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Anaesthetic drugs and survival: a Bayesian network meta-analysis of randomized trials in cardiac surgery

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Editor's key points

- Numerous studies have suggested that volatile agents provide myocardial protection in cardiac surgery.
- No adequately powered clinical trials have been conducted to evaluate the effect of volatile agents on mortality after cardiac surgery.
- Bayesian network meta-analysis allows indirect comparisons of drugs not otherwise compared in head-to-head trials.
- Volatile-based anaesthesia seems to reduce mortality after cardiac surgery when compared with TIVA.

Background. Many studies have compared desflurane, isoflurane, sevoflurane, total i.v. anaesthesia (TIVA), or all in cardiac surgery to assess their effects on patient survival.

Methods. We performed standard pairwise and Bayesian network meta-analyses; the latter allows indirect assessments if any of the anaesthetic agents were not compared in head-to-head trials. Pertinent studies were identified using BioMedCentral, MEDLINE/PubMed, Embase, and the Cochrane Library (last updated in June 2012).

Results. We identified 38 randomized trials with survival data published between 1991 and 2012, with most studies (63%) done in coronary artery bypass grafting (CABG) patients with standard cardiopulmonary bypass. Standard meta-analysis showed that the use of a volatile agent was associated with a reduction in mortality when compared with TIVA at the longest follow-up available [25/1994 (1.3%) in the volatile group *vs* 43/1648 (2.6%) in the TIVA arm, odds ratio (OR)=0.51, 95% confidence interval (CI) 0.33–0.81, *P*-value for effect=0.004, number needed to treat 74, I^2=0%] with results confirmed in trials with low risk of bias, in large trials, and when including only CABG studies. Bayesian network meta-analysis showed that sevoflurane (OR=0.31, 95% credible interval 0.14–0.64) and desflurane (OR=0.43, 95% credible interval 0.21–0.82) were individually associated with a reduction in mortality when compared with TIVA.

Conclusions. Anaesthesia with volatile agents appears to reduce mortality after cardiac surgery when compared with TIVA, especially when sevoflurane or desflurane is used. A large, multicentre trial is warranted to confirm that long-term survival is significantly affected by the choice of anaesthetic.

Keywords: anaesthesia; anaesthesia inhalation; cardiovascular surgical procedures

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Every year more than 200 million patients worldwide undergo major surgery and are exposed to significant morbidity and mortality. A recent international consensus conference identified only 12 drugs, techniques, or strategies associated with a reduction in perioperative mortality, and the only anaesthetic drugs included in this short list were volatile agents.[1]

Volatile agents have documented pharmacological but non-anaesthetic properties conferring cardiac protection and influencing perioperative[2–4] and long-term clinically relevant outcomes,[5 6] probably because of favourable transcriptional changes in protective and anti-protective proteins.[5] The mechanism of action is related, but not limited, to the modulation of cytosolic calcium concentration through the potassium mitochondrial channels.[7]

Five studies suggested that the beneficial effect of volatile agents (desflurane, isoflurane, and sevoflurane) might translate into reduced mortality rate when compared with total i.v. anaesthesia (TIVA) in cardiac surgery.[2–4 6 8] Even if no randomized study or meta-analysis of randomized studies in favour of TIVA exists, it should be acknowledged that several meta-analysis performed in cardiac surgery[9 10] and one large randomized trial performed in non-cardiac surgery[11] did not confirm the beneficial effects of volatile anaesthetics on clinically relevant outcomes. Perhaps this is why TIVA is still commonly used in cardiac surgery.

A network meta-analysis is a statistical technique for comparison of different treatments that were never directly compared in head-to-head trials. On the basis of statistical

inference, it is possible to establish which treatment is superior, reaching, through indirect comparison, reliable conclusions otherwise impossible to achieve. The primary objective of this study was therefore to determine whether anaesthetic techniques (TIVA *vs* volatile-based anaesthesia) confer a survival advantage for patients undergoing cardiac surgery. A secondary aim was to explore whether a particular volatile (desflurane, isoflurane, or sevoflurane) or TIVA (propofol) agent is associated with improved survival.

Methods

To address the question whether the choice of the anaesthetic might influence patients' survival after cardiac surgery, we carried out standard meta-analyses and Bayesian network meta-analyses to compare the effect on mortality of desflurane, isoflurane, sevoflurane, and TIVA.

