



Spinal Cord Stimulation versus Other Therapies in Patients with Refractory Angina: A Meta-analysis

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Background: An increasing number of patients with coronary disease suffer from angina that cannot be controlled by optimal medical management and revascularization. The purpose of this study was to evaluate the method of spinal cord stimulation (SCS) for the treatment of patients with refractory angina (RA).

Methods: We searched multiple databases, including PubMed, EMBASE, the Cochrane Library, and the Cochrane Central Register of Controlled Trials. The results of studies through March 2016 were included in our analyses. Systematic methodological appraisal and data extraction were conducted by two independent reviewers. All data analyses utilized the Review Manager 5.3, and the results were merged as weighted mean differences (WMD).

Results: Nine randomized controlled trials (RCTs) with a total of 364 patients who were diagnosed with RA were included in the analysis. After being pooled, the outcomes from the SCS treatment group did not differ from those from the coronary artery bypass grafting (CABG) or percutaneous myocardial laser revascularization (PMR) treatment groups. However, compared with ‘no SCS stimulation’ treatment groups, SCS significantly decreased nitrate drug usage (WMD: -2.03, 95% CI: [-3.12, -0.93], $p=0.0003$) and increased several indicators of health-related quality of life (HRQOL).

Conclusions: SCS appears to be a safe and effective management for RA although, it has similar efficacy when compared to PMR or CABG as a potential replacement therapy. However, before this method is used as a conventional treatment, more high-quality designed

multicenter RCTs are needed.

Key words: Refractory angina; Coronary disease; spinal cord stimulation, Clinical Trial, Meta-analysis

Introduction

Refractory angina is a type of coronary artery disease caused by coronary insufficiency that cannot be controlled by drug therapy, angioplasty and CABG; patients with RA face serious clinical problems. The clinical symptoms of RA are caused by reversible myocardial ischemia [1]. It has been estimated that approximately 350,000 patients each year are diagnosed with RA [2]. These patients mainly have severe physical limitations and a higher risk of heart attack, which reduces their quality of life despite optimal drug treatment. Various treatments for RA have been studied, such as spinal cord stimulation (SCS) [1, 3], enhanced external counterpulsation (EECP), CABG and PMR.

The SCS has been developed based on the “Gate control theory” [4] in which the segmental pain is inhibited. After the SCS was first implanted in the patients in 1967 [5], SCS was first used for RA in 1987 [6].

SCS was implanted at the level of the 6-8th thoracic vertebrae via an incision under anesthesia. Next, an electrode was inserted into the epidural space and advanced up to the 1st-2nd thoracic vertebrae under fluoroscopic guidance. Its location was adjusted up to the level where the patient experienced paresthesia and commensurate with the angina pain site. An extended wire was attached to a subcutaneous pulse-generator through an incision in

the left side of the flank that was below the left costal arch. A typical therapy for SCS is a low-amplitude stimulation three times per day for 1 hour in addition to using a strong stimulation during an angina attack. Patients can control the intensity of the stimulation when they feel pain. This method was recommended by the European Society of Cardiology (ESC) [7], the American Heart Association (AHA) and six additional scientific associations [8]. Here, we proceeded with a meta-analysis to evaluate the efficacy and safety of SCS for patients with RA.

Methods

Electronic literature search strategy

We searched several electronic databases including EMBASE, The Cochrane Library, MEDLINE, and The Cochrane Central Register of Controlled Trials from their inception to March 2016 for the selection of related articles. Our search terms included “spinal cord stimulation” and its synonyms, “refractory angina” and its synonyms, and the two terms combined. The electronic databases were searched by two independent investigators (Shaocheng Wang and Qixian Li). The abstracts of all articles identified as potentially related were retrieved and examined in the study selection process. Repetition of published trials was included only once.

Inclusion criteria

Studies qualified for inclusion if they were RCTs that included patients who were diagnosed with RA using pre-defined clinical criteria as well as those who received SCS therapy (whether alone or combined with other treatments). Reviews, observation studies, case reports, articles not relating to either SCS or refractory angina, and articles about SCS in syndrome X were excluded.

Data extraction and risk of bias assessment

Data extraction and risk of bias assessment were carried out by two independent investigators, with any disagreements being settled by a third investigator (Xiangrui Wang). We extracted the following outcome categories: exercise capacity, ischemic burden, anti-angina drug consumption, safety (morbidity, and SCS relevant complications), Canadian Cardiovascular Scale (CCS) class change and HRQOL.

