Outcomes of perioperative beta-blockade in patients undergoing noncardiac surgery: a meta-analysis


CRD summary
This review concluded that β-blockade in noncardiac surgery patients decreased the odds of developing a myocardial infarction but increased the odds of stroke; patients with lower baseline odds of developing stroke were at greater risk of β-blocker-induced stroke. This was a well-conducted review and despite poor reporting of the review methods, these conclusions are likely to be reliable.

Authors' objectives
To determine the benefits and harms associated with perioperative β-blocker use in noncardiac surgery.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions from 1960 to February 2009; search terms were reported. A manual search of reference lists from clinical trials and previous meta-analyses was undertaken to identify additional relevant trials.

Study selection
Randomised, double-blind, placebo-controlled trials that compared use of β-blockers with placebo were eligible for inclusion. Studies were undertaken in β-blocker-naïve patients who received noncardiac surgery where β-blockers were used perioperatively. Primary endpoints comprised myocardial infarction, stroke and all-cause mortality.

Included studies evaluated different doses of β-blockers (bisoprolol, metoprolol and propranolol). Most patients had coronary artery disease or at least one coronary artery disease risk factor. Half of the studies focused on vascular or thoracic surgery. The other studies assessed a mixed surgical patient population. Follow-up ranged from hospital discharge to one year postoperatively; in half of the studies follow-up was at day 30 postoperatively. Drug discontinuation was based upon heart rate per minute and systolic blood pressure.

The authors did not state how the studies were selected for review.

Assessment of study quality
Trial quality was assessed using the Jadad scale to assess randomisation, blinding and withdrawals; trials that scored less than 3 out of 5 were considered to be of low methodological quality.

The authors did not state how many reviewers assessed study quality.

Data extraction
Two reviewers independently extracted data for incidence of primary outcomes (all-cause mortality, myocardial infarction and stroke) to permit the calculation of odds ratios (ORs) and 95% confidence intervals (CIs). Discrepancies were resolved through discussion or adjudication by a third reviewer.

Methods of synthesis
Dichotomous data were combined to calculate pooled odds ratios using a DerSimonian and Laird random-effects model with 95% CIs. Combined estimates of absolute risk reduction with 95% CIs were estimated. Bayesian random-effects control rate meta-regression analyses were undertaken to assess whether the effects of β-blockers in noncardiac surgery were correlated with the odds of myocardial infarction or stroke in the control group; β-coefficients with 95% credible intervals were calculated. Heterogeneity was assessed using the $I^2$ statistic. Number needed to harm (NNH) and number needed to treat (NNT) were calculated. Sensitivity analysis was performed by separate analysis of studies with more than 30 days of follow-up. Publication bias was assessed using funnel plots and the Egger weighted regression statistic.
The trim and fill method was used to adjust for any potential publication bias.

**Results of the review**
Six trials (n=10,183, range 97 to 8,351) were included; all had a quality of score of 5.

Compared with placebo, perioperative β-blocker use yielded a significant reduction in patients' likelihood of developing myocardial infarction (OR 0.74, 95% CI 0.61 to 0.89, NNT=72; five studies) whereas the odds of developing stroke (OR 1.98, 95% CI 1.23 to 3.20, NNH 200; five studies) were significantly increased; there was also a non-significant increase in mortality (OR 1.21, 95% CI 0.98 to 1.49, NNH=157; six studies). There was no significant heterogeneity for these comparisons. Control-rate meta-regression determined that patients with highest baseline odds of stroke had decreased relative odds of having a stroke with a β-blocker versus placebo (β coefficient -0.97, 95% credible interval -1.04 to -0.90).

The results were robust with respect to excluding studies with duration of follow-up of less than 30 days. Funnel plots suggested evidence of publication bias, but trim and fill analysis showed that the overall conclusions were unchanged.

**Authors' conclusions**
When perioperative β-blockers were used in noncardiac surgery patients, there was a trade-off between reduction in myocardial infarction and increase in stroke, with a troubling trend toward an increase in mortality. Patients with lower baseline odds of developing stroke appeared to be at greater risk of β-blocker-induced stroke.

**CRD commentary**
The review addressed a clear question and was supported by appropriate inclusion criteria. Several relevant electronic sources were searched for studies in all languages, which reduced the possibility of language bias. The authors did not report any attempts to find unpublished studies, which increased the risk of publication bias. Publication bias was indicated by the funnel plot; the authors attempted to adjust for this by using the trim and fill method. The authors used appropriate methods to assess the quality of the included studies and these were deemed to be of high quality. Data extraction was undertaken in duplicate, which reduced the potential for reviewer error and bias; it was unclear whether such rigour was applied to study selection and quality assessment. It appeared that appropriate methods were used to synthesise data and assess statistical heterogeneity. The authors acknowledged a number of limitations with the included studies, such as a lack of head-to-head comparisons of the different drugs, various definitions for some endpoints and the restriction of the study population to β-blocker-naïve patients with cardiac risk factors, which may have limited the validity and generalisability of their findings. This was generally a well-conducted review and the authors' conclusions appear 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 further research was required to assess whether all patient populations had increased odds of stroke with these agents.

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