Does the early administration of beta-blockers improve the in-hospital mortality rate of patients admitted with acute coronary syndrome?

Brandler E, Paladino L, Sinert R

CRD summary
This systematic review provided conflicting evidence for a benefit in reducing in-hospital mortality for use of beta-blockers within eight hours of emergency department presentation of patients with an acute or suspected myocardial infarction. As removal of the largest study from the analysis significantly changed the results, the extent to which the authors' conclusions are reliable is unclear.

Authors' objectives
To evaluate the effectiveness of early administration of beta-blockers for improving the in-hospital mortality rate of patients admitted with acute coronary syndrome.

Searching
PubMed (from 1966), EMBASE (from 1980) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to May 2009. The bibliography of each retrieved article and relevant reviews were handsearched. Search terms were reported in a supplement.

Study selection
Randomised controlled trials (RCTs) of adult patients (18 years and older) with an acute or suspected myocardial infarction within 24 hours of onset of chest pain (acute coronary syndrome, ACS) and that compared intravenous or oral beta-blockers versus standard medical therapy with or without placebo were eligible for inclusion. Eligible studies had to administer beta-blockers within eight hours of presentation and assess the risk of in-hospital mortality. Studies were eligible for inclusion if the beta-blocker was given for chest pain by ambulance personnel or by primary care practitioners in the home or office. Beta-blockers used could be agents possessing Beta-1 antagonist properties whether or not they also had any Beta-2 antagonist effect. Studies that combined alpha- and beta-blocking agents were included. Use of other agents for secondary cardiac prophylaxis and therapies such as thrombolysis or angioplasty were not exclusion criteria. Studies of patients with chronic stable angina and studies where beta-blockers were used in the control group were excluded. In-hospital mortality was the primary endpoint.

The most frequently administered beta-blocker was propranolol, followed by metoprolol and atenolol; individual studies used practolol, labetalol, pindolol and timolol. Doses and route of administration varied. Details of cointerventions used were reported. Comparison groups mostly used standard care without a beta-blocker; one third of the studies used a placebo. Patient ages ranged from 31 to 82 years. The proportion of males ranged from 67% to 94%. Prevalence of myocardial infarction ranged from 0% to 100%.

Three reviewers independently performed the study selection.

Assessment of study quality
Methodological quality of RCTs was assessed using CONSORT (Consolidated Standards of Reporting Trials) criteria of randomisation, concealment, blinding, intention-to-treat (ITT) analysis, baseline comparisons, cointerventions and follow-up.

Two or three reviewers performed the quality assessment.

Data extraction
Data extraction was performed by one reviewer and checked by two reviewers. The number of events was extracted in order to calculate relative risk (RR) and 95% confidence intervals (CI).
Methods of synthesis
Relative risks were pooled using a random-effects model (Mantel-Haenszel). Between-study heterogeneity was determined using the $X^2$ test and $I^2$ and $T^2$ statistics. A sensitivity analysis explored the effect of excluding the largest study.

Results of the review
Eighteen relevant RCTs were identified (n=72,371, range 43 to 45,852; there was a discrepancy for the total number of patients between the tables and text). All studies except one were randomised; the other study used consecutive alternating patients. Allocation concealment occurred in eight RCTs. There was blinding (double blinding) in five RCTs. ITT analysis was used in 16 RCTs. Completeness of follow-up was not clear in some studies.

The pooled analysis found no significant difference in in-hospital mortality rate for beta-blocker groups compared to controls (RR 0.95, 95% CI 0.90 to 1.01; $I^2=0\%$). After the largest study (from 2005) was excluded, a significant but small benefit was found for use of beta-blockers compared to controls (RR 0.86, 95% CI 0.77 to 0.96). The authors noted that mortality in the control group tended to be larger in the studies published before 1984; this was presumed to be related to improvements in treatment with time. The largest study found a significant increase in rate of cardiogenic shock in the beta-blocker group (5.0%) versus the control group (3.9%).

Authors’ conclusions
This systematic review failed to demonstrate a convincing in-hospital mortality benefit for use of beta-blockers within eight hours of emergency department presentation of patients with an acute or suspected myocardial infarction.

CRD commentary
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched. It was unclear whether language restrictions were applied; if they were, some studies might have been missed. It appeared that unpublished studies were not considered. Publication bias was not assessed. Study quality was assessed using suitable criteria. Efforts were made to reduce error and bias in the review process; the reporting was not clear for validity assessment. Relevant study details were reported. Statistical heterogeneity was assessed. The statistical method used for the meta-analysis of the RCTs seemed appropriate. A sensitivity analysis was carried out and provided a reason to reconsider the evidence.

This was a generally well-conducted review. Most of the included RCTs were not double-blinded and many did not have allocation concealment and were, therefore, not high-quality studies. As the removal of the largest study from the analysis significantly changed the results, the extent to which the authors’ conclusions are reliable is unclear.

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

Research: The authors identified a need for a high-quality study where ACS patients were randomised to varying delays in beta-blockade after coronary reperfusion, with an objective assessment of cardiac performance, in order to assess whether the benefits outweighed the risks of the use of beta-blockers. Future studies should assess re-infarction rates, left ventricular remodelling, anti-arrhythmic effects or post-infarction angina.

Funding
Not stated.

Bibliographic details

PubMedID
20078433
DOI
10.1111/j.1553-2712.2009.00625.x

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Acute Coronary Syndrome /drug therapy /mortality; Adrenergic beta-Antagonists /administration & dosage; Angina Pectoris /drug therapy; Bias (Epidemiology); Drug Administration Schedule; Hospital Mortality; Humans; Randomized Controlled Trials as Topic; Risk; Risk Assessment; Time Factors

AccessionNumber
12010001550

Date bibliographic record published
19/05/2010

Date abstract record published
01/12/2010

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.