We used Review Manager software (RevMan, version 5.3) to construct ‘the risk of bias’ (Figure 1) and included six parameters of bias with each parameter divided into “high risk”, “low risk”, or “unclear risk”. This was evaluated by the same two independent reviewers.

| | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|----------------------|---|---|---|---|--|--------------------------------------|------------|
| De Jongste, M.J 1993 | ? | + | + | + | + | + | ? |
| De Jongste, M.J 1994 | ? | ? | + | + | + | + | ? |
| Eddicks, S 2007 | ? | ? | + | + | + | + | ? |
| Hautvast, R.W.M 1998 | ? | ? | + | + | + | + | ? |
| Lanza, G. A 2012 | ? | + | + | + | + | + | ? |
| Mannheimer, C 1998 | ? | + | + | + | + | + | ? |
| McNab, D 2006 | + | + | + | + | + | + | ? |
| Pede, F 2001 | ? | + | + | + | + | + | ? |
| Zipes, D. P 2012 | ? | + | + | + | + | + | ? |

Fig.1. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

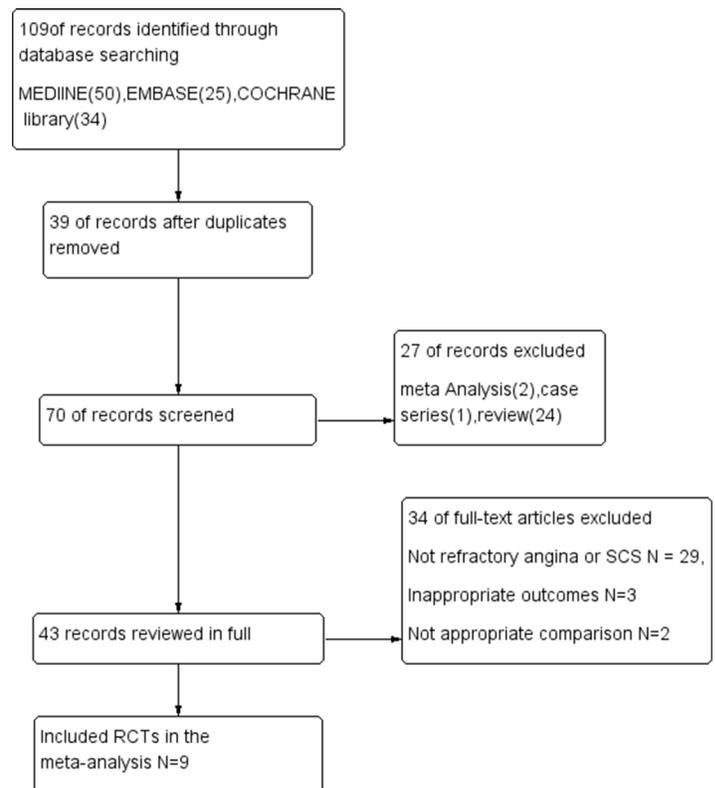


Fig. 2. Summary of study selection and exclude process.

Table 1.Characteristics of RCTs included in the meta-analysis

| Included of studies Country /year Design | Age-Mean (SD or range) Sex-% male Class Inclusion criteria | Intervention | | Outcomes | Follow up |
|---|--|----------------|-----------------|---|------------------------------------|
| | | N patients | N patients | | |
| De Jong, M.J Netherlands/1993 single-center RCT | 60.3 years (5) 70.8%male NYHA class III/IV Not suitable for revascularization | SCS ON N=12 | SCS OFF N=10 | Quality of life. Exercise capacity (treadmill time) Nitrate consumption | 1 year |
| De Jong, M.J Netherlands/1994 Single-center RCT | 18-76 years 62.8 years (3.1) 88.2%male NYHA class III/IV Not suitable for revascularization procedures Reversible ischemia on exercise | SCS ON N=8 | SCS OFF N=9 | Exercise (treadmill time) Health-related quality of life Nitrate drug usage Ischemic burden | 6-8weeks |
| Hautvast, R.W.M Netherlands/1998 Single-center RCT | Receiving optimal drug therapy 62.5 years (7.5) 56%male NYHA class III/IV Not suitable for revascularization procedures Receiving optimal drug therapy | SCS ON 13 | SCS OFF 12 | Angina attacks Nitrate consumption Exercise (treadmill time) Health-related quality of life | 6 weeks |
| Mannheimer, C Sweden/1998 Single-center RCT | 68.9 years (40-82) 80%male AHA angina class 3/4 Symptomatic indication for CABG and no benefit from CABG | SCS N=53 | CABG N=51 | Exercise capacity (workload time), Nitrate consumption Angina attack frequency Adverse events | 6 months 2 years 5 years |
| Pede, F Italy/2001 Single-center Cross Over RCT | 76 years (8) 60%male CCS class 3/4 Not suitable for revascularization procedures | SCS ON 15 | SCS OFF 15 | Ischemic burden | 48h |
| Eddicks, S., Germany/2007 Single-center Cross Over RCT | Reversible ischemia on exercise 65 years (8) 67%male CCS class 3/4 Angina pectoris >3 months Known coronary artery disease Reversible myocardial ischemia Optimal antianginal medication No benefit from revascularization | SCS1 N=12 | SCS 2 N=12 | Six-minute walk test Quality of life Angina attacks Nitrate usage CCS angina classification | 4 weeks |
| McNab, D UK/2006 Single-center RCT | 63.6 years 88%male CCS class 3/4 | SCS N=34 | PMR N= 34 | Exercise (treadmill time) Change in CCS Quality of life Adverse events | 3 months 12 months 24 months |
| Lanza, G. A Italy/2012 Multicenter RCT | 68 years (11.8) 52%male CCS class 3/4 Reversible myocardial ischemia Unsuitable for surgical and percutaneous coronary artery revascularization Stable picture of angina in the 2 months | SCS ON 10 | SCS OFF 8 | Angina episodes Nitrate consumption CCS angina class VAS score | 1 month 3 months |
| Zipes, D. P USA/2012 Multicenter RCT | 61.1 years (10.7) 73.5%male CCS class 3/4 Stable angina for two months Not a candidate for CABG or PCI Refractory angina despite optimal/maximal medical treatment | SCS ON 32 | SCS OFF 36 | Exercise capacity (treadmill time) Angina attacks Nitrate usage CCS class change Angina frequency Adverse Events | 6 months |

