

The Effectiveness and Cost-Effectiveness of Spinal Cord Stimulation for Refractory Angina (RASCAL Study): A Pilot Randomized Controlled Trial

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Background: Patients with “refractory angina” (RA) unsuitable for coronary revascularization experience high levels of hospitalization and poor health-related quality of life. Randomized trials have shown spinal cord stimulation (SCS) to be a promising treatment for chronic stable angina and RA; however, none has compared SCS with usual care (UC). The aim of this pilot study was to address the key uncertainties of conducting a definitive multicenter trial to assess the clinical and cost-effectiveness of SCS in RA patients, i.e., recruitment and retention of patients, burden of outcome measures, our ability to standardize UC in a UK NHS setting.

Methods: RA patients deemed suitable were randomized in a 1:1 ratio to SCS plus UC (SCS group) or UC alone (UC group). We sought to assess: recruitment, uptake, and retention of patients; feasibility and acceptability of SCS treatment; the feasibility and acceptability of standardizing UC; and the feasibility and acceptability of the proposed trial outcome measures. Patient outcomes were assessed at baseline (prerandomization) and three and six months postrandomization.

Results: We failed to meet our planned recruitment target (45 patients) and randomized 29 patients (15 SCS group, 14 UC group) over a 42-month period across four sites. None of the study participants chose to withdraw following consent and randomization. With exception of two deaths, all completed evaluation at baseline and follow-up. Although the study was not formally powered to compare outcomes between groups, we saw a trend toward larger improvements in both primary and secondary outcomes in the SCS group.

Conclusions: While patient recruitment was found to be challenging, levels of participant retention, outcome completion, and acceptability of SCS therapy were high. A number of lessons are presented in order to take forward a future definitive pragmatic randomized trial.

Keywords: Randomized controlled trial, refractory angina, spinal cord stimulation

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INTRODUCTION

Refractory angina (RA) has been defined as “a chronic condition characterized by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty and coronary bypass surgery. The presence of reversible myocardial ischaemia should be clinically established to be the cause of the symptoms. Chronic is defined as a duration of more than 3 months” (1). The commonest causes of unsuitability for revascularization are unfavorable coronary anatomy, unsuccessful response to receiving one or more previous coronary bypass procedures or percutaneous angioplasties, lack of suitable grafting material, significant extra cardiac comorbidities, or advanced age, often in combination of the above (1–4). Both increasing success and innovation in conventional approaches to treat angina and better survival rates following primary and subsequent coronary events have led to significant proportions of patients presenting with angina refractory to conventional treatment (4). The most recent published estimate of the incidence of RA is 25,000 to 75,000 new cases per year and an estimated prevalence of 300,000 to 900,000 patients in the United States (5). The wide variability in prevalence and incidence figures may be due to a lack of a standardized definition, as the diagnosis of refractory angina depends on the lack of revascularization alternatives, which vary in different contexts according to the availability of revascularization technology, appropriateness of medical treatment, and other interventions targeted to control anginal pain (6). RA patients experience severe chest pain leading to a high rate of hospitalization, resource use, and poor levels of health-related quality of life (HRQoL) (1,7).

RA patients can be offered a number of therapies including anti-angina drugs, sympathectomy, analgesics, angina management cognitive behavioral therapy, stimulation-induced analgesia, stellate ganglion block, epidural blocks, spinal cord stimulation (SCS), enhanced external counterpulsation, and percutaneous laser myocardial revascularization (3,8–10).

It has been suggested that SCS produces its effects in refractory angina via an interaction of the following mechanisms: 1) pain reduction; 2) a reduction of sympathetic tone; 3) reduced myocardial oxygen demand; and 4) improved coronary microcirculatory blood flow, resulting in a lessening of myocardial ischemia (11). Attenuation of pain is accomplished by stimulation of the dorsal columns and an accompanying decrease in the transmission of nociceptive impulses via the spinothalamic tract. This may occur via an increase in γ -amino butyric acid (GABA) release from dorsal horn interneurons and also by release of beta-endorphins, which is associated with decreased myocardial oxygen consumption. Human studies of norepinephrine spillover as well as other animal models have shown a clear effect of SCS on the sympathetic system with consequent reduction in oxygen demand (12–14). Further improvement of myocardial ischemia occurs due to improved blood flow at the coronary microvascular level, which is supported by studies showing increased homogenization of myocardial blood flow (15,16). Animal models have shown that SCS modifies the capacity of intrinsic cardiac neurons to generate activity (17). SCS also acts to suppress the excitatory effects that local myocardial ischemia exerts on such neurons.

Two systematic reviews and meta-analyses have indicated that SCS can improve anginal symptoms, functional status, and HRQoL of individuals with RA with no negative effects on mortality (18,19). However, trials to date have been small, range considerably in their methodological quality, and have included variable and

nonpragmatic comparators. In 2008, the National Institute for Health and Care Excellence (NICE) in the United Kingdom concluded that there was inadequate evidence to recommend the routine use of SCS and called for a pragmatic randomized controlled trial (RCT) that compares SCS against current usual care management for RA (20,21).

The overarching aim of this pilot study was to assess the feasibility of undertaking a definitive multicenter trial to assess the clinical effectiveness and cost-effectiveness of adding SCS to usual care in patients with RA. Before undertaking such a definitive study, a number of uncertainties exist. The specific objectives of this study were to address these key uncertainties: 1) assess recruitment, uptake, and retention of patients; 2) assess the feasibility and acceptability of SCS treatment from the point of view of patients and referring physicians; 3) assess the feasibility and acceptability of standardizing usual care; and 4) test the feasibility and acceptability of the proposed trial outcome measures in both groups.

METHODS

The study design and methods have been described in the published study protocol (22) and are summarized here.

Study Design

The Refractory Angina Spinal Cord stimulation and usual care study (RASCAL) study is a pragmatic multicenter external pilot RCT that allocated RA patients to receive SCS plus usual care (“SCS group”) or usual care alone (“UC group”). Recruitment took place in four English centers (The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust; Russells Hall Hospital, Dudley Group of Hospitals NHS Foundation Trust; Basildon University Hospital, Basildon and Thurrock University Hospitals NHS Foundation Trust; and Derriford Hospital, Plymouth Hospitals NHS Trust) between January 2011 and June 2014.

