Compound Salvia droplet pill, a traditional Chinese medicine, for the treatment of unstable angina pectoris: a systematic review

CRD summary
The authors reported that compound Salvia droplet pill has a significant effect on improving angina symptoms, electrocardiography and level of blood lipids in patients with unstable angina pectoris, with few side-effects. However, they concluded that the evidence is unreliable because of the low quality of the included trials. This was a well-conducted review and the conclusions are likely to be reliable.

Authors' objectives
To assess the efficacy and safety of compound Salvia droplet pill (CSDP) in the treatment of unstable angina pectoris (UA).

Searching
MEDLINE, EMBASE, the Cochrane CENTRAL Register and the Chinese Biomedical Database were searched from inception to January 2007 for articles in any language; the search terms were reported. Chinese Journals Full-text Database and Chinese Scientific Journal Database were also searched for theses and conference articles. The manufacturers of CSDP were contacted for published and unpublished studies.

Study selection
Randomised controlled trials (RCTs) or quasi-RCTs were eligible for inclusion. Studies were eligible for inclusion where CSDP was compared with placebo, where CSDP was compared with a current Western drug, or where CSDP in conjunction with any Western drug was compared with the Western drug alone. The included studies were all of CSDP combined with a Western drug compared with a Western drug alone. In the included studies, CSDP was administered at a dose of 270 mg, taken orally three times daily, for 2 weeks to 6 months. Western drug regimens in the included studies were routine therapy (comprising a platelet aggregation inhibitor (aspirin), nitrates, β-blockers, calcium-channel blockers and angiotensin-converting enzyme inhibitors) or routine therapy plus heparin, or isosorbide dinitrate alone or with aspirin. Studies where a diagnosis of UA was made in accordance with American Heart Association 'Nomenclature and criteria for diagnosis of ischaemic heart disease' or the World Health Organization (WHO) 'Guidelines for the management of patients with unstable angina and NSTEMI' were eligible for inclusion. The patients in the included studies were aged from 34 to 88 years and 61.5% were male. All of the included studies were of patients who met the WHO criteria for unstable angina. Primary outcomes eligible for inclusion were mortality due to ischaemic heart disease and the incidence of a heart event (acute myocardial infarction, severity arrhythmia, heart failure or revascularisation). Secondary outcomes eligible for inclusion were severity of angina pectoris, electrocardiography (ECG) improvement, incidence of hospitalisation and health-related quality of life. Studies of adverse events (threat to life, toxic response, anaphylaxis and resulting in the discontinuation of treatment) were eligible for inclusion. The outcomes reported in the included studies were mortality, cardiovascular events, frequency and duration of angina symptoms, ECG improvement, heart rate, blood-pressure, haemorheology and blood fat.

Three reviewers independently selected the articles for review. Any disagreements were resolved by discussion.

Assessment of study quality
The methodological quality was assessed according to criteria presented in the Cochrane Reviewers' Handbook. These criteria assess selection bias, performance bias, detection bias and attrition bias. Each study was then assigned a quality rating from A to C (low quality).

Two reviewers independently carried out the validity assessment, with any disagreements arbitrated by a third reviewer or resolved by contacting the authors for clarification where necessary. Two reviewers checked the inter-rater reliability of the validity assessment.
Data extraction
Three reviewers independently extracted the data, with any differences resolved by reviewing the original article or by discussion.

Methods of synthesis
Dichotomous data were combined using relative risks (RRs) with corresponding 95% confidence intervals (CIs). The effect size for continuous data was calculated using a weighted mean difference (WMD) with 95% CIs. Statistical heterogeneity was assessed using the $\chi^2$ and $I^2$ statistics. Fixed-effect models were used when no statistical heterogeneity was present. Where there was significant heterogeneity, a random-effects model was used. Publication bias was assessed by funnel plot analysis. A sensitivity analysis was performed in which trials with small sample sizes were excluded. The robustness of the results was tested by repeating the analysis using different statistical methods.

Results of the review
Seventeen RCTs (n=1,462) were included in the review.

All of the included studies were of a low quality. No studies reported the randomisation procedure, allocation concealment, blinding, withdrawals, intention-to-treat analysis or compliance.

Reduction of angina symptoms (11 studies, n=1,031): patients treated with CSDP in conjunction with Western drugs showed a significant reduction in angina symptoms compared with those treated with Western drugs alone (RR 1.23, 95% CI: 1.16, 1.30, p<0.00001). There was no evidence of heterogeneity. However, the funnel plot analysis revealed a potential risk of publication bias. The difference between groups remained when only the trials comparing CSDP with routine therapy were included (RR 1.20, 95% CI: 1.12, 1.29, p<.00001). A sensitivity analysis was conducted excluding a small sample trial; the difference between the groups remained significant (p<0.00001). CSDP in conjunction with routine therapy was superior to routine therapy alone in reducing the frequency of angina attacks (WMD 2.61, 95% CI: 1.24, 3.99, p=0.0002). A random-effects model was used because of the presence of significant statistical heterogeneity ($I^2=73.8\%$; p=0.01).

ECG improvement (10 studies, n=867): CSDP in conjunction with Western drugs significantly improved ECG compared with Western drugs alone (RR 1.34, 95% CI: 1.23, 1.46, p<0.00001). The difference between the groups remained significant when using a random-effects model (p<0.0001) and when a sensitivity analysis was conducted excluding the small sample trial (p<0.00001). There was no evidence of statistical heterogeneity.

Biochemistry outcomes: CSDP plus Western medication significantly improved blood fat outcomes compared with the use of Western drugs alone (4 studies; for TG, WMD 0.48, 95% CI: 0.21, 0.75, p=0.0006; for TC, WMD 0.95, 95% CI: 0.56, 1.34, p<0.00001). A random-effects model was used because of the presence of significant statistical heterogeneity (p<0.0001).

Cardiovascular events: there was no significant difference in the incidence of cardiovascular events between patients taking CSDP and Western drugs compared with those patients taking Western drugs alone.

Safety: the review reported only one main side-effect of CSDP: low-grade stomach discomfort with an incidence of 3.44%.

Authors’ conclusions
CSDP has a significant effect on improving angina symptoms, ECG and level of blood lipids in patients with UA, with few side-effects. However, the evidence is unreliable because of the low quality of the included trials.

CRD commentary
The review addressed a well-defined question and inclusion criteria for the intervention, participants, outcomes and study design were stated clearly. Several relevant databases were searched for studies in any language, thus minimising the risk of language bias. Attempts were made to identify unpublished material and publication bias was assessed in the analyses. The study selection, validity assessment and data extraction processes were conducted independently by more than one reviewer, thereby minimising the risk of reviewer error and bias. The decision to combine the studies in an
meta-analysis was appropriate, and statistical heterogeneity was assessed and taken into account in the analysis. This was a well-conducted review and the conclusions are likely to be reliable.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that rigorously designed, large-scale RCTs that include outcomes such as acute myocardial infarction, death, other heart events and quality of life, are required. Future trials should be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) protocol.

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