Calcium antagonists reduce cardiovascular complications after cardiac surgery: a meta-analysis

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CRD summary
This review assessed the efficacy of calcium antagonists for reducing mortality and complications following coronary artery bypass graft or valve surgery. The authors concluded that treatment reduced complications but not mortality. The review had some methodological and reporting limitations (participant characteristics were not reported), but the authors' conclusions were conservative and appear likely to be reliable.

Authors' objectives
To determine the efficacy of calcium antagonists (CAs) in reducing death, myocardial infarction (MI), ischaemia and supraventricular tachyarrhythmia (SVT) after cardiac surgery. In the review, the authors also investigated adverse events and the influence of prior medication use.

Searching
MEDLINE (from 1966 to December 2001) and EMBASE (from 1980 to December 2001) were searched without any language restriction. The search strategies were given in the review. The bibliographies of included studies were also surveyed for relevant articles.

Study selection
Study designs of evaluations included in the review
The authors aimed to include only randomised controlled trials.

Specific interventions included in the review
The inclusion criteria specified CAs administered immediately pre-operatively, intra-operatively, or within 48 hours post-operatively, and not administered exclusively as a cardioplegic additive. The drugs used in the included studies were diltiazem, nicardipine, verapamil, nifedipine and isradipine; details of the doses were given in the paper. The duration of treatment extended from intra-operatively to 7 days post-operatively. From the tabulated data, the control arms of the included studies were one or more of the following: nitroglycerin, nitroprusside, placebo or 'control' (unspecified).

Participants included in the review
The inclusion criteria specified participants undergoing coronary artery bypass graft or valve surgery. The exclusion criteria were organ transplant patients, people under 18 years of age and those with pre-existing SVT. No details of the demographics of the patients in the included studies were provided.

Outcomes assessed in the review
The inclusion criteria for the outcomes specified any of the following: death, MI (no definition), ischaemia, SVT (atrial fibrillation, atrial flutter, and supraventricular tachycardia) or creatinine clearance. Ischaemia was defined as ST-segment deviation on the electrocardiogram, or new wall motion abnormalities on the transoesophageal echocardiogram. Peri-operative outcomes were defined as occurring between the initiation of surgery and post-operative day 30. The authors also extracted data on adverse event outcomes: low cardiac output syndrome, inotropic support (need for inotropes or intra-aortic balloon pump support), post-operative pacing and post-operative blood loss.

How were decisions on the relevance of primary studies made?
The authors stated that the titles and abstracts were screened to exclude ineligible studies, but did not state who performed this screening. Two reviewers independently read the remaining (potentially eligible) studies. Any disagreements were resolved by consensus.
Assessment of study quality
Validity was assessed using the Jadad scale. The minimum score required for inclusion was one (out of a possible 5). Two reviewers independently rated the quality of the studies. Any disagreements were resolved by consensus.

Data extraction
Two reviewers independently abstracted the data onto standardized forms. The details abstracted were the patient characteristics, the type of surgery, treatments and outcomes. Treatment effects, odds ratios (OR) with 95% confidence intervals (CI), or weighted mean differences were calculated for the individual studies.

Methods of synthesis
How were the studies combined?
The studies were combined using a random-effects model to estimate the pooled treatment effects: OR with 95% CI for dichotomous outcomes and weighted mean differences for continuous outcomes. Funnel plots were used to investigate publication bias. A fixed-effect model was used to compare adverse events and prior medication use.

Primary analyses were the effects of CAs on the outcomes listed above. Secondary analyses were performed for each class of CA (diltiazem, verapamil, dihydropyridines) and for CAs compared specifically against nitroglycerin.

How were differences between studies investigated?
The Q test was used to investigate heterogeneity between the studies. The authors also conducted sensitivity analyses to investigate the effect of excluding the studies with the most favourable CA treatment effects, and the effect of study quality.

Results of the review
Forty-one studies (3,327 patients) were included: 36 (2,914 patients) following coronary artery bypass graft surgery, 2 (221 patients) following valve surgery and 3 (192 patients) following mixed types of surgery.

The authors stated that the majority of the included studies were unblinded. The median Jadad score was 1 (range: 1 to 4). Funnel plots were not presented, but the authors stated that they did not indicate the presence of publication bias.

CAs did not affect mortality (n=11); the OR was 1.01 (95% CI: 0.46, 2.22, P=1). When nimodipine studies were excluded, the OR was 0.66 (95% CI: 0.26, 1.70, P=0.4). There was no significant heterogeneity.

CAs significantly reduced MI (n=22); the OR was 0.58 (95% CI: 0.37, 0.91, P=0.02). There was no significant heterogeneity.

CAs significantly reduced ischaemia (n=20); the OR was 0.53 (95% CI: 0.39, 0.72, P<0.001). There was no significant heterogeneity.

CAs did not significantly reduce SVT (n=15); the OR was 0.73 (95% CI: 0.48, 1.12, P=0.15). There was significant heterogeneity among the studies. Subgroup analyses indicated that non-dihydropyridines significantly reduced SVT (OR 0.62, 95% CI: 0.41, 0.93, P=0.02), whereas dihydropyridines non significantly increased SVT (OR 2.69, 95% CI: 0.57, 12.64, P=0.2).

CAs increased post-operative creatinine clearance non significantly (n=5); the increase was 7.65 mL/minute (95% CI: -4.21, 19.51, P=0.2). There was significant heterogeneity between the studies. Post-hoc analyses were conducted to investigate this heterogeneity.

There were no significant differences between the CA and non-CA arms of the studies in any of the adverse events investigated.

Further results, including the effects of individual drugs, post-hoc, secondary and subgroup analyses, were reported in the review.
Authors' conclusions
The use of CAs during cardiac surgery significantly reduced the rates of MI, ischaemia and SVT.

CRD commentary
This was a well-written review with clear aims, and much of the methodology of the meta-analysis was reported clearly. The database search strategy appears to have been comprehensive, but the search was limited in its exclusion of unpublished data. The authors stated that the importance of unpublished data is debatable; the reviewer is of the opinion that this may have resulted in the exclusion of some studies, perhaps negative studies in particular, resulting in an overestimation of the beneficial effect of CAs. The authors attempted to assess publication bias by plotting funnel plots. These were not presented in the paper, although the authors stated that there was no obvious publication bias.

The authors did not provide any details of the participants in the included studies. It is therefore not possible to comment on the generalisability of the results to all groups of patients (e.g. by gender and age or severity of illness). In addition, the authors stated that there was clinical heterogeneity with regards to the participants' characteristics, drug dose and duration of therapy. The statistical methods used by the authors are standard meta-analytical tools, but it is unclear why the authors used fixed-effect models to investigate adverse events and prior medication use.

The authors' conclusions were suitably conservative.

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

Research: The authors recommended a large, simple, double-blind randomised controlled trial to assess the efficacy of CAs. They suggested that this should be performed amongst patients undergoing a coronary artery bypass graft, as this may be the group most likely to benefit from CAs.

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