Given the paresthesia associated with SCS, it was not possible to blind patients, clinicians, or researchers to group allocation. However, given the potential observer bias associated with assessing exercise capacity, we sought to blind those conducting this outcome assessment. The research nurses conducting the remainder of the data collection were independent of the delivery of patient care in the trial.

The study was reviewed by the Ethics committee NRES committee UK North East Northern and Yorkshire and received a favorable opinion in July 2011 reference: 11/NE/0175. The study was registered with ISRCTN65254102. All patients provided written informed consent prior to randomization.

Study Population

Patients were eligible for inclusion if they were 18 years of age or older with limiting angina despite optimal anti-angina therapy, had a Canadian Cardiovascular Society functional classification of angina of Class III or IV, and had angiographically documented coronary artery disease that was deemed not suitable for revascularization by the referring cardiologist or cardiothoracic surgeon. In addition, all eligible patients had to show demonstrable ischemia on functional testing and satisfactory multidisciplinary assessment in accordance with the British Pain Society guidelines for SCS (23).

Exclusions included a pacemaker or implanted defibrillator incompatible with SCS, a comorbidity considered by the assessing clinician

to overshadow the effect of the angina or render a patient an unsuitable candidate for neuromodulation (e.g., advanced spinal disease or deformity), poor cognitive ability, ongoing anticoagulation therapy (where anticoagulants cannot be safely discontinued without jeopardizing patient safety), or refusal to participate in the study.

Patients fulfilling these criteria were consented and offered entry to the study.

Study Procedure

Eligible patients were randomized sequentially to either the SCS or the UC group in a 1:1 ratio. The randomization sequence was computer generated and stratified by hospital, age, gender, and Canadian Cardiovascular Society functional classification of angina. The randomization sequence was prepared by the trial statistician (RT) and allocation concealment maintained by only revealing allocation of each participant by email correspondence to the study coordinator following completion of baseline outcomes.

Interventions

SCS

For the patients allocated to the SCS group, the intervention was started within six weeks from the date of randomization with an acute on-table trial of SCS followed by full implantation if the trial was successful. In case of failure to obtain >80% paresthesia coverage of the painful area or if painful sensations were generated when

the temporary stimulator was switched on, the procedure was aborted and the leads removed with no full implantation (“failed trial”). Participants who had a failed trial of SCS continued to receive treatment and follow-up as per the study protocol (both groups were to receive UC).

The SCS implant was performed by an experienced health professional (i.e., ≥15 SCS implants in the previous 12 months) at the Pain Departments across the four study sites. The procedure consisted of inserting one or two epidural leads of SCS through a needle into a thoracic epidural interspace under local anesthetic with patients either in prone, lateral, or sitting position according to patient and operator preference. The leads were positioned at C7/T1 (N = 7), T11/T12 (N = 1), T1/T2 (N = 5), and C2 (N = 1). Once in position, the leads were connected to an external stimulator and the position adjusted to obtain optimum coverage of the painful area. In cases where the paresthesia covered 80% or more of the painful area, the leads were anchored to the spine via a small incision and connected via tunneled subcutaneous extensions, where required, to an implanted pulse generator placed in the anterior abdominal wall or the buttock. Implanted participants were instructed on how to adjust their SCS device to generate a comfortable paresthesia level. They were instructed to do this regularly for two hours, three times per day to terminate any angina attack for as long as is necessary or before any exertion known or anticipated to generate angina pain.

UC

In order to standardize the delivery of UC, it was agreed by the site investigators that both groups of participants across the four

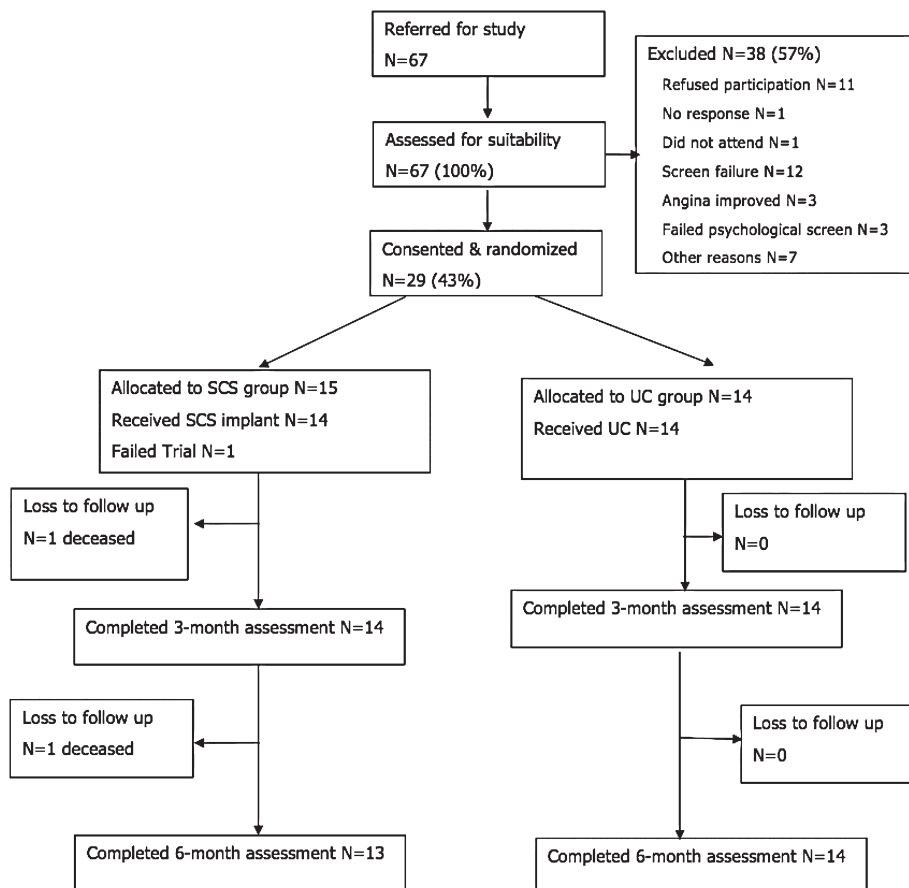


Figure 1. RASCAL study CONSORT diagram.

