naïve to TENS. It is unknown whether the duration of the carry-over effect is influenced by the duration of pre-treatment, i.e. does pre-treatment for 2 h afford a better response than 1 h?

The History and Background of the Carry-Over Effect

Since the first use of TENS by Wall and Sweet (13), the phenomenon of carry-over has been recognised. They described how a period of treatment of TENS used for simple pain relief produced analgesia which continued beyond the stimulation itself. However, this was in the context of chronic pain relief and well before an anti-ischaemic effect had been proposed for neurostimulation (Wall and Sweet's patients experienced cutaneous pain often after an old injury, described as being 'burning and stabbing pain of unknown origin'). Mannheimer and colleagues (1,2) were the first to report an anti-ischaemic effect with TENS in a study of patients with refractory angina, although, as discussed previously, the group used a non-randomised protocol in order to avoid any influence from the carry-over effect. Thus, these investigators cited this effect before it had actually been demonstrated in the context of relieving ischaemia. Sanderson and coworkers (5) were the first to describe the carry-over effect with respect to angina and its influence upon ischaemic parameters, but again, using a non-randomised protocol. The group studied patients with SCS switched off (baseline), followed by active SCS and finally without SCS off again (control). The tests were conducted serially upon the same day. Whilst most benefit was seen in the SCS phase, the control measurements were improved upon those made during the baseline tests. This result could, however, represent an adaptive mechanism such as ischaemic pre-conditioning or a training effect.

The final piece of evidence for carry-over effect was the AECG trial discussed in the introduction of this study. Patients were studied with two 48-h AECGs' pre- and post-SCS implantation. Custom-built filters were used to achieve interpretable ECG recordings, and the main measure of the study was total ischaemic burden, i.e. the amount of ST depression over time. Patients were instructed to use their stimulators for 1 h three times per day, which leads to a decrease in the amount of ST depression even between episodes of stimulation. The authors concluded that this provided evidence of the carry-over effect. These results fit with the anecdotal experience of SCS-implanting centres around the world. The AECG study, probably, gives the best level of evidence for a carry-over effect, although the non-randomised study design and patient selection is not without problems, and the results could reflect a regression to the mean phenomenon.

Mechanism of Action

DeJongste and colleagues (8), in trying to explain the carry-over effect, speculated that neurostimulation may lead to the modulation of spinothalamic cells within the spinal cord, which in turn may influence the manufacture and/or release of vaso-active compounds. Eliasson and colleagues (14) looked concentrations of beta-endorphin and calcitonin gene-related peptide in coronary sinus samples during SCS and right atrial pacing stress testing. No consistent changes were found with SCS and pacing to angina. In this study, as already discussed, the time to onset of anginal symptoms was not significantly increased, which would suggest that the nerves 'sensing' ischaemia and transmitting that sensation to the spinal cord and higher centres were not 'modulated'. Efferent nerves exerting some kind of beneficial effect upon the myocardium could have been involved and influenced by TENS, but this can only be speculation at present.

SUMMARY

This study has demonstrated an anti-ischaemic effect with TENS, when used to treat chronic stable angina sufferers in a randomised, placebo-controlled cross-over study. This effect does not require active stimulation and thus is not a simple 'masking of symptoms'. After 2 weeks of placebo treatment, there were no significant differences between placebo and baseline studies suggesting that little or none of this effect remains after 2 weeks.

LIMITATIONS OF THE STUDY

This was a randomised controlled trial using small number of patients. Thus, a cross-over design has been necessary, but this leads to the problem of using a suitable placebo control. An oral placebo has been compared to TENS, in the belief that it is better than sham-TENS, which would be readily identified as sham-treatment by most patients. However, we do not know whether taking a pill is a more potent placebo than using a device, or vice versa.

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