Comparison of the cerebroprotective effect of inhalation anaesthesia and total intravenous anaesthesia in patients undergoing cardiac surgery with cardiopulmonary bypass: a systematic review and meta-analysis

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ABSTRACT

Objective Neurological dysfunction remains a devastating postoperative complication in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), and previous studies have shown that inhalation anaesthesia and total intravenous anaesthesia (TIVA) may produce different degrees of cerebral protection in these patients. Therefore, we conducted a systematic literature review and meta-analysis to compare the neuroprotective effects of inhalation anaesthesia and TIVA.

Design Searching in PubMed, EMBASE, Science Direct/Elsevier, China National Knowledge Infrastructure and Cochrane Library up to August 2016, we selected related randomised controlled trials for this meta-analysis.

Results A total of 1485 studies were identified. After eliminating duplicate articles and screening titles and abstracts, 445 studies were potentially eligible. After applying exclusion criteria (full texts reported as abstracts, review article, no control case, lack of outcome data and so on), 13 studies were selected for review. Our results demonstrated that the primary outcome related to S100B level in the inhalation anaesthesia group was significantly lower than in the TIVA group after CPB and 24 hours postoperatively (weighted mean difference (WMD): 95% CI (CI): −0.41 (−0.81 to −0.01), −0.32 (−0.59 to −0.05), respectively). Among secondary outcome variables, mini-mental state examination scores of the inhalation anaesthesia group were significantly higher than those of the TIVA group 24 hours after operation (WMD (95% CI): 1.87 (0.82 to 2.92)), but no significant difference was found in arteriovenous oxygen content difference, cerebral oxygen extraction ratio and jugular bulb venous oxygen saturation, which were assessed at cooling and rewarming during CPB.

Conclusion This study demonstrates that anaesthesia with volatile agents appears to provide better cerebral protection than TIVA for patients undergoing cardiac surgery with CPB, suggesting that inhalation anaesthesia may be more suitable for patients undergoing cardiac surgery.

INTRODUCTION

Cardiopulmonary bypass (CPB) is a necessary and common procedure to support the patient’s circulation during cardiac surgery. Although previous studies1 2 reported that CPB does not increase the postoperative morbidity and mortality in patients undergoing coronary artery bypass graft surgery, it was demonstrated that the incidence of some postoperative complications for these patients remains high. Neurological dysfunction is one of the most commonly reported postoperative complications in patients undergoing cardiac surgery.3 4 Several factors including cerebral anoxia, embolism, excessive excitatory neurotransmitter release and systemic inflammatory response have been demonstrated to
contribute to postoperative neurological dysfunction. However, at present, there is no definitive clinical evidence regarding cerebral protection for patients undergoing cardiac surgery with CPB. Previous studies on animals support the hypothesis that anaesthetics can produce cerebral protection. Many recent studies have found that anaesthetic agents may be neuroprotective and may provide cerebral protection to surgery patients. However, clinical studies show that the relative effects of inhalation anaesthesia or total intravenous anaesthesia (TIVA) on neuroprotection in cardiac surgery with CPB remain controversial and much debated. Therefore, which option provides better cerebral protection to patients undergoing cardiac surgery with CPB is unknown. As inhalation anaesthesia and TIVA are the most commonly used strategies for general anaesthesia, it is important to clarify this issue. Moreover, as it is difficult to include patients in neurological dysfunction studies for cardiac surgery with CPB, the sample size of these previous studies was generally small. For these reasons, it is necessary to systematically review the available literature and perform a meta-analysis to compare the neuroprotective effects of inhalation anaesthesia and TIVA.

MATERIALS AND METHODS
The current systematic review and meta-analysis was performed according to the reporting items for systematic reviews and meta-analyses reported guidelines for randomised controlled trials.