research sites be offered the following sequence of UC therapies: an education session with a pain consultant; trial of a transcutaneous electrical nerve stimulation (TENS); serial thoracic sympathectomy (where no medical contraindications existed); and oral or systemic analgesics and adjuvant analgesia. UC was based on a survey of current RA management in the UK reported in the study protocol (22). It should be noted that thoracic sympathectomy, although common practice in the UK, may not be routinely used in other countries and is not recommended in the European Society of Cardiology (24) and American College of Cardiology/American Heart Association guidelines (25). These therapies were started, if possible, on the day of randomization and were received sequentially where this was felt to be clinically appropriate by the investigator. Participants who had already tried and failed to obtain relief from any of the sequence of therapies above, were moved onto the next

therapy. Following completion of the above sequence, the treating physician was able to apply any therapy deemed appropriate, with the exception of repeat coronary artery bypass graft, percutaneous revascularization (or stenting), percutaneous myocardial laser revascularization, or enhanced external counterpulsation. Any patient with a significant and sudden downturn in their symptoms could be reevaluated by their cardiologists, including repeat angiography and a reappraisal of revascularization options if the angiographic findings had changed. Given the pragmatic nature of this pilot trial, we did not seek to control the pattern of accepted UC

Table 1. Baseline Demographic Characteristics.

	UC group, N = 14 N (%) or mean (SD)	SCS group, N = 15 N (%) or mean (SD)
Participant characteristics		
Gender (number of men)	10 (71%)	11 (73%)
Age (years)	66.5 (2.1)	65.4 (3.0)
BMI (kg/m ²)	30.9 (6.9)	32.5 (5.8)
Ethnicity		
Caucasian	14 (100%)	15 (100%)
CCS Classification		
Class III	9 (64.3%)	9 (60%)
Class IV	5 (35.7%)	6 (40%)

BMI, body mass index; CCS, Canadian Cardiovascular Society functional classification of angina; SCS, spinal cord stimulation; UC, usual care.

Table 2. Patient Satisfaction at Six-Month Follow-Up.

	SCS group N median (range)	UC group N median (range)
Satisfied with the pain relief *?	13 4 (2 to 4)	14 3 (2 to 4)
Based on experience so far, would you have agreed to this treatment [†] ?	13 4 (2 to 4)	14 3 (2 to 4)
How acceptable was each treatment [‡] ?		
Education session with consultant	12 4 (3 to 4)	13 4 (3 to 4)
TENS machine	8 2 (1 to 4)	12 3 (1 to 4)
Thoracic sympathectomy	1 1 (1 to 1)	4 3.5 (2 to 4)
Medications	11 3 (1 to 4)	14 3 (2 to 4)

*4: very satisfied; 3: satisfied; 2: not satisfied; 1: very unsatisfied.[†]4: definitely yes; 3: yes; 2: no; 1: definitely no.[‡]4: extremely acceptable; 3: acceptable; 2: not acceptable; 1: extremely unacceptable.SCS, spinal cord stimulation; TENS, transcutaneous electrical nerve stimulation; UC, usual care.

Table 3. Primary and Secondary Outcome Scores at Baseline and Follow-Up.

	Baseline		Three-month follow-up			Six-month follow-up		
	SCS group N Mean (SD)	UC group N Mean (SD)	SCS group N Mean (SD)	UC group N Mean (SD)	SCS-UC difference* Mean (95% CI)	SCS group N Mean (SD)	UC group N Mean (SD)	SCS-UC difference* Mean (95% CI)
Primary outcome								
<i>Seattle Angina Questionnaire</i>								
Physical limitations	15 33.3 (15.4)	14 32.1 (15.3)	14 41.1 (18.6)	13 33.9 (15.8)	-7.3 (-21.5 to 6.7)	14 38.5 (19.4)	14 33.9 (15.8)	-3.5 (-14.6 to 7.7)
Angina stability	15 36.7 (18.5)	14 26.8 (6.7)	14 44.6 (20.0)	14 32.1 (15.3)	-8.2 (-23.7 to 7.2)	13 46.2 (26.9)	14 37.5 (19.0)	0.5 (-16.9 to 17.9)
Angina frequency	15 29.3 (12.8)	14 27.1 (12.7)	14 32.8 (23.2)	14 32.8 (16.8)	-17.8 (-33.1 to -2.5)	13 46.2 (26.3)	14 31.4 (21.7)	-12.8 (-29.1 to 3.5)
Treatment status	15 80.0 (23.5)	14 73.2 (20.7)	14 85.7 (18.9)	14 83.9 (18.6)	4.1 (-9.3 to 17.5)	13 90.4 (16.2)	13 76.9 (21.6)	-9.1 (-24.6 to 6.3)
Quality of life	15 36.7 (16.0)	14 30.4 (10.6)	14 55.4 (20.0)	14 35.7 (16.1)	-19 (-32.6 to -5.3)	13 63.5 (21.9)	14 42.8 (22.8)	-22.3 (-39.2 to -5.3)
Secondary outcomes								
<i>Frequency of angina attacks (per week)</i>	15 22.0 (17.1)	14 14.6 (13.6)	12 11.2 (18.1)	14 16.1 (15.1)	-8 (-22 to 6) Rate ratio: 0.48 (0.37 to 0.62)	13 13.1 (19.8)	14 19.5 (20.9)	-11 (-27 to 5) Rate ratio: 0.41 (0.33 to 0.52)
<i>Exercise capacity</i>								
Six-minute walking distance (m)	13 121 (98)	12 175 (100)	Not assessed	Not assessed	—	10 191 (81)	9 140 (78)	60 (-4 to 123)
EQ-5D tariff	15 0.27 (0.34)	14 0.50 (0.26)	14 0.53 (0.24)	14 0.52 (0.22)	-0.1 (-0.3 to 0.1)	13 0.55 (0.29)	14 0.48 (0.24)	-0.2 (-0.4 to 0)
<i>Short-Form 36</i>								
Physical functioning	15 26.7 (23.4)	14 22.5 (17.4)	14 32.5 (16.9)	14 25.0 (21.6)	4.5 (-7.9 to 16.8)	13 31.1 (20.2)	14 28.6 (28.0)	0.1 (-18.8 to 18.9)
Role limitations caused by physical problems	15 3.3 (8.8)	14 1.8 (6.7)	14 16.1 (23.2)	14 5.4 (14.5)	10.6 (-5.8 to 27.1)	13 13.4 (21.9)	14 5.4 (10.6)	5.9 (-6.4 to 18.2)
Role limitations caused by emotional problems	15 33.3 (43.6)	14 33.3 (43.6)	14 69.0 (46.2)	14 47.6 (42.8)	26.6 (-6.6 to 59.4)	13 71.7 (40.5)	14 40.4 (47.2)	28.8 (-2.6 to 60.3)
Energy/vitality	15 28.7 (21.2)	14 27.5 (17.6)	13 38.8 (16.1)	14 26.8 (15.9)	9.6 (-1.5 to 20.7)	13 38.8 (18.5)	14 26.8 (18.5)	16.4 (4.6 to 28.2)
Mental health	15 53.3 (23.5)	14 58.8 (19.7)	13 67.1 (23.4)	14 62.3 (20.9)	8.5 (-5.2 to 22.2)	13 72.6 (16.6)	14 63.7 (17.8)	11.5 (1.3 to 21.7)
Social functioning	15 30.8 (24.5)	14 41.1 (13.4)	15 49.1 (34.8)	14 45.5 (18.7)	6.8 (-11.4 to 25.1)	13 52.9 (24.6)	14 47.3 (23.1)	9.8 (-7.1 to 26.6)
Bodily pain	15 22.2 (14.5)	14 29.6 (10.4)	13 36.9 (18.3)	14 35.4 (17.7)	4.0 (-11.6 to 19.6)	13 42.3 (16.9)	14 35.4 (11.3)	8.8 (-3.7 to 21.4)
General health	15 56.0 (10.6)	14 53.2 (8.4)	13 57.7 (11.6)	14 50.7 (9.2)	3.3 (-5.1 to 11.7)	13 54.2 (7.9)	14 52.1 (12.0)	-0.1 (-7.4 to 7.2)

