Title          Perioperative dexmedetomidine and outcomes after adult cardiac surgery: A systematic review and meta-analysis protocol

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Contributions    All authors contributed to develop and finalize the study protocol. Literature and data extraction by SH and MG; adjudication on data disagreement by DM; statistical analysis by SH; manuscript written, reviewed and approved by all authors.
**Protocol amendments**  This document represents the primary study protocol and has been drafted with the guidance of the PRISMA explanatory statement on systematic review and meta-analysis protocols.¹ In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

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**Introduction**

Although cardiac surgery is one of the most frequently performed surgeries in the developed world perioperative complications are common. There is a wide spectrum of perioperative complications including delirium (estimated to occur in 30-50% of patients), atrial fibrillation (30%), acute kidney injury (20-25%), myocardial ischaemia or infarction, and overt stroke. While the precise pathophysiology of these varied clinical complications remains incompletely understood focal ischaemia-reperfusion injury and perioperative inflammation may represent a common thread, with an aetiological contribution to each of the aforementioned complications.

Dexmedetomidine is an α-2 adrenergic agonist that may offer organ protection through combined modulation of the sympathetic nervous system and anti-inflammatory effects. It also provides sedative, anxiolytic and analgesic effects and is approved by both the FDA and TGA for sedation of intubated patients in an intensive care unit or sedation of patients for surgical procedures. While several studies report that dexmedetomidine is associated with reduced rates of mortality,\(^2\) delirium,\(^2, 3\) AKI,\(^4, 5\) atrial arrhythmias\(^6\) and other complications following cardiac surgery others do not support such benefits.\(^7-9\) However, marked variation between studies in terms of primary endpoints and other reported outcomes, dose and timing of dexmedetomidine, as well as other methodological limitations may all contribute to conflicting results and ongoing uncertainty regarding the true role of dexmedetomidine for the prevention of complications in adult cardiac surgery.

**Objective:** Through a process of systematic review and meta-analysis we plan to evaluate the currently available evidence to determine the best estimates of
the safety and efficacy of perioperative dexmedetomine in adult cardiac surgery. We will specifically evaluate the impact of dexmedetomidine, commenced preoperatively, intraoperatively or postoperatively, in adults undergoing any type of cardiac surgery. Efficacy outcomes for analysis will be selected to include markers of perioperative renal injury, perioperative neurological injury, perioperative myocardial injury, arrhythmias, duration of mechanical ventilation and length of stay in the intensive care unit and hospital, and mortality. Safety outcomes for analysis will be selected to include markers of cardiovascular instability including hypotension, inotropic or vasopressor support, need for pacing or brady-arrhythmias and non-fatal cardiac arrest.
Methods

Eligibility criteria:

- Studies of perioperative intravenous dexmedetomidine in adult patients (age ≥ 18 years) undergoing any cardiac surgery. Studies of broad cohorts of patients that included some patients who underwent cardiac surgery will not be included.
- Intravenous dexmedetomidine commenced preoperatively, intraoperatively or postoperatively, with all dosing regimens included.
- Comparator group may be placebo or any non-dexmedetomidine pharmacological agent.
- Specific outcomes for analysis include postoperative AKI, renal replacement therapy, delirium, stroke or other neurological deficits persisting for greater than 24 hours, AF or other arrhythmias, myocardial infarction, inotropic or vasopressor support or hypotension, need for cardiac pacing, non-fatal cardiac arrest, duration of ventilation, length of stay in the intensive care unit or hospital, and mortality. Eligible studies must report at least one of these outcomes.
- All study types (prospective, retrospective, randomized and observational) included.
- There are no language, time or publications status restrictions.

Information sources: A formal search of MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials will be undertaken according to a pre-defined search strategy. Reference lists of included studies or other relevant reviews identified through the search process will be scanned for any additional
studies for inclusion. Titles and/or abstracts of retrieved publications will be independently screened by two reviewers (SH and MG) to assess for eligibility. Full reports for all studies not excluded at this stage will then be obtained. Reviewers will not be blinded to study authors, institution or other details. Lack of consensus between these two reviewers will be resolved by discussion and agreement with a third reviewer (DM) and, if necessary, a fourth reviewer (YS). At least 2 attempts will be made to contact authors of eligible studies to ascertain additional information to facilitate maximal data extraction for analysis or resolve other uncertainties. A bibliography of included studies will then be circulated to all members of the systematic review team to ensure that all relevant material has been captured.

