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Efficacy of spinal cord stimulation as an adjunct therapy for chronic refractory angina pectoris☆

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ABSTRACT

Introduction: Patients with chronic refractory angina whose symptoms are not controlled with conventional therapies have a poor quality of life. Adjunctive therapies, such as spinal cord stimulation (SCS) may be considered in these cases. We sought to examine whether SCS is associated with changes in exercise capacity and angina severity in these patients.

Methods: We searched Pubmed, Medline and other databases until December 2015. Two reviewers independently extracted data and assessed risk of bias. Exercise capacity included exercise duration and rate pressure product, determined via an exercise test. Angina severity included daily angina frequency and nitrate consumption.

Results: A total of 518 participants (1048.25 person-years of follow-up), from 14 studies met our inclusion criteria. The mean age was 66.8 years and 68.5% were men. SCS implant duration ranged from 3 weeks to 5 years (median: 6 months). Using random effects meta-analysis, we found that SCS was associated with a higher exercise duration (1.90 min, 95% CI 1.71, 2.06) and lower angina severity, 1.55 less daily angina episodes, (95% CI −1.75, −1.33), 1.54 less daily nitrates consumed, (95% CI −1.81, −1.26), and a 22 points higher SF-36 angina frequency score (95% CI 10.76, 32.81; $p < 0.0001$) on follow-up. The change in rate pressure product was not significant.

Conclusion: This meta-analysis suggests that SCS, as an adjunct therapy to medical management, may be associated with a longer exercise duration and lower angina frequency and nitrate consumption in patients with chronic refractory angina pectoris who are not candidates for percutaneous intervention or revascularization.

1. Introduction

Angina pectoris is a disabling chest discomfort that is the result of ischemic atherosclerotic coronary artery disease associated with impaired coronary blood flow [1,2]. Myocardial ischemia can occur with at least 60% narrowing of a coronary artery diameter, but angina may not begin until the stenosis is greater than 75%. Treatment to improve myocardial ischemia includes either reducing oxygen demand (with beta-blockers, calcium channel blockers) or improving oxygen supply (with nitrates, and revascularization procedures such as coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty) [1,3]. For most patients, these therapies are sufficient to control symptoms. However, there are a growing number of patients surviving acute ischemic events who develop chronic angina pectoris that is refractory to conventional therapies. The estimated prevalence of chronic refractory angina is 100,000 in the United States, with similar numbers in Europe [3]. According to the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology Foundation (AHA/ACCF), patients with chronic refractory angina pectoris are categorized as having stable angina pectoris, coronary artery disease on a recent coronary angiogram, severe angina despite typical anti-anginal medications, and functional class 3–4 symptoms on the Canadian Cardiovascular Society classification. Also, these patients are not candidates for CABG or percutaneous coronary interventions (PCI) [3,4].

Prior studies have found that patients with refractory angina had a significantly impaired quality of life compared to those who had undergone revascularization procedures for symptomatic coronary artery disease (CAD) [5]. They have severely limited physical activity and

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tremendous psychological stress due to an awareness of the increased risk of a myocardial infarction [1,5]. These patients also experience numerous hospital admissions due to an acute myocardial infarction or unstable angina [1]. Thus, in addition to optimizing pharmacological treatment, adjunctive therapeutic modalities should be considered for symptomatic relief and quality of life improvement. One such therapeutic modality is spinal cord stimulation (SCS). Spinal cord stimulation is a technique that uses electrical stimulation via electrodes placed near the spinal cord to relieve chronic pain [6]. Although commonly used for the treatment of neuropathic or ischemic pain that is unresponsive to traditional pharmacological or physiotherapy treatments, SCS is also being used for patients with chronic refractory angina pectoris and peripheral vascular disease.

According to the ESC and AHA/ACCF guidelines, SCS falls under a class IIb recommendation as an alternative therapy for patients with chronic stable angina who are refractory to medical therapy and not candidates for percutaneous intervention or revascularization [3,4]. Although several studies have shown improvement in exercise duration, rate pressure product and angina frequency for patients with chronic refractory angina who underwent SCS, others have found no change [1,5,7–10]. Thus, the data remain inconclusive on the use of SCS as an adjunctive therapeutic modality for this group of patients. Given that patients with refractory angina have a poor quality of life due to debilitating pain and are very restricted in their daily activities, adjunctive therapies such as SCS are worth considering. Therefore, we sought to examine whether SCS is associated with exercise capacity and angina frequency and nitrate consumption in patients with chronic refractory angina pectoris who are not candidates for revascularization.

2. Methods

2.1. Literature search

We performed a literature search (TFI, RM and BT) for all relevant publications using Medline/Pubmed, Embase, Web of Science, the Wiley Cochrane Library, the Cochrane Database, Google Scholar, and clinicaltrial.gov databases through December 2015 using the following terms: “spinal cord stimulation,” OR “SCS” OR “neurostimulation” OR “spinal cord stimulator” OR “spinal stimulation” OR “nerve stimulation” AND “refractory angina,” OR “refractory angina pectoris” OR “chronic stable angina” OR “alternative therapy for angina” OR “angina pectoris” OR “angina.” We also searched reference lists to identify additional potential studies and referenced proceedings of the European Society of Cardiology, American Heart Association, and American College of Cardiology Foundation.