*Between-group difference adjusted for baseline score and stratification variables (i.e., center, CCS class, age <65 vs. ≥65 years.CCS, Canadian Cardiovascular Society functional classification of angina; SCS, spinal cord stimulation; UC, usual care.

treatments received by participants in either SCS or UC groups over the period of study. However, UC treatments received by both groups were documented.

Outcome Measures

We collected the following pilot study outcomes:

1. Recruitment and retention: We documented procedures for recruiting patients in both groups and any problems that have arisen during this process. Retention was assessed by documenting the number of dropouts and lost to follow-up in both groups.
2. Feasibility and acceptability of design: We quantified the time for attainment of recruitment numbers against preplanned targets, the proportion of suitable patients who failed to provide consent, and the ratio of participants screened vs. randomized.
3. Feasibility and acceptability of treatment: Patients were asked to assess their willingness to recommend SCS or UC to other patients. This was assessed by three questions based on a Likert response scale: Are you satisfied with the pain relief provided by your treatment? Very Satisfied/Satisfied/Unsatisfied/Very Unsatisfied; Based on your experience so far, would you have agreed to this treatment? Definitely Yes/Yes/No/Definitely No; Can you tell us how acceptable these treatments were to you? [list of treatments provided] Extremely acceptable/Acceptable/Not acceptable/Extremely unacceptable /Not Applicable.
4. Feasibility and acceptability of proposed patient outcome measures: quantified as the number of returned and complete outcome assessments available for assessment.
5. Outcome variance: Mean and standard deviation for all outcomes were calculated for each group at all assessment visits (to inform power calculations for a definitive trial).

Patient outcome measures were collected at baseline (prerandomization), and three and six months postrandomization by a clinic visit undertaken by the research nurse. The study's

primary outcome parameter was disease-specific HRQoL assessed using the UK version of the Seattle Angina Questionnaire (SAQ) (26). The SAQ quantifies patients' physical limitations caused by angina, the frequency of and recent changes in their symptoms, their satisfaction with treatment, and the degree to which they perceive their disease to affect their quality of life. Each scale is transformed to a score of 0 to 100, where higher scores indicate better function (e.g., less physical limitation, less angina, and better quality of life). Secondary outcomes included: angina attacks recorded by diary for a week; exercise capacity assessed by a symptom-limited treadmill; and generic HRQoL assessed using the EuroQol (EQ-5D-3L) converted into single (utility) indices using the UK tariff (27) and Short Form-36 (SF-36) questionnaires (28,29). Exercise capacity was assessed at baseline and six months follow-up only. Where patients were unable or unwilling to undertake a symptom-limited treadmill test, a six-minute walk test was instead undertaken. To allow comparison over time, each participant performed the same exercise tests at baseline and follow-up. The nature and frequency of device-specific and nondevice complications and adverse events (serious and nonserious) were collected for both groups at each follow-up visit and in-between visits.

Statistical Analysis

Study sample size was chosen to inform the feasibility objectives of this study, i.e., provide sufficiently precise estimates of the likely rates of recruitment and retention, and to yield estimates of the variability of the primary and secondary outcomes to inform power calculations for a subsequent full-scale RCT. We sought to recruit and randomize a total of 45 RA patients (15 per center) over a 20-month period.