Search strategy: The proposed search strategy for MEDLINE is [cardiac surgery.mp OR exp Thoracic Surgery OR exp Cardiac Surgical Procedures OR open heart surgery.mp OR heart surgery.mp OR coronary artery bypass.mp OR exp Coronary Artery Bypass OR cardiopulmonary bypass.mp OR exp Cardiopulmonary Bypass] AND [dexmedetomidine.mp OR exp Dexmedetomidine OR exp Adrenergic alpha-2 Receptor Agonists or alpha 2 adrenergic receptor agonist.mp]. Results will be limited to human studies only. The search will be updated toward the end of the review.

Study records: The Covidence.org platform will be used to facilitate manuscript handling, processing and storage.

Data collection: Data extraction will be independently performed in duplicate (SH and MG) with data collection facilitated by use of a standardized electronic data collection form.
Extracted study variables: First author, date of publication, funding source, sample size, study design, study cohort, timing, dose and duration of dexmedetomidine, comparator.

Extracted outcomes: Efficacy outcomes will include postoperative AKI, renal replacement therapy, delirium, stroke or other neurological deficits persisting for greater than 24 hours, AF, other tachy-arrhythmias, myocardial infarction, duration of mechanical ventilation, length of stay in the intensive care unit or hospital, and mortality. Safety end-points will include hypotension, vasopressor/inotropic support, the need for cardiac pacing or brady-arrhythmias and non-fatal cardiac arrest. Study-specific definitions of outcomes will be accepted (and noted) for the purposes of data extraction. Where existing studies report composite outcomes we will request authors provide data on individual outcomes in a useable format. A decision on the appropriateness of a pooled analysis of study-reported composite outcomes will be made after all data has been extracted, allowing an assessment of the variability in individual outcomes used by different studies to generate their composite end-points.

Risk of bias assessment: Risk of bias will be assessed at both a study level and outcome level. Risk of bias will be evaluated using the Cochrane risk of bias tool according to sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'. We will consider each item in the risk of bias assessment independently with no attempt to collate an assign an overall score. For included trials published after July 1st, 2005 we will scree the Clinical Trial Register at the International Clinical Trials Registry
platform of the World Health Organization (http://apps.who.int/trialsearch) to assess for evidence of reporting bias.

**Statistical analysis:** Analyses will be conducted using RevMan (RevMan, version 5.3 for Windows; The Cochrane Collaboration, Oxford, UK; 2014). Dichotomous outcomes will be assessed using the Peto method to calculate odds ratio (OR) and 95% confidence interval (CI) with either a fixed effect or random effect model selected according to the observed degree of heterogeneity. Statistical heterogeneity will be assessed using the $I^2$ statistic. For dichotomous outcomes, single cells showing zero events will automatically have 0.5 added to that cell to maintain its contribution to the analysis. Studies reporting no events for a given endpoint in either the control or treatment arm will be excluded from analysis for that endpoint. Numerical endpoints will be analyzed as weighted mean difference with 95% CI. Attempts will be made to convert data into mean (standard deviation) according to existing recommendations. In studies without range data, standard deviation will be imputed, based on the standard deviation of pooled study data.

Sensitivity analyses will include sequential exclusion of each study, stratified analysis according to study type (observational vs. randomized) and stratified analysis according to timing and dose of dexmedetomidine. Additional sensitivity and subgroup analyses to explore observed heterogeneity will be undertaken as appropriate. Funnel plots will be used to assess for evidence of publication bias. If it becomes apparent that a quantitative pooled analysis is inappropriate for the available data then a systematic narrative synthesis will be provided to summarize and explain the characteristics and findings of included studies.
The quality of evidence for all outcomes will be judged using the Grading of Recommendations Assessment, Development and Evaluation working group methodology (GRADE). The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias. Results will be synthesized into a comprehensive manuscript for submission and publication in an appropriate peer-reviewed journal.
References:


