Efficacy of clonidine for prevention of perioperative myocardial ischemia: a critical appraisal and meta-analysis of the literature

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Authors' objectives
To determine whether clonidine premedication can reduce the occurrence of peri-operative myocardial ischaemia.

Searching
MEDLINE was searched from 1980 to 1999 using the following MeSH terms: 'myocardial ischaemia', 'coronary disease', 'myocardial infarction', 'coronary arteriosclerosis', 'coronary thrombosis', 'angina pectoris', 'prospective studies', 'clinical trials', 'randomized controlled trials', 'controlled clinical trials', 'intervention studies'. Only English language articles were considered. Personal files and the reference lists of all retrieved studies and reviews were also examined. No attempt was made to obtain the results of unpublished studies. The first authors of each included study were contacted for additional published studies.

Study selection
Study designs of evaluations included in the review
Controlled clinical trials were eligible for inclusion in the review. All included studies were randomised controlled trials (RCTs).

Specific interventions included in the review
Studies of peri-operative clonidine were eligible for inclusion. Studies included in the review used clonidine at doses of 2 to 5 microg/kg (oral or intravenous), 3 microg/kg per hour (intravenous) or 0.2 mg/day transdermal plus 0.3 mg oral. Administration timing is reported. Clonidine appears to have been compared to placebo in all of the included studies.

Participants included in the review
Studies of adult patients undergoing surgery during general anaesthesia were eligible for inclusion in the review. The patients in the included studies were undergoing either coronary artery bypass grafting or unspecified noncardiac surgery. The mean ages in the studies ranged from 59 to 70 years.

Outcomes assessed in the review
Studies which assessed mortality rate, myocardial ischaemia or myocardial infarction were eligible for inclusion in the review. The outcomes were assessed at various times pre-surgery, during surgery or post-surgery. The definitions of myocardial ischaemia and infarction varied between the trials and were detailed in the paper. Bradycardia and hypotension were also reported.

How were decisions on the relevance of primary studies made?
Two reviewers independently reviewed the titles and abstracts of all articles and retrieved all potentially relevant studies. Three authors then independently applied the inclusion criteria to the full manuscripts. Two of these authors were blinded to the journal, authors, institution, and magnitude and direction of the results. Any disagreements were discussed and resolved by consensus.

Assessment of study quality
The authors used the methodological quality scoring system established by Cronin et al. (see Other Publications of Related Interest no.1). The criteria used in this system were not stated. Studies with low quality scores (4 points or lower) were excluded from further analysis. Two authors applied the validity criteria independently. One was blinded to the journal, authors, institution, and magnitude and direction of results. Any disagreements were discussed and resolved by consensus.
Data extraction
Two reviewers extracted the data and any disagreements were resolved by consensus. One reviewer was blinded to the journal, authors and institution. The data were recorded in terms of the number of patients rather than number of events. Data were extracted on the following: study identification; the number of patients; the observation period; clonidine dose and route; the time of administration; quality scores; outcome definitions; and results. The first author of each study was contacted for missing data.

Methods of synthesis
How were the studies combined?
A meta-analysis was used to calculate the pooled odds ratios (ORs) and 95% confidence intervals (CIs) using a fixed-effect model. A fail-safe number was calculated to assess the potential impact of publication bias using Orwin’s formula (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Homogeneity was assessed using the Q value. When significant heterogeneity was found, plans were made to identify the source.

It was decided a priori to analyse the data separately according to other medication that causes bradycardia (beta-adrenoceptor antagonists or calcium-channel blockers) and the type of surgery (cardiac or noncardiac). The first of these subgroup analyses did not appear to have been carried out in the review; a different subgroup analysis of intravenous versus oral clonidine was reported.

Results of the review
Seven RCTs (n=664) were included.

The methodological quality scores ranged from 6 to 10.5. The correlation between the observers for this score was high (kappa: 0.73 to 1).

The pooled OR of myocardial ischaemia in patients receiving clonidine was lower than in those receiving placebo (OR 0.49, 95% CI: 0.34, 0.71). Heterogeneity of this data was negative (Q=6.45, p less than or equal to 0.05).

Subgroups. Coronary artery bypass grafting (5 trials): the pooled OR was 0.52 (95% CI: 0.29, 0.93; Q=5.20, p less than or equal to 0.05).
Noncardiac surgery (2 trials): the pooled OR was 0.47 (95% CI: 0.29, 0.77; Q=1.19, p less than or equal to 0.05).
Oral clonidine (5 trials): the pooled OR was 0.48 (95% CI: 0.32, 0.71; Q=4.29, p less than or equal to 0.05).
Intravenous clonidine (2 trials): the pooled OR was 0.60 (95% CI: 0.19, 1.84; Q=2.03, p less than or equal to 0.05).
Hypotension (3 trials): the results were inconsistent between the trials. There was significant heterogeneity in this result.
Bradycardia: the pooled OR was 1.16 (95% CI: 0.72, 1.87).

Assessment of publication bias: if six studies averaging 91 patients per study with an effect size of 0 for clonidine treatment were added to the meta-analysis, this would not nullify the findings.

Authors’ conclusions
This meta-analysis suggested that clonidine given pre- or intraoperatively reduces myocardial ischaemic episodes in patients with coronary arterial disease and in those at risk for this disease, but does not increase the incidence of bradycardia.
CRD commentary
The selection criteria for studies in this review were clearly stated for the study design, population, outcomes and intervention, but not for the comparator. However, there may have been deviations from these criteria in the review itself. The ORs for mortality and myocardial infarction were not presented.

The literature search was limited to MEDLINE and to English language literature, which means that some studies may have been missed. The authors of the studies were contacted but no attempt was made to retrieve unpublished studies.

The validity of the included studies was assessed using a published checklist and was used to exclude studies of poor quality, but all other trials were considered similar in terms of their quality. Insufficient details of the included studies were presented; for example, it was not reported what the comparator to clonidine was in any of the studies.

Details of the review process were reported. These seem to have been adequate in terms of minimising bias in the study selection, validity assessment and data extraction processes.

While there was no statistical heterogeneity between the trials, there appeared to be potentially important clinical heterogeneity in terms of the outcome definitions, times of outcome assessment, and participants (i.e. people with and without existing heart disease). One of the planned subgroup analyses was not undertaken but the intravenous versus oral clonidine subgroup analysis appears to have been conducted post hoc. In addition, it is unclear how reliable the outcome of myocardial ischaemia is as a surrogate marker for myocardial infarction and death.

In the publication, some of the references were listed incorrectly in the tables.

The authors' conclusions about the reduction in cardiac ischaemic episodes are suitably cautious given the limitations highlighted. However, the review incorrectly concluded that there is evidence that clonidine does not increase bradycardia; it should have reported no evidence of effect.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors strongly recommend a definitive prospective trial seeking the benefits of clonidine.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.