Given the pilot nature of this trial, we did not seek to formally inferentially test and report *p* values for the comparison of outcomes either between or within SCS and UC groups. Instead, we report mean and standard deviation (or relevant summary statistics) for both groups for all assessments at each follow-up

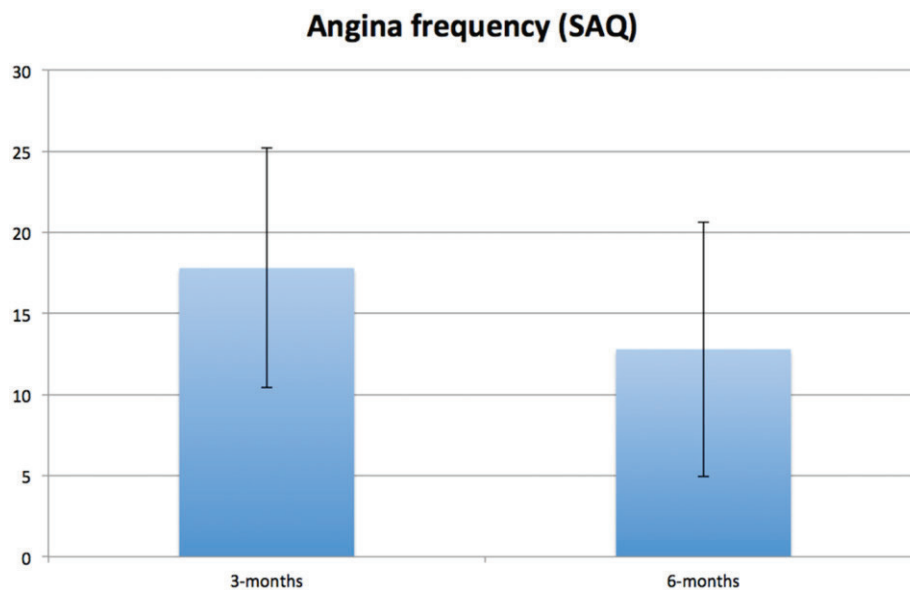


Figure 2. Between-group mean difference at three and six months for angina frequency (SAQ) adjusted for baseline score and stratification variables (i.e., center, CCS class, age <65 vs. ≥65 years). Error bars represent standard error of difference. Positive between-group difference in SAQ indicates superior scores for SCS group compared with UC group. CCS, Canadian Cardiovascular Society functional classification of angina; SAC, Seattle Angina Questionnaire; SCS, spinal cord stimulation; UC, usual care.

point based on the intention-to-treat principle (i.e., according to the original randomization). We also report the mean (and 95% CIs) between group difference in outcomes at three- and six-month follow-up adjusting for baseline outcome score and stratification variables. The between-group difference in angina frequency is also reported as a rate ratio. All analyses were conducted using STATA (Release 13.1; College Station, TX, USA: StataCorp LP).

RESULTS

Recruitment, Retention, and Feasibility of Design

Study enrollment, allocation to the SCS and UC groups, and follow-up of study participants are summarized in the CONSORT flow diagram shown in Figure 1. Sixty-seven patients were screened and a total of 29 RA patients were randomized (SCS group: 15; UC group: 14), a screening to randomization ratio of 2.3:1. The original forecast was a recruitment rate of 1.5 patients per month. However, the actual recruitment rate across the initial three sites was 0.7 patients per month. Given this lower recruitment rate, the period of recruitment had to extend by 22 months and took place over a total of 42 months (January 2011 to June 2014) and a fourth center was opened (on month 24).

None of the patients recruited into the study declined his/her treatment allocation and none of the referring physicians counseled patients against their treatment allocation. No participants chose to withdraw from the study. No patients required repeat angiography during the study period.

Baseline Characteristics and Assessments

There appeared to be good balance between SCS and UC group participants in terms of their baseline demographic characteristics (Table 1). However, there was evidence of imbalance in some of the

primary and secondary assessment scores as summarized in Table 1. Other cardiovascular morbidities included hypercholesterolemia ($N = 23$), family history of coronary artery disease ($N = 22$), hypertension ($N = 19$), insulin-dependent diabetes mellitus ($N = 5$), body mass index > 30 ($N = 14$), and smoking (current smoker $N = 3$; previous smoker $N = 19$). Previous treatments include coronary artery bypass graft ($N = 24$), TENS ($N = 7$), stents ($N = 14$), percutaneous coronary intervention ($N = 6$), stellate ganglion blocks ($N = 3$), and anti-angina medications ($N = 29$). Seventy-six percent (22/29) of the patients were taking eight or more different cardiovascular medications, including anticoagulants, antiplatelets, beta blockers, ACE-inhibitors or angiotensin receptor blockers, aldosterone antagonists, and the full range of available antianginal agents.

Acceptability of Treatment Received

Participants in both SCS and UC groups generally rated their acceptability with treatment as good (Table 2). The number of patients receiving UC therapies was equal to the number of responders to the patient's satisfaction/acceptability questionnaire. In the SCS group, one patient received thoracic sympathectomy after randomization but before SCS implantation. Eight patients used TENS following randomization and until the SCS implantation. Patients in the SCS group did not use TENS following SCS implant. Median satisfaction with pain relief and agreement to receipt of treatment were 4 (i.e., rating of "very satisfied" and "definitely yes," respectively) in the SCS group and 3 (i.e. rating of "satisfied" and "yes") in the UC group. There was some evidence of higher scores for SCS than UC. Acceptability of specific UC therapies was variable.

Feasibility of Outcome Collection and Outcome Results at Follow-Up

Primary and secondary outcome measures were completed by all 29 randomized patients at baseline. Allowing for two deaths,