*: 1 stimulation for 3 × 2 h/day with conventional output

2 stimulation for 24 h/day with 0.1 V output

*: CCS: Canadian Cardiovascular Scale; AHA: American Heart Association; NYHA: New York Heart Association:

CABG: coronary artery bypass graft; PMR: percutaneous myocardial laser revascularization.

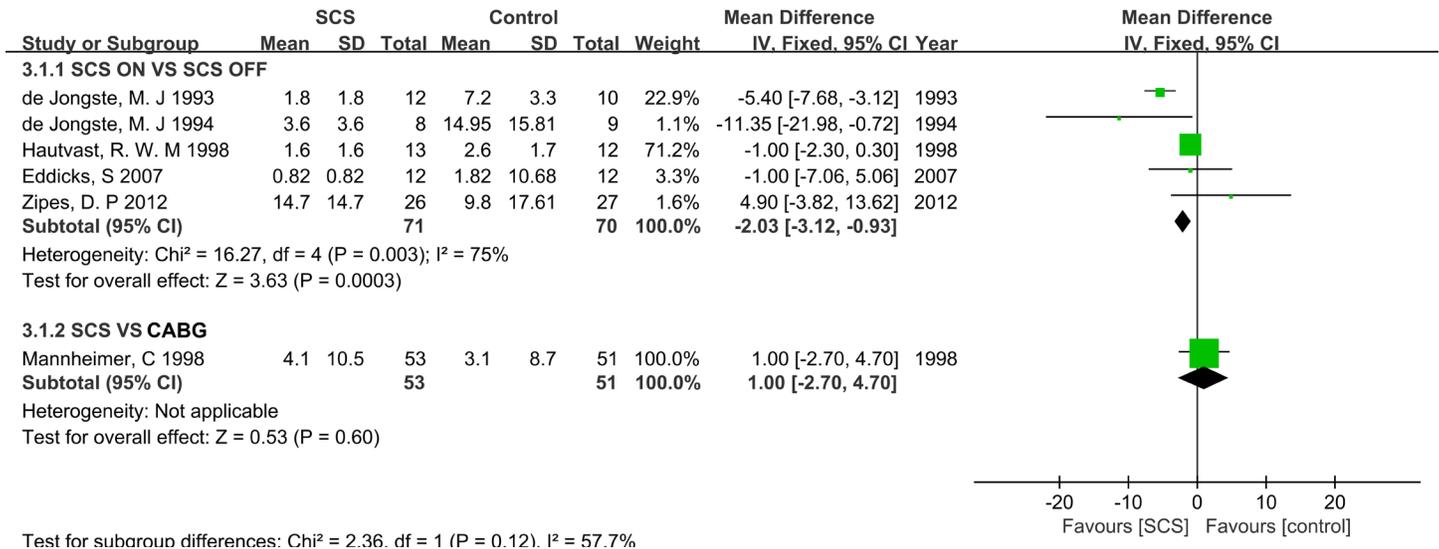


Fig. 3. Forest plot of nitrate drug usage – differences among groups.

Data presentation and analysis

Nine RCTs, which included 364 patients with RA, were used in this meta-analysis. These studies were separated into two categories: SCS vs active intervention (CABG or PMR) [9, 10] and active SCS (SCS ON) vs no or inactive SCS (SCS OFF) [11-17]. Quantitative data was then entered into the Cochrane RevMan5.3 software. All results were converted into mean ± standard deviation (SD). We translated data reported only as median, size, and range into mean ± SD using a method previously reported [18]. Results were recorded as WMD with a 95% confidence interval (CI). In addition, the WMD was considered statistically significant if the 95% CI was not equal to 0.