2.2. Inclusion and exclusion criteria

The Preferred Reporting Items for Systematic Reviews and Materials Statement (PRISMA) framework was used for the meta-analysis. For non-randomized studies, we followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) consensus statement. Two independent reviewers (TFI and RM) screened studies and extracted data from articles. Cohen's kappa was calculated to determine inter-rater reliability. The following inclusion criteria were used:

(1) Patients with chronic refractory angina who are
   a. Refractory to medical therapy (have received treatment for underlying coronary artery disease)
   b. Not candidates for percutaneous intervention or revascularization
(2) Patients had undergone implantation of a spinal cord stimulator
(3) Patients had follow-up measurements of exercise duration, rate pressure product, angina frequency, or nitrate consumption

Exercise capacity included exercise duration (minutes) and rate pressure product, as measured during an exercise treadmill test or bicycle ergometer. Angina severity included angina frequency (daily angina attacks) and daily nitrate consumption. Some studies also included the Short Form (SF) 36 Health Survey to determine quality of life. The SF-36 questionnaire is a 36-item patient-reported, validated questionnaire that assesses quality of life and has been widely used in patients with ischemic heart disease [11]. It includes a question on angina frequency, which is converted to a point score. The higher the score, the less disability. We included the angina frequency score component from the SF-36 survey in our analysis.

We excluded studies conducted in animals and cell lines, human studies that did not present data before and after SCS implantation, literature reviews, cross-sectional studies, or conference abstracts when data from a published study was not available (Supplemental Table 1). Studies were also excluded if nitrate consumption or exercise variables were not reported, or if final results were not yet published. Fig. 1 outlines the process of selecting studies.

2.3. Data extraction and analysis

We extracted the following variables from each study: authors, year of publication, geographic location, age, gender, sample size, method of measurement, exercise duration at baseline, exercise duration at the end of follow-up, rate-pressure product at baseline (mm Hg/min × 1000), rate pressure product at follow-up, angina frequency at baseline, angina frequency at follow-up, nitrate consumption at baseline, nitrate consumption at follow-up and follow-up duration after spinal cord stimulator implantation. We chose exercise duration as a primary outcome for our analysis because walking distance/time is a known prognostic indicator in patients with chronic cardiovascular diseases, with those unable to perform more than 400 m on a 6-minute walk test having increased risk of mortality [12]. We used exercise duration in this analysis instead of distance because only two studies provided information on exercise distance. Also, angina frequency and nitrate consumption were included as a primary outcome because they are important measures of angina severity and quality of life.

We evaluated the studies with regards to similarity of baseline patient characteristics, angina frequency, exercise duration and duration of follow-up. The primary endpoint was exercise tolerance (as measured by exercise duration and rate pressure product) and angina severity (as measured by angina frequency and nitrate consumption). We used a random effects meta-analysis to calculate the weighted mean difference in exercise duration, rate pressure product, angina episodes per day and nitrate consumption per day after SCS implantation. In sensitivity analysis, we also included the fixed effects model to examine the robustness of our findings. The Comprehensive Meta-Analysis software was used to create forest plots and assess risk of bias.

2.4. Quality assessment

To determine the extent to which we can be confident about our summary estimate, the quality of the included evidence was assessed according to a modified version of the Jaded rating scale, also used by Borjesson et al. (Supplementary Table 2) [13,14]. This scale poses the following questions to assess study quality: 1) How relevant was the study to the desired topic? 2) If a trial study, was it randomized? 3) Was there a control group? 4) Was there follow-up to the studies? 5) Were the withdrawals described? A study with a score of 0–1 points is considered low quality, 2–3 points is considered

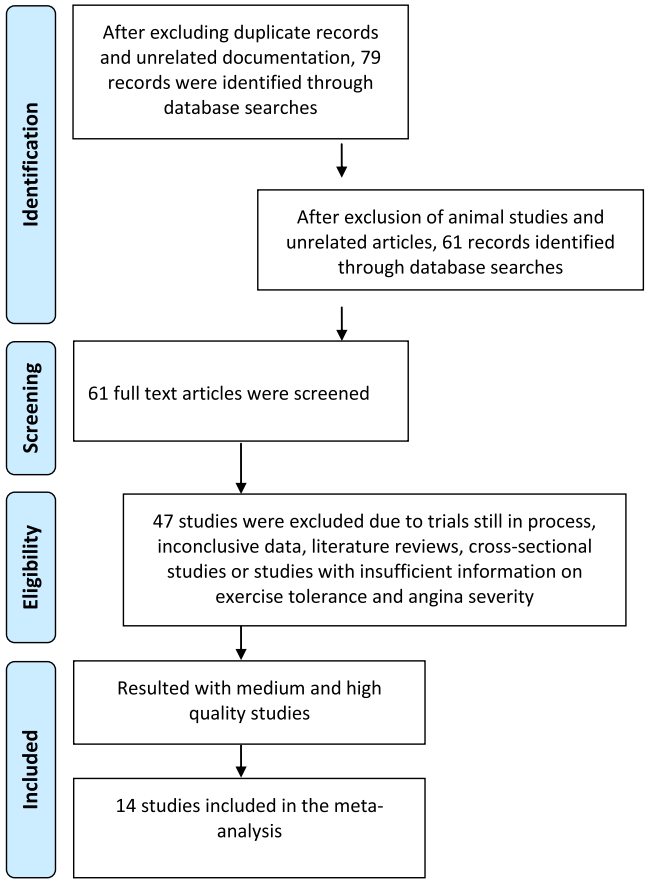

Fig. 1. Flow diagram illustrating the process of study selection.

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