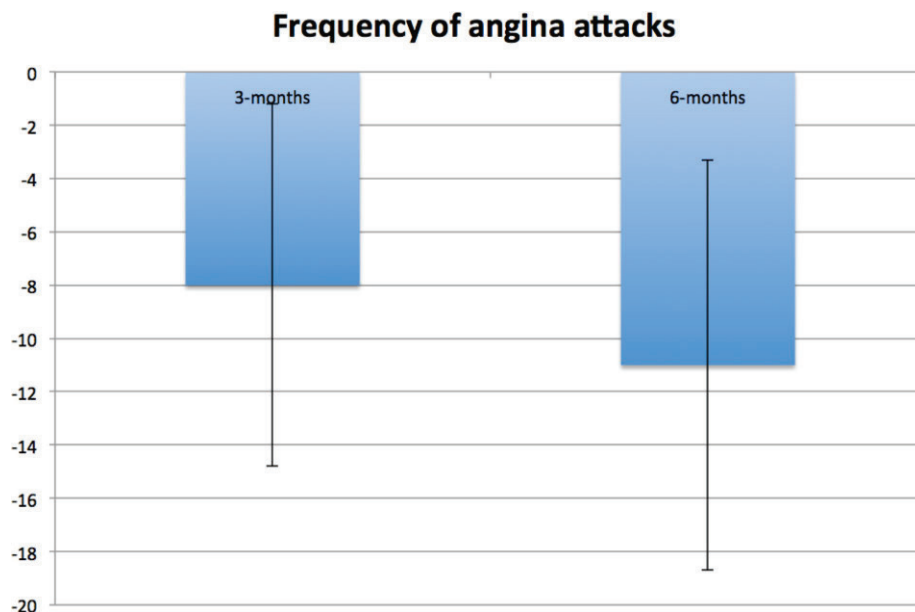


Figure 3. Between-group mean difference at three and six months for frequency of angina attacks adjusted for baseline score and stratification variables (i.e., center, CCS class, age < 65 vs. ≥ 65 years). Error bars represent standard error of difference. Negative between-group difference indicates larger reduction in angina frequency in SCS group compared with UC group. CCS, Canadian Cardiovascular Society functional classification of angina; SCS, spinal cord stimulation; UC, usual care.

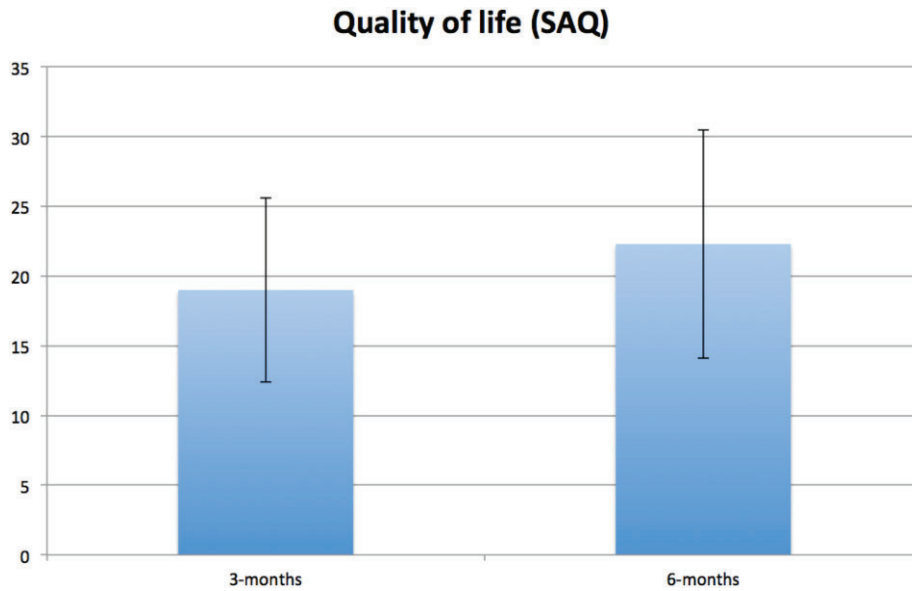


Figure 4. Between-group mean difference at three and six months for SAQ angina quality of life score adjusted for baseline score and stratification variables (i.e., center, CCS class, age <65 vs. ≥65 years). Error bars represent standard error of difference. Positive between-group difference in SAQ indicates superior scores for SCS group compared with UC group. CCS, Canadian Cardiovascular Society functional classification of angina; SAC, Seattle Angina Questionnaire; SCS, spinal cord stimulation; UC, usual care.

outcomes were completed at three and six-month follow-up in the 27 remaining participants. While the vast majority of patients undertook the six-minute walk test, only two patients were able to perform a symptom-limited treadmill test. Primary and secondary outcome results at three months and six months follow-up are shown in Table 3. There was a consistent pattern of a positive change in both SCS and UC groups in outcomes at three- and six-month follow-up compared to baseline, i.e., increases in SAQ scores, exercise capacity, EQ-5D tariff, and SF-36 scores, and a reduction in the frequency of angina attacks. The magnitude of these outcome improvements appeared to be higher for the SCS than the UC group (Figs. 2–6).

Adverse Events

Two participants died of causes related to their RA (i.e., cardiogenic shock and cardiac arrest) but were judged to be unrelated to study procedures. Both were randomized to the SCS group; one receiving a permanent implant and the other failing the SCS screening trial.

A total of 25 adverse events were recorded over the six-month study follow-up (see Table 4). Of these, four were related to SCS therapy: two cases of superficial infection, one case of pain over the implant, and one case of inadequate paresthesia coverage. Five adverse events were related to antiangina therapy and included three cases of headache, one case of diplopia, and one

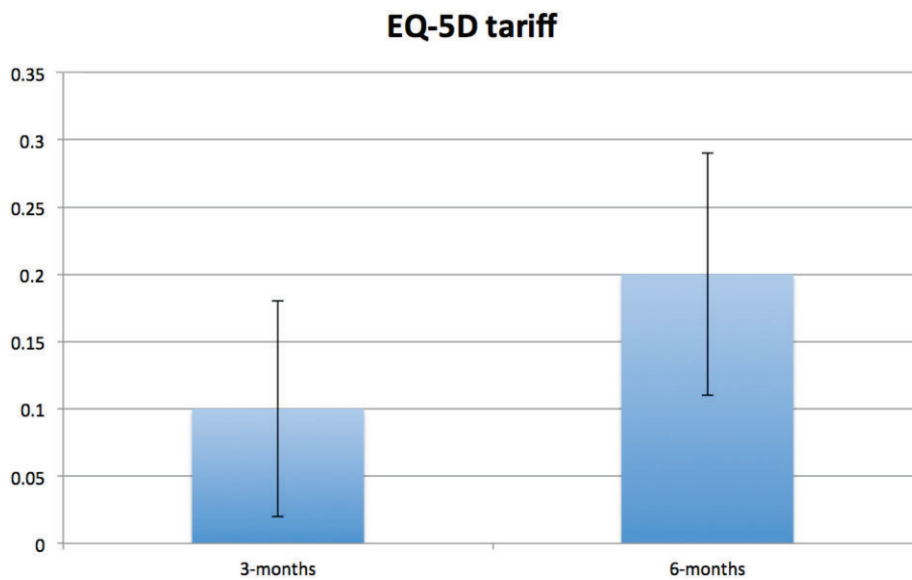


Figure 5. Between-group mean difference at three and six months for EQ-5D tariff adjusted for baseline score and stratification variables (i.e., center, CCS class, age <65 vs. ≥65 years). Error bars represent standard error of difference. Positive between-group difference in EQ-5D tariff indicates superior scores for SCS group compared with UC group. CCS, Canadian Cardiovascular Society functional classification of angina; SCS, spinal cord stimulation; UC, usual care.