Results

Study characteristics

We searched the electronic databases using the keywords and their synonyms. After checking the titles and abstracts, 109 relevant studies were initially selected. Thirty-nine repeated studies and 27 non-RCT records (including 24 reviews, 2 meta-analyses, and 1 case report) were excluded. In addition, 34 full-text articles were excluded because they were not related to RA or SCS or had inappropriate intervention (Figure 2). Ultimately, nine studies, which included 364 patients, were analyzed in the present study.

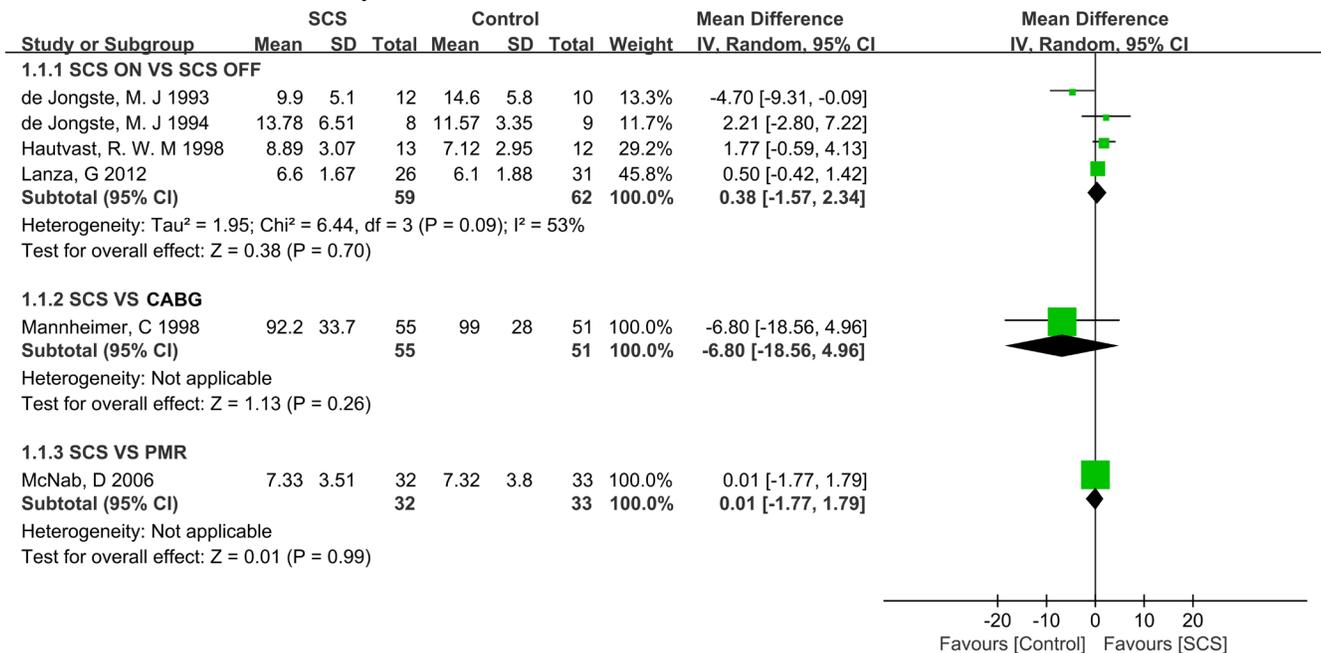


Fig. 4. Forest plot of exercise capacity – differences among groups.

Patients were divided into three SCS groups according to the previous report [15]: control (24 h/day with 0 output), 3 × 2 h/day or 24 h/day with conventional output and 3 × 2 h/day with a subthreshold output. We chose the results of 3 × 2 hours/day as the SCS group in the present study. The characteristics of the identified studies are presented in Table 1.

Nitrate drug usage

Six studies [10, 11, 13-15, 17] presented data on nitrate drug usage. As shown in

Figure 3, five studies compared ‘SCS ON’ with ‘SCS OFF’, which had a significant reduction in nitrate drug usage following SCS (WMD: -2.03, 95% CI: [3.12, -0.93], $p=0.0003$). However, the χ^2 and I^2 were 16.27 and 75%, respectively, which suggested heterogeneity among the studies. One study compared SCS with CABG, and this difference was not statistically significant.