When head-to-head treatment comparisons are not available or conclusive, network meta-analyses can provide estimates of treatment efficacy of multiple treatment regimens. Different treatments are analysed by statistical inference, rather than simply summing up trials that evaluated the same drug management compared with control, so that the results come from combining both direct and indirect estimates. To model the binomial data, we applied the Bayesian hierarchical model using Markov Chain Monte Carlo (MCMC) approaches.

Search strategy and study selection

Pertinent studies were independently searched in BioMedCentral, MEDLINE/PubMed, Embase, and the Cochrane Central Register of clinical trials by two expert investigators. Literature searches were last updated on June 1, 2012. The full PubMed search strategy was developed according to Biondi-Zoccai and colleagues[12] and is available in the Appendix. Further hand or computerized searches involved the recent (2010–2012) conference proceedings from the International Anaesthesia Research Society, American Heart Association, American College of Cardiology, American Society of Anesthesiologists, and European Society of Cardiology congresses.

Study selection

References obtained from database, literature searches with cross-check of references, experts, and manufacturers were first independently examined at a title/abstract level by two investigators and then, if potentially pertinent, retrieved as complete articles. No language restriction was imposed and non-English articles were translated and included in the analyses. The following inclusion criteria were used for potentially relevant studies: random allocation to treatment and comparison between a TIVA and an anaesthesia plan including administration of isoflurane, desflurane, or sevoflurane or a comparison between volatile agents, performed in cardiac surgical patients with no restriction in dose and time of administration. The exclusion criteria were duplicate publications (in this case, the article reporting the longest follow-up was abstracted), non-human experimental studies, and lack of outcome data. Studies in which epidural analgesia/anaesthesia was given to all patients were included.[13 14] Studies in which ischaemic pre-conditioning or remote ischaemic pre-conditioning were performed in all patients were excluded because ischaemic pre-conditioning has pathways of cardiac protection that are similar to those of volatile anaesthetics[15 16] even if the cardiac protective properties of volatile agents are not limited to pre-conditioning. Two investigators independently assessed compliance to selection criteria and selected studies for the final analysis, with divergences finally resolved by consensus.

Data abstraction and study characteristics

Year of publication, setting, number of patients, volatile agent, anaesthetic comparator, and length of follow-up were collected (Table 1) together with baseline (age, diabetes, ejection fraction, chronic obstructive pulmonary disease, use of beta-blockers, and management of sulfonylurea, theophylline, or allopurinol) (Supplementary Table S1) and procedural (cardioplegia, time of cross-clamping, and number of coronary artery grafts) (Supplementary Table S2) data. Furthermore, we extracted and pooled data on mechanical ventilation, intensive care unit (ICU) stay, hospital stay, troponin I (ng ml^{-1}), myocardial infarction (as per author definition), and use of inotropic agent.

'Total Intravenous Anaesthesia' was defined as a group not receiving volatile agents. 'Propofol' was defined as a TIVA group receiving propofol as main hypnotic agent and not receiving volatile agents. 'Volatile' (desflurane, isoflurane, or desflurane) was defined as a group receiving a volatile agent (even if added on top of a TIVA regimen and irrespectively on time of administration).

The endpoint of the present systematic review and meta-analysis of randomized trials was to identify differences in mortality at the longest follow-up available between volatile agents and TIVA and to identify whether one or more anaesthetics were superior or inferior in terms of survival, using standard meta-analyses and Bayesian network meta-analyses. If we found that the study had missing or incomplete data on survival, we contacted all authors by letter, e-mail, or both.

The methodological details[17–21] for the internal validity and risk of bias assessment, for the statistical analyses and for the details on the conduction of the Bayesian network meta-analyses are reported as Supplementary data. In summary, the internal validity was evaluated according to the Cochrane Collaboration methods; the overall risk of bias was expressed as low, moderate, or high; the evidence of publication bias was assessed by analytic appraisal based on both Peters' and Begg's test; the heterogeneity assumption among studies within direct contrast was evaluated by means of Cochran *Q*-test and by I^2 by Higgins and Thompson;[17] the validity and the symmetry of the entire Bayesian network meta-analysis was investigated visually by a graph of the network configuration. The presence of effect-modifiers attributable to heterogeneity was considered acceptable if the χ^2 *P*-value was >0.10. Mortality data from individual studies