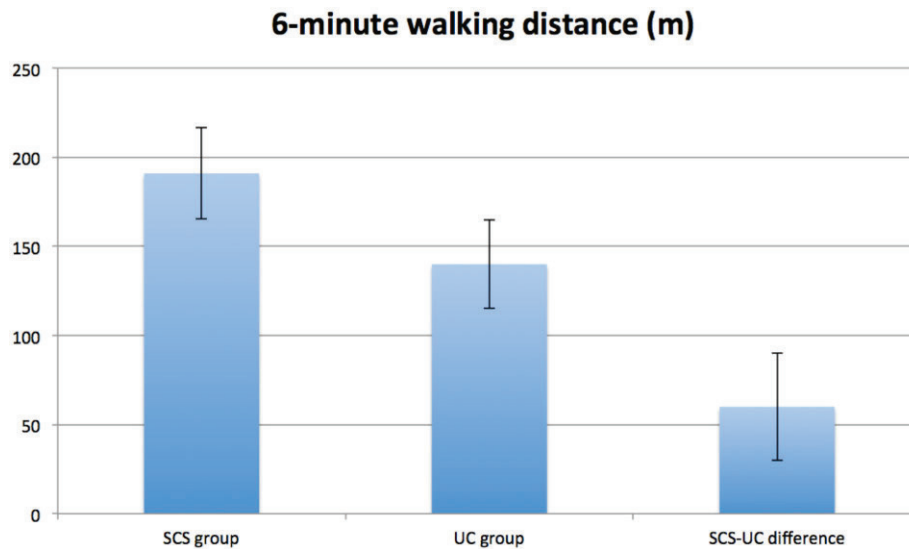


Figure 6. Exercise capacity at six months for SCS and UC group and between-group mean difference for six-minute walking distance adjusted for baseline score and stratification variables (i.e., center, CCS class, age <65 vs. ≥65 years). Error bars represent standard error of difference. Positive between-group difference in six-minute walking distance indicates superior scores for SCS group compared with UC group. CCS, Canadian Cardiovascular Society functional classification of angina; SCS, spinal cord stimulation; UC, usual care.

case of dizziness. Twelve participants required hospitalization (six SCS group, six UC group), five for the treatment of chest pain, one for intravenous antibiotic treatment of SCS-related infection. Five admissions were unrelated to angina or study procedures (hemiplegic migraine and epilepsy, vestibular pathology, pulmonary edema and septic shock, migraine, cellulitis left leg). The patient admitted with pulmonary edema and septic shock made a full recovery.

DISCUSSION

A pilot study was undertaken to inform progression to a fully powered randomized trial to determine the clinical effectiveness and cost-effectiveness of the addition of SCS to UC compared

with UC alone in patients with RA. Patient recruitment was found to be challenging in this pilot; we failed to achieve the target study sample size, recruiting and randomizing 29 patients out of the original target of 45. Nevertheless, once patients were randomized, we found participant retention and outcome completion to be very high; except for two patients who died due to their disease during the study, there was no loss to follow-up and all participants provided outcomes at three- and six-month follow-up.

Although not formally powered to compare outcomes either within or between groups, we did see evidence of an improvement in HRQoL demonstrated by the disease-specific SAQ as well as generic quality of life questionnaires, exercise capacity, and reduction in angina frequency at follow-up in both the SCS and UC groups, with a trend towards larger improvements in the SCS group.

Table 4. Serious Adverse Events Observed During the Study Period.

Site	Randomized to:	Serious adverse event	Category	Device related
01	UC	Hemiplegic migraine and epilepsy	Hospitalization	No
	UC	Central chest pain (unstable angina)	Hospitalization	No
	UC	Migraine and nonepileptic seizures, right occipital nerve neuralgia and chest pain	Hospitalization	No
	SCS	Ongoing microvascular angina	Hospitalization	No
02	SCS	Exacerbation of angina—unrelieved by GTN spray	Hospitalization	No
	SCS	Cardiogenic shock	Death	No
03	UC	Chest pains	Hospitalization	No
	UC	Chest pains	Hospitalization	No
	SCS	Cardiac arrest	Death	No
	SCS	Vestibular pathology	Hospitalization	No
	SCS	SCS infection	Hospitalization	Yes
	UC	Pulmonary edema and septic shock	Hospitalization	No
	SCS	Migraine	Hospitalization	No
04	SCS	Cellulitis left hand	Hospitalization	No
		No SAEs reported		

GTN, glyceryl trinitrate; SAE, serious adverse event; SCS, spinal cord stimulation; UC, usual care.

This trend can be partly explained by baseline differences and without a sham comparator we cannot rule out the possibility of a placebo effect contributing to improvements with SCS. In addition, SCS appeared to be a safe therapy in RA; there was one device-related serious adverse event over the six-month follow-up period of the trial. One patient randomized to SCS had a failed test trial, a success rate of 93%. These findings are in agreement with those of previous clinical studies and systematic reviews of SCS in RA (18,19,30–32). RA is a condition affecting an elderly population with numerous comorbidities. We did not find this to be a barrier to SCS implant or usage in this population.

