Nicorandil treatment in patients with acute myocardial infarction: a meta-analysis

CRD summary
The authors concluded that nicorandil treatment as an adjunct to coronary reperfusion therapy improved microvascular function, increased left ventricular ejection fraction and reduced left ventricular end-diastolic volume index. In view of the limited search, lack of information on study quality, heterogeneity between studies and possible publication bias, these conclusions should be interpreted with some caution.

Authors' objectives
To evaluate the effects of nicorandil treatment as an adjunct to reperfusion therapy after acute myocardial infarction.

Searching
MEDLINE and Google Scholar were searched to October 2007. Search terms were reported.

Study selection
Prospective and retrospective cohort studies of nicorandil treatment after acute myocardial infarction were eligible for inclusion, provided the nicorandil was intracoronary or intravenous and was administered before or during coronary reperfusion therapy (with or without subsequent oral nicorandil). Outcomes in the review were peak creatine kinase (as an estimate of infarct size), microvascular function and (at follow-up) left ventricular end-diastolic volume index (LVEDVI) and left ventricular ejection fraction (LVEF). Microvascular function was assessed by rates of thrombolysis in myocardial infarction (TIMI) flow grades of 2 or less on coronary angiography after reperfusion. LVEVDI was expressed in mL/m².

The mean or median age of participants in the included studies was 58 to 68 years. Most were male (range 52% to 89%). In most studies a loading dose of 2mg to 4mg of nicorandil was followed by continuous intravenous infusion of 2mg/hour to 8mg/hour, usually for 24 to 48 hours and at a fixed dose. Few studies reported use of subsequent oral nicorandil. The most common method of coronary reperfusion was primary percutaneous coronary intervention. LVEF was usually measured by left ventriculography at a mean or median of four months after acute myocardial infarction. The included studies were randomised controlled trials (RCTs) or retrospective cohort studies, in most cases from single centres.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
The quality criteria considered were: blinding; method of sequence generation in randomised studies; and description of withdrawals. Two reviewers independently conducted the assessment. Disagreements were resolved by consensus.

Data extraction
Mean differences were calculated for continuous outcomes and risk ratios (RRs) for dichotomous outcomes, with 95% confidence intervals (CIs). In studies with three arms, data were extracted from one nicorandil and one control arm only. Studies in which the intervention and control groups were split into two categories by clinical characteristics (for example, coronary flow grade) were analysed as two separate comparisons. Two reviewers independently extracted the data. Disagreements were resolved by consensus.

Methods of synthesis
Studies were combined using the DerSimonian random-effects model to calculate pooled effect sizes and pooled risk ratios, with 95% CIs. The effects of differing doses of nicorandil were assessed by meta-regression analysis. Heterogeneity was assessed using the Q test. Publication bias was assessed with funnel plots. If statistically significant heterogeneity was detected, it was explored using a trim-and-fill method.
Results of the review
Seventeen studies were included in the review (n=1,982, range 27 to 545): 15 RCTs (n=1,627) and two retrospective cohorts (n=355).

Nicorandil versus controls: Rates of TIMI flow grade 2 or less were significantly lower in the intervention group (RR 0.63, 95% CI 0.44 to 0.91, p=0.01; 10 RCTs). There was no statistically significant heterogeneity (p=0.35). There was no statistically significant difference between the groups in peak creatine kinase value (15 studies). LVEF was significantly higher in the intervention group (3.7%, 95% CI 1.8 to 5.7; 11 studies) and LVEVDI was significantly lower (-8.8 mL/m², 95% CI -14.4 to -3.3; seven RCTs).

There was statistically significant heterogeneity for the analyses of peak creatine kinase, LVEF and LVEVDI (all p≤0.001). Corrected estimation using trim-and-fill methods did not change the statistical significance of the findings. No statistically significant association between effect size and nicorandil dose was found for any outcome.

Authors’ conclusions
Nicorandil treatment adjunctive to coronary reperfusion therapy improved microvascular function after reperfusion in patients with acute myocardial infarction. Also, it increased LVEF and lowered LVEVDI.

CRD commentary
The objectives and inclusion criteria of the review were clear. Only two databases were searched for studies and the search was apparently limited to published articles, so it was possible that some studies were missed. It was unclear whether the search was also limited by language. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently assess study validity and extract the data; it was unclear whether this precaution also applied to study selection. Some relevant aspects of study validity were assessed, but others (such as allocation concealment) were not mentioned. The results of the validity assessment were not reported. Moreover it was questionable whether it was appropriate to pool RCTs with retrospective studies, especially as there was no separate analysis of the higher quality RCT data. The authors noted that most studies that reported beneficial effects from the intervention were small and/or single-centre studies. Funnel plots appeared to indicate possible publication bias, which was explored using the trim-and-fill method. Publication bias alone did not appear to explain the statistical heterogeneity detected in the analyses and (as the authors acknowledged) there were marked clinical and methodological differences between the studies.

In view of the limited search, lack of information on study quality, heterogeneity between the studies and possible publication bias, the authors’ conclusions should be interpreted with some caution.

Implications of the review for practice and research
Practice: The authors stated that nicorandil may be a promising adjunctive therapy to improve outcomes after acute myocardial infarction.

Research: The authors stated that there was a need for further studies to evaluate the effects of nicorandil on microcirculatory outcomes.

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