Refractory angina pectoris

SCS has been used for treatment of refractory angina in Europe for 20 years, and much of the literature on SCS comes from European centers. Several systematic reviews have been published. In 2009, Taylor et al included 7 RCTs in a systematic review of SCS in the treatment of refractory angina. (7) The authors noted that trials were small and varied considerably in quality. They concluded that "compared to a 'no stimulation' control, there was some evidence of improvement in all outcomes following SCS implantation with significant gains observed in pooled exercise capacity and health related quality of life"; however, "further high quality RCT and cost effectiveness evidence is needed before SCS can be accepted as a routine treatment for refractory angina."

In 2008, a systematic review of the literature based on the Swedish Council on Technology Assessment in Health Care report on SCS in severe angina pectoris was published.(8) Seven controlled studies (5 of them randomized), 2 follow-up reports, and a preliminary report, as well as 2 nonrandomized studies determined to be of medium-to-high quality were included in the review. The largest RCT included 104 subjects and compared SCS and coronary artery bypass graft (CABG) in patients accepted for CABG and who were considered to have only symptomatic indication (i.e., no prognostic benefit) for CABG, according to the American College of Cardiology/American Heart Association guidelines, to run an increased risk of surgical complications, and to be unsuitable for percutaneous transluminal coronary angioplasty. Between-group differences on nitrate consumption, anginal attack frequency, and self-estimated treatment effect were not statistically significant at the 6-month follow-up.(9) At the 5-year follow-up, significantly fewer patients in the CABG group were taking long-acting nitrates, and between-group differences on quality of life and mortality were not significant. (10) Other studies included in the Swedish systematic review include one by McNab et al from 2006, which compared SCS and percutaneous myocardial laser revascularization (PMR) in a study with 68 subjects.(11) (Note: PMR is currently considered investigational through Medical Policy Reference Manual review.) Thirty subjects in each group completed a 12-month follow-up, and differences on mean total exercise time and mean time to angina were not significant. Eleven in the SCS group and 10 in the PMR group had no angina during exercise. The remaining RCTs included in the systematic review included 25 or fewer subjects.

Several RCTs were published after the systematic review but had limitations, such as small sample size and short follow-up. In 2012, Zipes et al published an industry-sponsored, single-blind, multicenter trial with sites in the United States and Canada. (12) This study, however, was terminated early. The Data and Safety Monitoring Board recommended that the study be terminated for futility after the interim analysis. A total of 118 patients with severe angina, despite maximal medical treatment were enrolled in the study. Of these, 71 patients (60%) underwent SCS implantation with the Intrel III neurostimulator (Medtronic). The remaining 47 patients were found not to meet eligibility criteria postenrollment or there were other issues, e.g., withdrawal of consent. The investigators had originally been planning to randomize up to 310 patients, but enrollment was slow. Implantation was successful in 68 patients; this group was randomized to high-stimulation (n=32) or a low-stimulation control (n=36). The low-stimulation control was designed so that patients would feel paresthesia, but the effect of stimulation would be subtherapeutic. The primary outcome was a composite variable of major adverse cardiac events (MACE), which included death from any cause, acute myocardial infarction (MI), or revascularization through 6 months. Fifty-eight of 68 patients (85%) contributed data to the 6-month analysis; analysis was by intention to treat. The proportion of patients experiencing MACE at 6 months did not differ significantly between groups (12.6% in the high-stimulation group and 14.6% in the low-

stimulation group; p=0.81). The sample size of this study was small, and it may have been underpowered for clinically meaningful differences.

A small 2011 RCT from Italy randomly assigned 25 patients to 1 of 3 treatment groups: SCS with standard levels of stimulation (n=10), SCS with low-level stimulation (75% to 80% of the sensory threshold) (n=7), or very low-intensity SCS (n=8). (13) Thus, patients in groups 2 and 3 were unable to feel sensation during stimulation. After a protocol adjustment at 1 month, patients in the very low-intensity group were re-randomized to one of the other groups after which there were 13 patients in the standard stimulation group and 12 patients in the low-level stimulation group. At the 3-month follow-up (2 months after re-randomization), there were statistically significant between-group differences in 1 of 12 outcome variables. There were a median of 22 angina episodes in the standard stimulation group and 10 in the low-level stimulation group (p=0.002). Nonsignificant variables included use of nitroglycerin, quality of life (VAS), Canadian Cardiovascular Society angina class, exercise-induced angina, and 5 subscales of the Seattle angina questionnaire.

Section summary

Numerous small RCTs have evaluated SCS as a treatment for refractory angina. While some studies have reported benefit, the majority have not. In 2 of the larger, more recent RCTs that enrolled more than 100 patients, there was no benefit on the primary outcomes. Overall, this evidence is mixed and not sufficient to allow conclusions on whether health outcomes are improved.

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