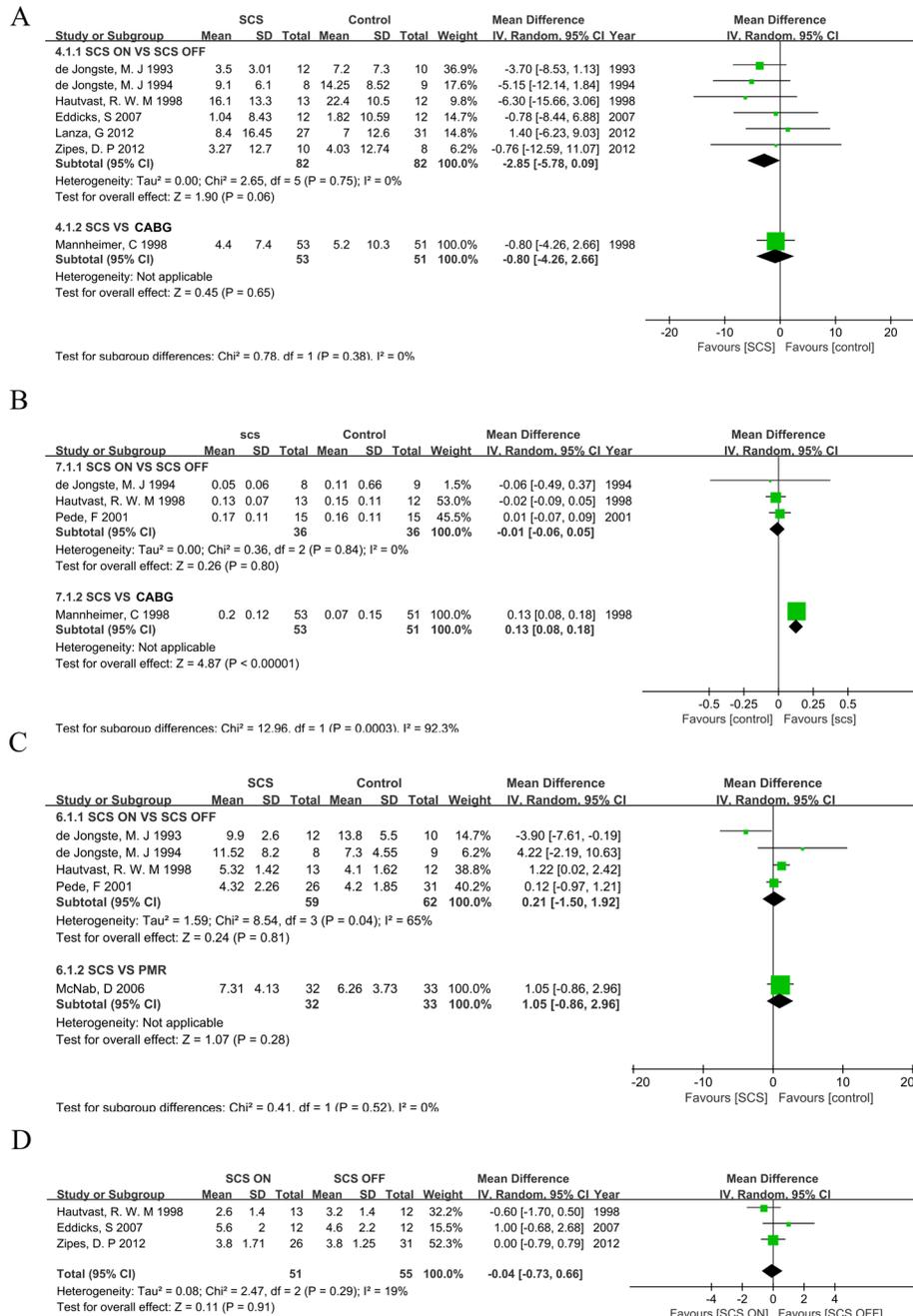


Fig. 5. Forest plot of ischemic burden – differences among groups: (A) angina attack frequency, (B) ST-depression, (C) time to angina, (D) Visual analogue scale.

Exercise capacity

Six [9-11, 13, 14, 17] of the included studies provided data on exercise capacity (treadmill time and peak workload). Of the four studies comparing 'SCS ON' with 'SCS OFF', the pooled analysis showed a higher level of exercise capacity following SCS (WMD: 0.38, 95% CI: [-1.57, 2.34], $p=0.7$, Test of heterogeneity: $\chi^2=6.44$, $I^2=53\%$,

$p=0.09$), but the difference was not statistically significant. No difference was found between SCS and CABG or PMR (Figure 4).

Ischemic burden

Four outcomes (angina attack frequency, magnitude of ST-depression, Time to angina, and visual analogue scale) were included in the ischemic burden group. Angina attack

