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Volatile anesthetics versus total intravenous anesthesia for patients undergoing coronary artery bypass grafting: a protocol for an updated meta-analysis and trial sequential analysis

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ABSTRACT

Background

The benefit of volatile anesthetics in coronary artery bypass grafting (CABG) patients remains controversial. We aim to conduct an updated meta-analysis to assess whether the use of volatile anesthetics during CABG could reduce mortality as well as other outcomes.

Methods

We searched eight databases from inception to June 2019. RCTs comparing the effects of volatile anesthetics versus total intravenous anesthesia (TIVA) in CABG patients were included. The primary outcomes were operative mortality and one-year mortality. The second outcomes included length of stay in intensive care unit (ICU), length of stay in hospital, and postoperative safety outcomes (myocardial infarction, heart failure, arrhythmia, stroke, delirium, postoperative cognitive impairment, acute kidney injury, and the use of intra-aortic balloon pump (IABP) or other mechanical circulatory support). Trial sequential analysis (TSA) was performed to control random errors.

Results

This updated meta-analysis will test the hypothesis that the use of volatile anesthetics during CABG would not result in a lower mortality than TIVA. We also aim to examine the effect of volatile anesthetics on length of stay in intensive care unit (ICU), length of stay in hospital, and other postoperative safety outcomes. Moreover, we use trial sequential analysis (TSA) to determine whether the currently available evidence is sufficient and conclusive.

Conclusion

This updated meta-analysis may overturn the beneficial effect of volatile anesthetics, impact the choice of anesthesia for thousands of CABG patients, and further alter current guideline recommendations regarding this issue.

EXTERNAL LINK

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THIS PROTOCOL ACCOMPANIES THE FOLLOWING PUBLICATION

Jiao X, Lin X, Ni X, Li H, Zhang C, Yang C, Song H, Yi Q, Zhang L (2019) Volatile anesthetics versus total intravenous anesthesia in patients undergoing coronary artery bypass grafting: An updated meta-analysis and trial sequential analysis of randomized controlled trials. PLoS ONE 14(10): e0224562. doi: 10.1371/journal.pone.0224562

GUIDELINES

This meta-analysis was conducted in accordance with the Cochrane Handbook, as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

Search Strategy

1 We searched Pubmed, Embase(Ovid), the Cochrane Library, and three Chinese databases: China Knowledge Resource Integrated Database (CNKI), VIP Database and Wanfang Database (until June 2019). We also searched ongoing clinical trials databases such as “http://clinicaltrials.gov” and “http://www.controlled-trials.com/”. The search terms included: volatile anesthetics, halothane, sevoflurane, desflurane, isoflurane, enflurane, methoxyflurane, ether, and coronary artery bypass **Search strategy in PubMed.docx** . Morever, the references of included studies were manual checked for additional studies.

Inclusion criteria

2 Inclusion criteria with reference to PICOS criteria was as follows: (1) participant: patients undergoing general anesthesia for CABG. (2) Intervention: an anaesthesia plan that included a volatile anesthetic (such as halothane, sevoflurane, desflurane, isoflurane, enflurane, or ether) without restriction in time and dose of administration. (3) Comparison: TIVA (such as propofol, fentanyl, sufentanil, midazolam, thiopental, or etomidate). (4) Outcomes: the primary outcomes were operative mortality and one-year mortality. The second outcomes included length of stay in ICU, length of stay in hospital, and postoperative safety outcomes (myocardial infarction, heart failure, arrhythmia, stroke, delirium, postoperative cognitive impairment, acute kidney injury, the use of intra-aortic balloon pump (IABP), and the use of other mechanical circulatory support). Eligible studies should report at least one of the above outcomes. According to the Society of Thoracic Surgeons, operative mortality is defined as “① all-cause death occurring during the hospitalization in which the operation was performed, even if after 30 days; and ② all-cause death occurring after hospital discharge, but within 30 days of the operation”. (5) Study design: RCT.

Exclusion criteria

3 Exclusion criteria was as follows: (1) CABG combined with valve surgery; (2) epidural anesthesia was included in the anesthetic plan; (3) with no outcome data; (4) full-text not availabie; (5) not published in English or Chinese.

Study selection

4 Two independent reviewers (XF Jiao and XF Ni) screened the titles and abstracts to determine potentially revelant studies firstly. Then they evaluated the full-text articles of potentially revelant studies for eligibility. Reviewers resolved the disagreements by consensus, and if necessary asked for a third reviewer’s adjudication.

Data extraction

5 Two independent reviewers (XF Jiao and XF Ni) extracted data from each included study using a pre-piloted data extraction form **Data extraction form.xlsx** . This data extraction form included general study information, general patient characteristics, sample size, intervention, comparison, and outcomes. Postoperative safety outcomes occurring during the hospitalization or within 30 days of the operation were extracted in our meta-analysis.

Risk of bias in individual studies

6 Two independent reviewers (XF Jiao and XF Ni) evaluated the risk of bias of each selected study using the Cochrane risk of bias tool. This tool consists of seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. According to the Cochrane Handbook for Systematic Reviews of Interventions, we assessed the risk of bias per outcome across trials as: low risk of bias (if the seven items were all evaluated as low risk of bias); unclear risk of bias (if one or more items were evaluated as unclear risk of bias); high risk of bias (if one or more items were evaluated as high risk of bias).

Quality of evidence

7 We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the overall level of evidence strength of each outcome. By considering five categories of limitations (risk of bias, inconsistency, indirectness, imprecision, and reporting bias), the GRADE approach provided a rating of quality of evidence (high, moderate, low, or very low) for each outcome.

Data synthesis and analysis

8 For dichotomous data, we extracted the number of events and total number of each group, and adopted the risk ratio (RR) with 95% confidence intervals (CI) as the effect measure. For continuous data, we extracted mean and standard deviation (SD), and adopted mean difference (MD) with 95% confidence intervals (CI) as the effect measure. If the included studies only provided the median, range, and/or the first and third quartiles, we first transformed these data to the sample mean and SD through published formulas. If there were more than one volatile anesthetics group or TIVA group in the included studies, these groups were combined for the pooled analyses. I-squared (I^2) test was used to assess the heterogeneity. If the heterogeneity was acceptable ($I^2 \leq 50\%$), a fixed effect model was used. Otherwise, if the heterogeneity was significant (I^2>50%), a random effects model was used, and sensitivity analysis was conducted by excluding one or more studies at a time to assess the stability of results. Moreover, if ten or more studies were included, the funnel plot was used to assess publication bias. Statistical analyses were conducted by RevMan 5.3.

Trial sequential analysis (TSA)

9 **Trial sequential analysis (TSA)**
For all primary and secondary outcomes, we conducted TSA to reduce the risk of random errors. TSA is a method that calculates the required information size (RIS) for a meta-analysis, constructing both the trial sequential monitoring boundaries for benefit or harm and the futility boundary before reaching the RIS. The risk of type I error was set at 5% with a power of 80%. For dichotomous outcomes, we initially calculated the RIS to detect a 20% relative risk reduction (RRR), as this value was believed to represent a reasonable intervention effect in most therapeutic areas. If the boundary RIS was ignored due to too little information use, we then tested for a 30% RRR. We used the median event proportion of TIVA groups (excluding the zero-event trials) as the control group event proportion. For continuous outcomes, we calculated the RIS based on empirical estimation from TSA software. TSA was conducted by TSA viewer version 0.9.5.10 Beta (www.ctu.dk/tsa).