Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis

Wijeysundera D N, Naik J S, Beattie W S

CRD summary
This review examined the effect of alpha-2-adrenergic antagonists on deaths and cardiovascular complications in patients having surgery. The authors concluded that alpha-2-adrenergic antagonists reduce deaths and heart attacks in patients having vascular surgery. They also concluded that these drugs reduce ischaemia during cardiac surgery. This was a reasonably well-conducted review and the conclusions are probably reliable.

Authors' objectives
To investigate the effects of alpha-2-adrenergic antagonists on peri-operative mortality and cardiovascular complications in adults undergoing surgery.

Searching
MEDLINE (from 1966 to May 2002), EMBASE (from 1980 to May 2002) and the Cochrane Controlled Trials Register (Issue 2, 2002) were searched; some search terms were given. In addition, the references of included studies and published reviews were checked. The search was restricted to published trials but the authors of the included studies were contacted for additional data. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
The inclusion criterion was published randomised controlled trials (RCTs).

Specific interventions included in the review
The inclusion criteria were pre- (within 24 hours), intra- or post-operative (within 48 hours) administration of clonidine, dexmedetomidine or mivazerol given intravenously, intramuscularly, orally or transdermally.

Participants included in the review
The inclusion criteria were adults undergoing surgery under general or neuroaxial (spinal or epidural) anaesthesia. Trials that included participants given local anaesthesia or peripheral nerve blockade alone were excluded from the review. Also excluded were trials that included patients who were pregnant, organ transplant recipients, or patients suffering from substance withdrawal.

Outcomes assessed in the review
The inclusion criteria were death, myocardial infarction, myocardial ischaemia or supraventricular tachyarrhythmia. Ischaemia was defined as an ST-segment deviation on an electrocardiogram or new wall motion abnormalities on a transoesophageal echocardiogram. Supraventricular tachyarrhythmias included atrial fibrillation, atrial flutter and supraventricular tachycardia.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed abstracts and full papers of primary studies for inclusion in the review.

Assessment of study quality
Validity was assessed using the Jadad scale (see Other Publications of Related Interest). Studies that scored less than 1 were excluded from the review. Three reviewers independently assessed the validity of the included studies.
Data extraction
Three reviewers independently performed the data extraction. Data were extracted on the number of patients, disease status, surgical intervention, alpha-2-agonist, control group, quality and outcomes.

Methods of synthesis
How were the studies combined?
Studies reporting each outcome were combined in meta-analyses for all types of surgery and for vascular surgery. Both fixed-effect and random-effects models were used.

How were differences between studies investigated?
Subgroup analyses were performed for the effect of each alpha-2-agonist on mortality, myocardial infarction and ischaemia. Other subgroup analyses explored the effect of different procedures (cardiac, vascular and nonvascular surgery) on each of these outcomes. Sensitivity analyses were also carried out to assess the effects of including only studies with a statistically significant result, and to assess the effects of including only higher quality studies with a Jadad score of at least 3.

Results of the review
Twenty-three studies with 3,395 patients were included in the review.

Fifteen studies assessed clonidine, six assessed dexmedetomidine and two assessed mivazerol. Twenty-two studies compared alpha-2-agonists with placebo, and one compared dexmedetomidine with propofol.

Fifteen studies (n=3,128) reported 78 deaths (2.5%). Patients given alpha-2-agonists had lower mortality (relative risk, RR=0.64, 95% confidence interval, CI: 0.42, 0.99, P=0.05). Tests for heterogeneity did not detect significant differences among the trials (P=0.92).

The individual alpha-2-agonists each showed similar but non significant effects on mortality. The RR was 0.48 (95% CI: 0.15, 1.6, P=0.20) for clonidine, 0.57 (95% CI: 0.17, 1.88, P=0.40) for dexmedetomidine and 0.69 (95% CI: 0.42, 1.15, P=0.15) for mivazerol.

Thirteen studies (n=3,090) reported myocardial infarctions with 188 (6%) occurrences. Patients given alpha-2-agonists showed a lower rate of events, but this difference was not significant (RR 0.85, 95% CI: 0.65, 1.11, P=0.20). Tests for heterogeneity did not detect significant differences between the trials (P=0.55). The RR was 0.61 (95% CI: 0.25, 1.48, P=0.30) for clonidine, 0.47 (95% CI: 0.11, 2.03, P=0.30) for dexmedetomidine and 0.91 (95% CI: 0.68, 1.21, P=0.50) for mivazerol.

Sixteen studies (n=1,320) reported ischaemia with 336 (25.5%) occurrences. Patients given alpha-2-agonists had a reduced rate of ischaemia (RR 0.76, 95% CI: 0.63, 0.91, P=0.003). Tests for heterogeneity did not detect significant differences between the trials (P=0.59). However, the subgroup analyses showed a greater reduction in RR for patients given clonidine (RR 0.67, 95% CI: 0.54, 0.84, P=0.0005) than for those given dexmedetomidine (RR 0.85, 95% CI: 0.57, 1.27, P=0.40) or mivazerol (RR 1.14, 95% CI: 0.67, 1.97, P=0.60).

Four studies (n=243) reported supraventricular tachyarrhythmias with 33 (12%) occurrences. There was no difference in the rate of occurrence between groups given alpha-2-agonists and others (RR 1.04, 95% CI: 0.56, 1.93, P=0.90). Tests for heterogeneity did not detect significant differences between the trials (P=0.87).

Ten studies assessed cardiac surgery. In these studies alpha-2-agonists significantly reduced myocardial ischaemia (RR 0.71, 95% CI: 0.54, 0.92, P=0.01). There were also non significant reductions in mortality (RR 0.49, 95% CI: 0.12, 1.98, P=0.30) and myocardial infarction (RR 0.83, 95% CI: 0.35, 1.96, P=0.70). Tests for heterogeneity did not detect significant differences between the trials on any outcome.

Eight studies assessed vascular surgery. In these studies alpha-2-agonists significantly reduced mortality (RR 0.47, 95% CI: 0.25, 0.90, P=0.02) and myocardial infarction (RR 0.66, 95% CI: 0.46, 0.94, P=0.02). There was also a non significant reduction in ischaemia (RR 0.83, 95% CI: 0.64, 1.07, P=0.15). Tests for heterogeneity did not detect
significant differences between the trials on any outcome.

Three studies assessed nonvascular surgery and found no significant effect of alpha-2-agonists on mortality (RR 1.05, 95% CI: 0.52, 2.09, P=0.90), infarction (RR 1.35, 95% CI: 0.83, 2.21, P=0.2) or ischaemia (RR 0.20, 95% CI: 0.02, 1.62, P=0.13).

Further analyses explored the effect of prior medication with calcium antagonists or beta-blockers, and the occurrence of adverse events during different categories of surgery.

Authors' conclusions
Alpha-2-adrenergic agonists reduce mortality and myocardial infarction following vascular surgery. They also reduce ischaemia during cardiac surgery, and may have an impact on mortality and myocardial infarction.

CRD commentary
The review question and the inclusion criteria were clear. The search was adequate, and the attempts to contact authors might have reduced selection bias. However, unpublished studies were not included in the search strategy, although the authors stated that they used funnel plots to assess publication bias and found no evidence of it. The authors reported that they used appropriate measures to reduce bias and error in study selection, data extraction and validity assessment processes. The validity assessment was reasonable and was used in a sensitivity analysis to assess the impact of study validity on the results.

The decision to use meta-analyses was reasonable. However, it was unclear whether a fixed-effect or random-effects model is reported as the authors stated that both were employed. The use of a sensitivity analysis to explore the effect of only including trials with statistically significant results does not add any value to the analysis. A relatively large number of subgroup analyses were carried out. It is unclear if these were a priori or post hoc in design and, if the latter is the case, the results may require cautious interpretation since a large number of post-hoc analyses is likely to produce some statistically significant results by chance alone.

The authors’ conclusions are appropriate given the results of the meta-analyses conducted, although the conclusion with respect to ischaemia does not take into consideration the significant clinical heterogeneity among studies and the fact that one subgroup (patients treated with clonidine) appears to be responsible for the overall difference in RR.

Implications of the review for practice and research
Practice: The authors supported the use of alpha-2-adrenergic agonists to reduce peri-operative cardiovascular complications following vascular or cardiac surgery.

Research: The authors stated that large randomised trials are needed to evaluate the use of alpha-2-adrenergic agonists during cardiac and vascular surgery.

Bibliographic details

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Other publications of related interest
Indexing Status
Subject indexing assigned by NLM

MeSH
Adrenergic alpha-Agonists /administration & dosage /therapeutic use; Arrhythmias, Cardiac /prevention & control; Cardiac Surgical Procedures /mortality; Clonidine /administration & dosage /therapeutic use; Dexmedetomidine /administration & dosage /therapeutic use; Humans; Imidazoles /administration & dosage /therapeutic use; Myocardial Infarction /prevention & control; Perioperative Care; Preoperative Care; Randomized Controlled Trials as Topic; Registries

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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.