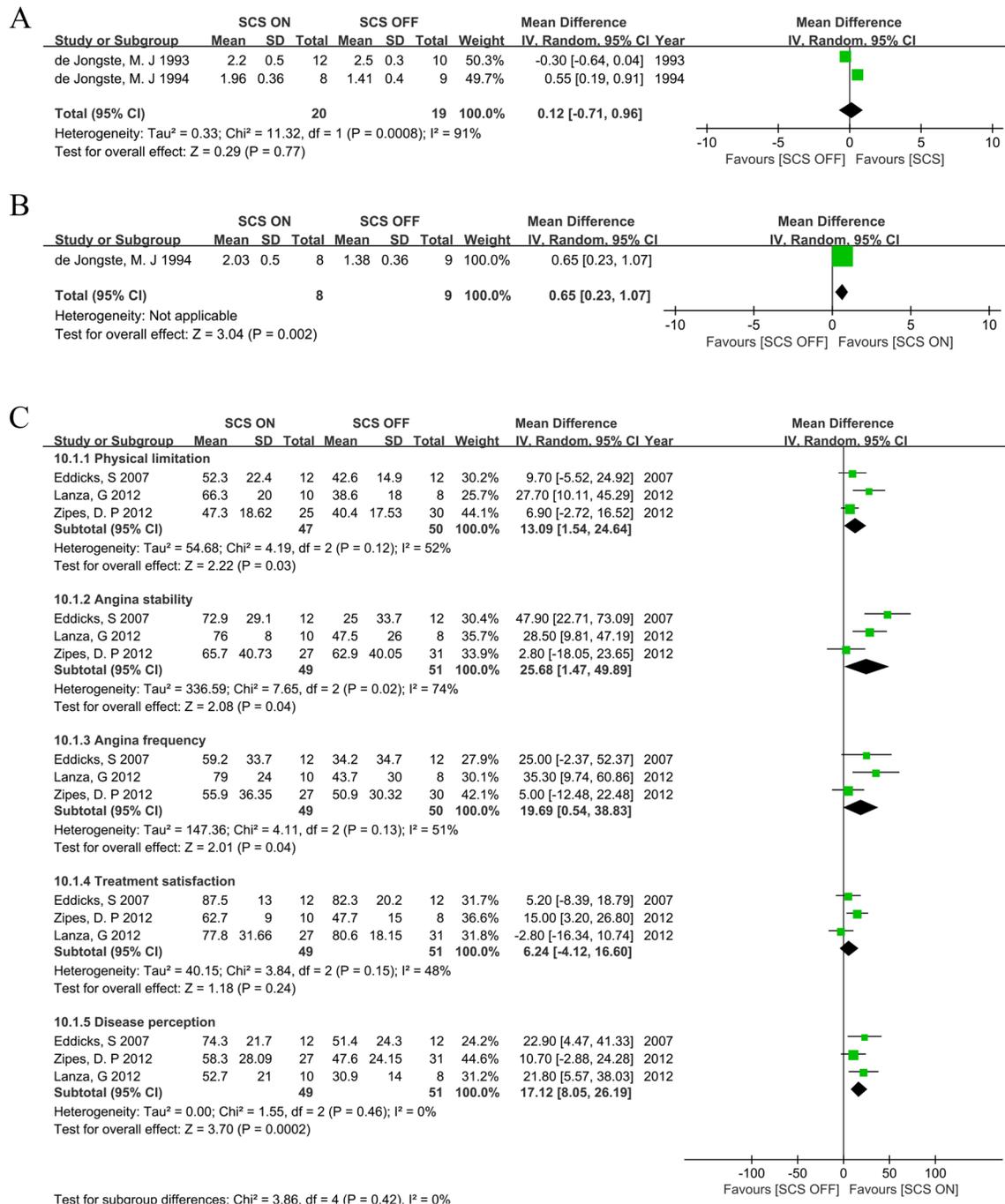


Fig. 6. Forest plot of health related quality of life – difference among groups: (A) Daily activity score, (B) Social activity score, (C) Seattle Angina Questionnaire.