Literature search
This meta-analysis was restricted to published studies that investigated the cerebral protective effects of anaesthetics in patients with CPB. The PubMed database, EMBASE, MEDLINE, Science Direct/Elsevier, Cochrane Library and China National Knowledge Infrastructure were searched by two independent reviewers up to August 2016, without restrictions on language or study type. The search terms combined text words and medical subject headings (MeSH) terms. For example,
| Study             | Mean age(no. inhalation/TIVA) | Setting                        | Case | Volatile agents | Comparator | Outcomes                          |
|-------------------|-------------------------------|-------------------------------|------|-----------------|------------|-----------------------------------|
| Min and Yanlin 2007<sup>17</sup> | 36–62                         | CPB-cardiac surgery            | 15/15 | Isoflurane      | Propofol   | SjvO<sub>2</sub>%, CBP time       |
| Huaping 2015<sup>18</sup>         | 40–65                         | CPB-cardiac valve replacement | 15/15 | Sevoflurane     | Propofol   | S100B, MMSE                      |
| Lei et al 2010<sup>19</sup>       | 60–70                         | CPB-CABG                       | 15/15 | Isoflurane      | Propofol   | S100B                            |
| Newman et al 1998<sup>20</sup>    | 56±12/61±14                   | CPB-cardiac valve replacement | 16/15 | Isoflurane      | Thiopental | CBF, CMRO<sub>2</sub>, D<sub>a-v</sub>O<sub>2</sub>, SjvO<sub>2</sub>%, CBP time |
| Woodcock et al 1987<sup>21</sup>  | 55.5±9.9/63.1±6.5             | CPB-CABG                       | 16/21 | Isoflurane      | Thiopental | CBF, CMRO<sub>2</sub>, CBP time   |
| Guçlu et al 2014<sup>22</sup>     | 57.37±9.8/57.33±7.2           | CPB-cardiac surgery            | 10/10 | Sevoflurane     | Midazolam  | CBP time                         |
| Kanbak et al 2004<sup>23</sup>    | 56±7.6/54.5±5.9               | CPB-CABG                       | 20/20 | Isoflurane      | Propofol   | S100B, CBP time                  |
| Baki et al 2013<sup>24</sup>      | 64.57±10.84/66.45±13.04       | CPB-CABG                       | 60/61 | Desflurane      | Propofol   | S100B, CBP time                  |
| Singh et al 2011<sup>25</sup>     | 60.10±7.9/59.54±8.83          | CPB-CABG                       | 15/15 | Sevoflurane     | Midazolam  | S100B, CBP time                  |
| Tingting et al 2007<sup>26</sup>  | 52±5/48±7                     | CPB-cardiac valve replacement  | 20/20 | Isoflurane      | Propofol   | S100B, D<sub>a-v</sub>O<sub>2</sub>, SjvO<sub>2</sub>%, CBP time |
| Jianrong et al 2009<sup>27</sup>  | 44±8/43±7                     | CPB-cardiac valve replacement  | 30/30 | Isoflurane      | Propofol   | S100B, D<sub>a-v</sub>O<sub>2</sub>, SjvO<sub>2</sub>%, CBP time |
| Shudong 2015<sup>28</sup>         | 49.5±2.6/49.1±2.4             | CPB-cardiac valve replacement  | 15/15 | Sevoflurane     | Propofol   | S100B, MMSE                      |
| Jiying et al 2010<sup>29</sup>    | 75±5/74±4                     | CPB-CABG                       | 25/25 | Desflurane      | Ketamine   | S100B, MMSE                      |

CABG, coronary artery bypass grafting; CBF, cerebral blood flow; CMRO<sub>2</sub>, cerebral metabolic rate of oxygen consumption; CPB, cardiopulmonary bypass; D<sub>a-v</sub>O<sub>2</sub>, arteriovenous oxygen content difference; MMSE, mini-mental state examination; O<sub>2</sub>ER, cerebral oxygen extraction; SjvO<sub>2</sub>, jugular bulb venous oxygen saturation; TIVA, total intravenous anaesthesia.
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Table 2  Methodology quality of the included RCTs

| Study                     | Jadad score | Randomisation | Allocation concealment | Blinding | Attrition | Score |
|---------------------------|-------------|---------------|------------------------|----------|-----------|-------|
| Min and Yanlin 2007       | 1           | 1             | 0                      | 1        | 0         | 2     |
| Huaping 2015              | 1           | 0             | 0                      | 0        | 0         | 1     |
| Lei et al 2010            | 1           | 0             | 1                      | 0        | 0         | 2     |
| Newman et al 1998         | 1           | 0             | 0                      | 0        | 0         | 1     |
| Woodcock et al 1987       | 1           | 0             | 0                      | 0        | 0         | 1     |
| Guçlu et al 2014          | 1           | 0             | 1                      | 0        | 0         | 1     |
| Kanbak et al 2004         | 1           | 2             | 1                      | 0        | 0         | 4     |
| Baki et al 2012           | 1           | 2             | 1                      | 0        | 0         | 4     |
| Singh et al 2011          | 2           | 2             | 1                      | 0        | 0         | 5     |
| Tingting et al 2007       | 1           | 0             | 0                      | 0        | 0         | 1     |
| Jianrong et al 2009       | 1           | 0             | 0                      | 0        | 0         | 1     |
| Shudong 2015              | 1           | 0             | 0                      | 0        | 0         | 1     |
| Jiying et al 2010         | 2           | 2             | 1                      | 0        | 0         | 3     |

RCTs, randomised controlled trials.

Table 2  Methodology quality of the included RCTs

| Study or Subgroup | Jadad score | Randomisation | Allocation concealment | Blinding | Attrition | Score |
|-------------------|-------------|---------------|------------------------|----------|-----------|-------|
| 1.1 S100B (pre-CPB) |             |               |                        |          |           |       |
| Huaping 2015      | 2           | 0.4           | 0.05                   | 25       | 0.44      | 0.08  | 6.8% | -0.02 [-0.06, 0.02] |
| Jannings et al 2009 | 0.45       | 0.17          | 0.46                   | 15       | 0.60      | -0.01 [-0.15, 0.13] |
| Shudong 2015      | 0.05       | 0.13          | 0.04                   | 30       | 0.01      | 0.00 [-0.00, 0.01] |
| Jannings et al 2010 | 0.50       | 0.12          | 0.17                   | 15       | 0.63      | 0.01 [-0.10, 0.12] |
| Singh et al 2011  | 0.05       | 0.01          | 0.04                   | 60       | 0.40      | 0.01 [-0.22, 0.04] |
| Lei et al 2010    | 0.33       | 0.06          | 0.32                   | 15       | 0.67      | 0.01 [-0.04, 0.06] |
| Subtotal (95% CI) | 160         |               |                        |          |           |       |
| Heterogeneity: Tau² = 0.00; Chi² = 1.84, df = 5 (P = 0.87); I² = 0% |
| Test for overall effect: Z = 1.03 (P = 0.30) |

Table 2  Methodology quality of the included RCTs

| Study or Subgroup | Jadad score | Randomisation | Allocation concealment | Blinding | Attrition | Score |
|-------------------|-------------|---------------|------------------------|----------|-----------|-------|
| 1.2 S100B (post-CPB) |            |               |                        |          |           |       |
| Jannings et al 2010 | 0.43       | 0.21          | 1.42                  | 15       | 0.49      | -0.07 [-0.12, -0.04] |
| Singh et al 2011  | 0.9        | 1.68          | 0.68                  | 60       | 0.68      | -0.16 [-0.44, 0.12] |
| Shudong 2015      | 0.79       | 0.111         | 0.141                 | 30       | 0.129     | -0.17 [-0.23, -0.11] |
| Lei et al 2010    | 0.99       | 0.22          | 0.82                  | 15       | 0.58      | 0.17 [0.02, 0.32] |
| Jannings et al 2009 | 3.23       | 0.78          | 2.78                  | 15       | 2.33      | 0.45 [0.06, 0.86] |
| Subtotal (95% CI) | 160         |               |                        |          |           |       |
| Heterogeneity: Tau² = 0.22; Chi² = 116.86, df = 5 (P = 0.00001); I² = 96% |
| Test for overall effect: Z = 1.99 (P = 0.05) |

Table 2  Methodology quality of the included RCTs

| Study or Subgroup | Jadad score | Randomisation | Allocation concealment | Blinding | Attrition | Score |
|-------------------|-------------|---------------|------------------------|----------|-----------|-------|
| 1.3 S100B (24th postoperatively) |            |               |                        |          |           |       |
| Singh et al 2011  | 0.48       | 1.28          | 1.71                  | 60       | 1.9       | -2.13 [-1.81, -0.65] |
| Jannings et al 2010 | 1.44       | 0.13          | 2.32                  | 15       | 0.15      | -0.07 [-0.94, 0.80] |
| Shudong 2015      | 0.333      | 0.028         | 0.592                 | 30       | 0.037     | -0.26 [-0.28, -0.24] |
| Jannings et al 2010 | 0.14       | 0.16          | 0.21                  | 15       | 0.13      | -0.07 [-0.17, 0.03] |
| Shudong 2009      | 0.49       | 0.13          | 0.45                  | 15       | 0.15      | 0.04 [-0.06, 0.14] |
| Jannings et al 2010 | 0.53       | 0.09          | 0.45                  | 15       | 0.11      | 0.08 [0.01, 0.15] |
| Subtotal (95% CI) | 160         |               |                        |          |           |       |
| Heterogeneity: Tau² = 0.10; Chi² = 429.90, df = 5 (P = 0.00001); I² = 99% |
| Test for overall effect: Z = 2.31 (P = 0.02) |

Table 2  Methodology quality of the included RCTs

| Study or Subgroup | Jadad score | Randomisation | Allocation concealment | Blinding | Attrition | Score |
|-------------------|-------------|---------------|------------------------|----------|-----------|-------|
| Total (95% CI)    | 480         | 483           | 100.0%                 | -0.20 [-0.29, -0.11] |
| Heterogeneity: Tau² = 0.04; Chi² = 1545.21, df = 17 (P = 0.0001); I² = 99% |
| Test for overall effect: Z = 4.00 (P < 0.0001) |
| Test for subgroups: Chi² = 95.0, df = 2 (P = 0.000); I² = 79.0% |

Figure 2  Forest plot showing the meta-analysis outcomes of the difference in S100B levels of inhalation anaesthesia and TIVA groups. TIVA, total intravenous anaesthesia.
Figure 3  Forest plot showing the meta-analysis outcomes of the difference in MMSE scores of inhalation anaesthesia and TIVA groups. MMSE, mini-mental state examination; TIVA, total intravenous anaesthesia.

Eligibility criteria
Inclusion criteria
Original articles in which all patients undergoing cardiac surgery with CPB were randomly allocated to receive the inhalation anaesthesia or TIVA. Patients underwent cardiac surgery with no restriction on dose and the administration time of anaesthetics.

Exclusion criteria
Case reports, review articles, duplicate publications and studies without outcome data were excluded. Studies involving patients with cerebrovascular disease, central nervous system disorders, use of psychotropic drugs or a history of alcohol or substance abuse were also excluded.

Outcomes
In the included studies, S100B levels in serum were detected before CPB (pre-CPB), after CPB (post-CPB) and 24 hours postoperatively. The primary outcomes were protein S100B levels in serum post-CPB and 24 hours postoperatively. The secondary outcomes included mini-mental state examination (MMSE) scores assessed preoperatively and 24 hours postoperatively, the jugular bulb venous oxygen saturation (SjvO₂), arteriovenous oxygen content difference (D(a-v)O₂) and cerebral oxygen extraction ratio (O₂ER) were tested at cooling and rewarming during CPB.

Study selection and validity assessment
Study selection was completed by two independent reviewers by screening abstracts and titles of all included papers from the literature search. All the relevant papers were retrieved according to the inclusion criteria. Then based on the abstracts and titles, the second screening of full texts was performed to check if there was an ambiguous decision. Only randomised controlled trials were included in the analysis. Disagreements were resolved through consensus or by a third reviewer. According to the primary criteria for randomised and controlled trials, quality assessment was performed by two reviewers.