The main strengths of this study were its randomized trial design and the ability to retain patients once recruited. However, the pilot did have limitations. Although study logs recorded 67 patients to be screened, it was apparent from discussions with the study sites that many more patients were deemed to not fulfill the study entry criteria from the referral letter such as: no clear demonstrable ischemia, severe spinal pain, and the presence of other implanted devices. Slow patient recruitment, resulting in study termination, has been previously reported in an evaluation of SCS for RA; however, the possible reasons for slow recruitment were not discussed (32). Causes for the slow recruitment in our study include higher than expected screening failures; the majority of screening failures were subjects referred with symptoms typical of RA but no demonstrable reversible ischemia on functional testing. The requirement to demonstrate reversible ischemia on functional testing was agreed by the study steering committee at its initial meeting to be important to provide a homogenous population suffering from chest pain related to ischemia rather than other potential causes such as atypical and functional chest pain. We believe that this single inclusion criterion had the most profound effect on our ability to recruit to this study. The requirement for demonstration of ischemia as the etiology of RA is explicit in the definition of RA coined by the European Task Force (33). By contrast, the UK RA group defined the condition as chronic stable angina that persists despite optimal medication and when revascularization is unfeasible or where the risks are unjustified (34). It has been recently proposed that the definition of RA should be more precise by specifying the reason for revascularization unsuitability, such as microvascular dysfunction, epicardial stenosis, or generalized lesions (35). Finally, the study encountered protracted negotiations with the Primary Care Trusts relating to excess treatment costs (ETC) associated with the devices and the implant procedure, which resulted in significant delays.

Implications for Planning a Future Trial

The study demonstrates the importance of a pilot and feasibility research prior to conducting a fully funded powered RCT (36). The key finding from the pilot trial is the need for a multifaceted approach to ensure the recruitment of patients in order to meet the needs of a future definitive trial. Based on a minimally important difference of 10 (37) on the SAQ and the conservative estimates of both standard deviation of 20 and attrition rate of 20% (except for two deaths, we saw no loss to follow-up in this pilot), a definitive trial will need to recruit 110 patients per group at 90% power and 5% alpha. Future studies exploring SCS use in RA may wish to adopt the UK group definition, which does not stipulate the demonstration of reversible ischemia as a cause for the angina but takes a more patient-centered view of the condition. We observed a variation in the point of diagnosing RA between the sites. The definition of RA was seen to differ in some centers where some of the research sites required an attempt of all potential medication choices before diag-

nosing patients as suffering from RA and referring to the study. Recruitment rates may be increased with greater education regarding the treatment options for these patients and the involvement of general practitioners and patient groups. SCS implantation by cardiologists should also be considered. We however would like to point out that we have during the recruitment period of this study contacted GP practices and invited them to refer patients with no success. A number of elderly subjects required some assistance with outcome measure completion from the study nurse. The six-minute walk test was more acceptable to an RA population than the treadmill test. A future trial should include use of the six-minute walk test in preference to the treadmill as well as provision of a study-independent professional to conduct exercise tests in a blinded manner. The patients randomized to UC considered the treatment options available to be acceptable and based on their experience would have agreed to receive these treatments. Subgroup analysis should include analysis of patients allocated to the SCS group with respect to prior treatments with therapies affecting the nervous system, such as TENS, stellate ganglion blockade, or sympathectomy vs. naive patients. We conclude that the study outcome measures are acceptable and appropriate for a future RCT. Collection of some of the interim data by post with telephone guidance where required should be considered by a future RCT. This will reduce the patient burden in an elderly population with multiple comorbidities.

CONCLUSION

In summary, there were several difficulties associated with recruitment of patients for this study, including a higher than expected screening failure, difficulty in confirming whether individual patients met the entry criteria of reversible ischemia, a lack of consensus on the point at which a diagnosis of RA is reached, and protracted negotiations with local hospitals and primary care trusts relating to agreement of device and procedure costs for the trial. By contrast, we managed to retain and collect three- and six-month outcomes from all surviving participants. We found SCS therapy and trial outcome measures to be acceptable and appropriate for future RCTs. Although we were not formally powered to investigate within- or between-group treatment differences, compared with baseline, there were trends across a number of the outcomes (including exercise capacity and HRQoL) of larger improvements in the SCS compared with UC group at three and six months. In addition, SCS appeared to be a safe therapy; there was one device-related serious adverse event over the six-month follow-up period of the trial.

Acknowledgements

We wish to thank Dr. Duncan McNab for chairing the study steering committee. We acknowledge the unrestricted grant of some SCS device materials from Medtronic and Boston Scientific.

Authorship Statements

Rui Duarte, Sam Eldabe, Rod Taylor, and Morag Brookes authored the final manuscript; all authors commented on the manuscript and approved the final manuscript. Sam Eldabe, Simon Thomson, Jon Raphael, Mark deBelder, and Ed Davies recruited patients into the study on the four sites. Mark deBelder acted as study cardiology advisor, Morag Brookes was study coordinator, and Rod Taylor was study statistician.

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COMMENTS

This pilot randomized controlled trial (RCT) on SCS for chronic refractory angina (CRA) certainly deserves merits.

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The authors are to be congratulated on an excellent paper, which is a remarkable example of how to systematically approach the challenges of clinical investigation.

Refractory angina (RA) has no universally recognized definition and there are at least two versions. The more rigorous interpretation requires the demonstration of reversible ischemia (European Study Group and Task Force) while a more clinically oriented understanding (UK refractory angina group) does not. In this elegant pilot study, the authors could show that the more restrictive version of the concept does exclude a majority of patients who would, based on clinical criteria, qualify as suffering from RA. Hence the study suggests that a randomized controlled trial would prove difficult to perform should the criteria of the European Society of Cardiology be adopted.

Second the study is not tied to the industry and is therefore devoid of the unintentional (and sometimes intentional) promotional interpretations, which too often plague the clinical studies on neuromodulation. Another advantage of governmental funding (here the National Institute for Health Research - UK) is that the effect of SCS on RA could be studied generically, i.e. independently of manufacturers or types of device that were used. This helps focusing the debate on the core issue and prevents irrelevant digressions about hypothetical advantages of one type of system over another.

Third there is a clear view on how a future randomized controlled trial should be designed. Hence this pilot study provides credible information for patient selection, power calculation and at the same time it allows assessing the outcomes that have the best chance to be used with the majority of the patients.

And finally the authors, very wisely, avoid statistical analysis, sticking to the rigorous interpretation of a pilot study. So there is no proof, no p

value or sophisticated statistics to support the tendencies that are presented. But to anyone who understands numbers and trends, the results of the RASCAL study undeniably smell very good.

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Comments not included in the Early View version of this paper.