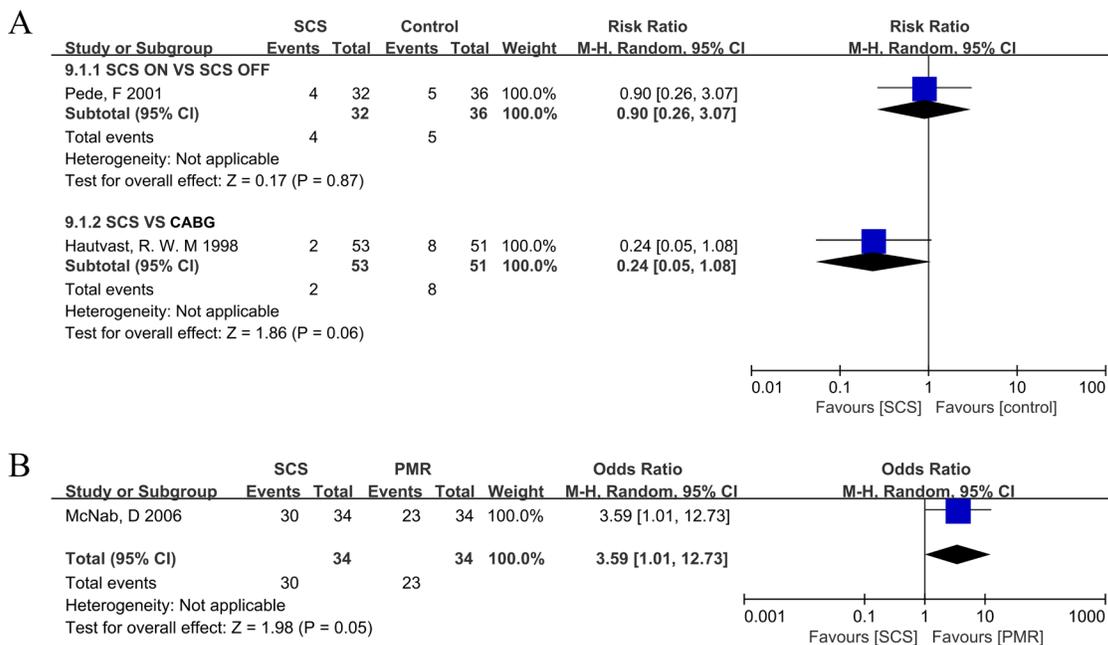


Fig. 7. Forest plot of adverse events – difference among groups: A (cerebrovascular events), B (total events)

frequency was reported in seven studies. Of the six studies that compared ‘SCS ON’ with ‘SCS OFF’ [11, 13, 14, 16, 17], the pooled analysis exhibited a lower level of angina attack frequency following SCS (WMD: -2.85, 95% CI: [-5.78, 0.09], $p=0.06$, Test of heterogeneity: $\chi^2=2.65$, $I^2=0\%$, $p=0.75$), and no difference was found between SCS and CABG for angina attack frequency [10](Figure 5A).

Four studies presented data on the magnitude of ST-depression; three of these studies compared ‘SCS ON’ with ‘SCS OFF’ [11, 12, 14] and there were no significant differences in the two groups (WMD: -0.01, 95% CI:[0.06, 0.05], $p=0.8$, test of heterogeneity: $\chi^2=0.36$, $I^2=0\%$, $p=0.8$). When comparing SCS to CABG, there was a significant increase in ST-depression [10](WMD: 0.13, 95% CI: [0.08, 0.18], $p<0.00001$) (Figure 5B).

Five studies provided data on Time to angina. Four of these studies compared ‘SCS ON’ with ‘SCS OFF’ [11-14], and

in addition, one study compared SCS with PMR [9]. No statistical significance was found for Time to angina when comparing ‘SCS ON’ with ‘SCS OFF’ (WMD: 0.21, 95% CI: [-1.5, 1.92], $p=0.81$, test of heterogeneity: $\chi^2=8.54$, $I^2=65\%$, $p=0.04$). There was also no difference in Time to angina when SCS was compared to PMR (Figure 5C).

VAS was recorded in three studies [14, 15, 17], and the pooled analysis did not demonstrate statistical significance when comparing ‘SCS ON’ to ‘SCS OFF’ (WMD: -0.04, 95% CI: [-0.73, 0.66], $p=0.91$, test of heterogeneity: $\chi^2=2.47$, $I^2=19\%$, $p=0.29$) (Figure 5D).

Health-related quality of life

Five studies presented data on HRQOL including the daily activity score (ADL), social activity score (SAS), and Seattle Angina Questionnaire (SAQ). ADL was recorded in two studies [11, 13] that compared ‘SCS ON’ with SCS

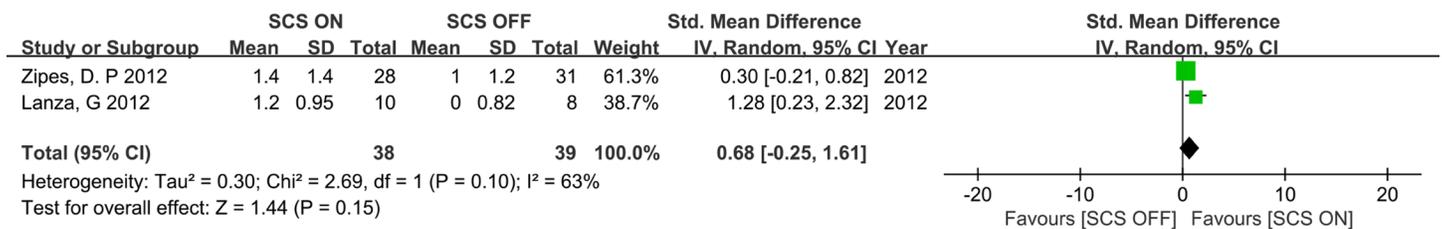


Fig. 8. Forest plot of Canadian Cardiovascular Scale class change – difference among groups.

OFF', but the pooled analysis did not achieve statistical significance (Figure 6A).

One study presented data on SAS that compared 'SCS ON' with 'SCS OFF' [11], and there was a significant increase in SAS following SCS (WMD:0.65, 95% CI: [0.23,1.07], $p=0.02$) (Figure 6B).

