The safety of perioperative esmolol: a systematic review and meta-analysis of randomized controlled trials

CRD summary
The review concluded that esmolol was associated with an increased incidence of unplanned hypotension, but infusion reduced this and was both safe and effective in providing protection against myocardial ischaemia in patients undergoing noncardiac surgery. Concerns with the evidence quality and sample size as well as potential errors and biases within the review, warrant caution when interpreting the authors’ conclusions.

Authors' objectives
To determine the efficacy and safety of esmolol, a β1-specific adrenergic receptor agonist, in noncardiac surgery.

Searching
PubMed was searched from 1960 to June 2009 for articles published in any language. Search terms were reported. The related articles feature of PubMed and Science Citation Index were searched. The manufacturer of Esmolol was contacted for regulatory data. Reference lists of selected studies and reviews were searched.

Study selection
Randomised controlled trials of esmolol versus control in patients who underwent noncardiac surgery were eligible for inclusion. Trials had to provide information on esmolol dosing protocols. Treatment groups had to be comparable. The primary outcome was incidence of unplanned hypotension. Secondary outcomes included bradycardia, myocardial infarction and myocardial ischaemia. Definitions for outcomes were those used in individual studies. Changes in arterial blood pressure and heart rate were reported. Trials that used other vasoactive medicines were excluded.

The included trials studied esmolol via bolus or infusion (various doses) versus placebo, methohexital, nicardipine, fentanyl, alfentanil, remifentanil and propofol in patients who underwent elective noncardiac surgery. The included patients generally had few cardiac risk factors. Where reported, the type of surgery varied widely. Studies were conducted between 1986 and 2009. Studies were classified as assessing: treatment of established intraoperative hypertension; induction of planned intraoperative hypotension; effects of esmolol administration on the need for anaesthesia; and prophylaxis against hypertension, tachycardia or myocardial infarction.

Two reviewers independently performed study selection. Disagreements were resolved by consensus.

Assessment of study quality
Trial quality was assessed independently by two reviewers according to the trial size, randomisation, allocation concealment, blinding and intention-to-treat.

Data extraction
Two reviewers independently extracted means and standard deviations for continuous outcomes; binary data were also extracted. Extracted data were used to calculate odds ratios (OR) and weighted mean differences (WMD), together with 95% confidence intervals (CI). Disagreements between reviewers were resolved by discussion. Study authors were contacted for missing data. Where more than one dose of esmolol was compared to control, each dose was compared to control or the different doses were grouped together.

Methods of synthesis
A random-effects meta-analysis was undertaken to obtain pooled odds ratios and WMDs, together with 95% CIs. Statistical heterogeneity was assessed using $I^2$, $T^2$ and $X^2$. Meta-regression was undertaken to determine the dose-response relationships between esmolol dose and hypertension. Sensitivity analysis was undertaken based on model type (fixed-effect versus random-effects), ways of handling missing data (continuity correction, adding 0.5 to cells with zero events, versus no continuity correction) and method of esmolol administration (bolus versus infusion). Post hoc
subanalysis was conducted by eliminating studies in which the goal was to induce hypertension and/or tachycardia.

Results of the review

Sixty-seven trials (66 distinct trials) were included in the review (n=3,766 patients, as reported in the text): 33 trials of bolus dosing and 34 trials of infusion. Sample size ranged from 10 to 548 (median 40). Trial quality was variable: 30 trials were double blind, five were single blind and two were open label; few trials reported intention-to-treat.

Primary outcome (results from forest plot): Compared with control, esmolol was associated with a statistically significant increase in the incidence of unplanned hypotension (OR 2.14, 95% CI 1.50 to 3.05; 16 trials). Subgroup analyses showed that the results were not significant with infusion and were statistically significant with bolus (OR 2.28, 95% CI 1.55 to 3.37; 10 trials). There was no evidence of statistical heterogeneity.

Secondary outcomes: There was no statistically significant difference in the rates of bradycardia. Results were not significant for myocardial infarction, but there was a statistically significantly lower risk of myocardial ischaemia with esmolol compared with control (OR 0.17, 95% CI 0.02 to 0.45; seven trials).

Meta-regression indicated a relationship between initial dose of esmolol and unplanned hypertension (r²=0.408).

Authors' conclusions

Esmolol was associated with an increased incidence of unplanned hypotension, but infusion reduced this rate and had potential to be both safe and effective in providing protection against myocardial ischaemia in patients undergoing noncardiac surgery.

CRD commentary

Inclusion criteria for the review were broadly defined. Two relevant data sources were searched. There were no language restrictions. Publication bias was not assessed and could not be ruled out. Attempts were made to reduce reviewer error and bias throughout the review process. Quality assessment indicated the variable quality of the included data (acknowledged by the authors). A random-effects meta-analysis was undertaken and statistical heterogeneity was assessed, which was appropriate. Only a small number of studies reported outcomes and there were discrepancies in the reporting of results between the text and tables.

Given the concerns with the evidence quality and sample size as well as potential errors and biases within the review, caution is warranted when interpreting the authors' conclusions.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further studies in high-risk patients with longer duration infusions were needed to evaluate the safety and efficacy of esmolol to reduce the frequency of myocardial infarction after noncardiac surgery.

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