Three studies reported data on SAQ [15-17] and included these five aspects: physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception. There was a significant increase when 'SCS ON' to 'SCS OFF' was compared in physical limitation (WMD: 13.09, 95% CI: [1.54, 24.64], $p=0.03$, test of heterogeneity: $\chi^2=4.19$, $I^2=52\%$, $p=0.12$), angina stability (WMD: 25.68, 95% CI: [1.47, 49.89], $p=0.04$, test of heterogeneity: $\chi^2=7.65$, $I^2=74\%$, $p=0.02$), angina frequency (WMD: 19.69, 95% CI: [0.54, 38.83], $p=0.04$, test of heterogeneity: $\chi^2=4.11$, $I^2=51\%$, $p=0.13$) and disease perception (WMD: 17.12, 95% CI: [8.05, 26.19], $p=0.0002$, test of heterogeneity: $\chi^2=1.55$, $I^2=0\%$, $p=0.46$). There was a trend towards a high level of treatment satisfaction for SCS when compared to SCS OFF (WMD: 6.24, 95% CI: [-4.12, 16.6], $p=0.24$, test of heterogeneity: $\chi^2=3.84$, $I^2=48\%$, $p=0.15$), but the result was not statistically significant (Figure 6C).

Adverse events

Three studies showed data on SCS relevant adverse events, including cerebrovascular events [10, 12] as well as total events excluding SCS/PMR related events[9]. There was no difference in cerebrovascular events when comparing 'SCS ON' to 'SCS OFF' and there seemed to be a trend towards lower cerebrovascular events in SCS when compared to CABG (OR: 0.21, 95% CI: [0.04, 1.05], $p=0.06$) (Figure 7A), but this trend did not yield statistical significance. There was a higher level of total events with SCS compared to PMR (OR: 3.59, 95%CI: [1.01, 12.73], $p=0.05$) (Figure 7B).

CCS class change

Two studies reported the CCS (Canadian Cardiovascular Scale) class change [16, 17], although the pooled result showed a trend towards an increase in the CCS class change (WMD: 0.76, 95%CI: [-0.02, 1.54], $p=0.06$, test of heterogeneity: $\chi^2=2.2$, $I^2=55\%$, $p=0.14$) following SCS, but it was not statistically significant (Figure 8).

Discussion

This meta-analysis included nine studies with 364 patients diagnosed with RA. Our purpose was to compare the efficacy and safety of SCS with other treatment options. The patients' inclusion criteria were roughly similar to

the following criteria: AHA III/IV or CCS class 3/4 and unsuitable for revascularization. Seven trials compared SCS with non-stimulation treatments, and the other two trials compared SCS with active-intervention treatments (CABG or PMR).

Our study revealed that SCS significantly decreased nitrate drug usage, angina attack frequency, and increased the HQROL including the social active score and SAQ (physical limitation, angina stability, angina frequency, and disease perception) when compared to 'SCS OFF' and there was a tendency to reduce the CCS class; no statistically significant difference and no difference was noted for exercise capacity and adverse events, respectively. The improvement of SCS outcome was similar to CABG or PMR, although CABG as a therapy for RA remained questionable [3]. SCS has been suggested to conceal angina symptoms, thereby increasing the risk of cerebrovascular events. However, we found that there was no significant difference in such events when 'SCS ON' was compared to 'SCS OFF', and it had less cerebrovascular events when compared to CABG. Our analysis showed there was an increased number of total events excluding SCS/PMR related to SCS when compared to PMR.

There are several hypotheses about SCS, but the mechanism remains unclear [19]. One study indicated that the beneficial effects were less likely to increase blood flow, but redistribution of local blood flow might play an important role in the improvement of myocardial ischemia [20]. Another study proposed that SCS stabilizes the intrinsic cardiac nervous system and improves cardiac function [21].

Our analysis has several limitations that are worth discussing. First, most of the included studies did not report their experimental methods, which increased the difficulty of estimating their quality of methodology and determining their risk of bias and potential effects of SCS. Second, when comparing SCS to inactive SCS, there was a shortage of data because the implantation procedure is difficult for patient blinding and the procedure may generate a placebo effect. However, sham operations cannot be performed for ethical reasons [22], making the placebo effect unavoidable. Third, small-scale trials might not achieve sufficient statistical power to detect potential clinical differences between treatments. To conquer these limitations, we pooled the results in the 'SCS ON' and 'SCS OFF' trials. Moreover, the treatment of most 'SCS ON' groups did not only use SCS but combined them with drug therapy such as nitrate drugs, and the various drug sources were not disclosed because different company products may have different efficacies that may influence final outcomes.

In summary, SCS decreased nitrate drug usage, angina attack frequency, and partially increased the HRQOL for patients with RA. The finite evidence based on the nine quality RCTs in this meta-analysis supports the 2007 ACC/AHA Grade IIb evidence classifications and Level B recommendation for SCS in RA patients [23]. Considering the relatively sparse evidence to support SCS as an alternative therapy, our study would support a wider range of applications of SCS in RA. In addition, high quality multicenter RCTs and more appropriate methods for patient recruiting are needed before SCS can be used as a routine therapy for RA.

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