Data extraction and statistical analysis
Three reviewers extracted all data recorded as authors, publication year, number of cases, mean age of participants, anaesthetics, study setting and outcomes. Disagreements between reviewers were resolved by consensus. In the study, meta-analysis was performed using Review Manager (RevMan) software (V.5.2, Nordic Cochrane Centre, Cochrane Collaboration, 2012, Copenhagen, Denmark) by two reviewers.
Figure 5  Forest plot showing the meta-analysis outcomes of the difference in SjvO₂ of inhalation anaesthesia and TIVA groups. SjvO₂, jugular bulb venous oxygen saturation, TIVA, total intravenous anaesthesia.

Table 3  Egger test of publication bias

| Std_Eff | Coefficient | SE  | t     | p>|t| (95% CI)                  |
|---------|-------------|-----|-------|----------------------------|
| bias(S100B) | -2.67       | 2.35 | -1.14 | 0.27 | (-7.65 to 2.32)            |
| bias(MMSE)  | 2.89        | 5.30 | 0.54  | 0.61 | (-10.08 to 15.85)          |
| bias(D(a-v)O₂) | 186.01   | 99.93 | 1.86  | 0.14 | (-91.44 to 463.46)         |
| bias(O₂ER%)  | 13.87       | 6.58 | 2.12  | 0.12 | (5.59 to 42.14)            |
| bias(SjvO₂%) | 2.12        | 19.48 | 0.11  | 0.92 | (-45.56 to 49.79)          |

D(a-v)O₂, arteriovenous oxygen content difference; MMSE, mini-mental state examination; O₂ER, cerebral oxygen extraction; SjvO₂, jugular bulb venous oxygen saturation.

The weighted mean differences (WMD) of outcomes in randomised controlled trials (RCTs) and their 95% CI were presented. Heterogeneity across studies was tested by the p value and the I² statistic, which is a quantitative measure of inconsistency. A random-effects model was used to analyse the summary estimate when the p value was <0.1 or the I² value was >50%. Otherwise, a fixed-effects model was applied. In the meta-analysis, potential publication bias was detected by Egger test. Publication bias was assumed existed if the p<0.05.

RESULTS

Characteristics of the included studies

A total of 1485 studies were retrieved. Of these, 1148 remained after duplicate articles were eliminated. After screening titles and abstracts, 445 studies were potentially eligible. Based on the exclusion criteria, 13 studies were ultimately selected (figure 1). All reviewers agreed to include all 13 papers. Although all of these RCTs were considered to have a low risk of bias, nine studies included no details on the method of
random sequence generation and allocation. Only one study provided the details about the blinding of the data collection.  

‘Inhalation anaesthesia’ was defined as a group receiving a volatile agent like isoflurane, sevoflurane or desflurane. In the included studies, patients in the ‘volatile anaesthesia’ group had not received propofol, thiopental or ketamine during the surgery and CPB. The patients in the ‘TIVA’ group had received only intravenous anaesthetics, but not volatile agents. These studies involved 549 patients, including 272 patients with inhalation anaesthesia and 277 patients with TIVA (table 1). Patients’ age ranges in ‘inhalation anaesthesia’ and ‘TIVA’ groups were 44–75 years and 43–74 years, respectively. The mean age of patients was unavailable for three studies. All the articles had reported exclusion/inclusion criteria. Of these, seven studies had used isoflurane versus TIVA, four studies

Figure 7  The plot of sensitivity analysis of S100B levels.

Figure 8  The plot of sensitivity analysis of MMSE scores. MMSE, mini-mental state examination.
had used sevoflurane versus TIVA and two studies had used desflurane versus TIVA in patients.

**Methodology quality of the included trials**

Methodology quality of the included studies was assessed using a modified Jadad scale. A score of 4–7 indicated a high-quality study, and a score of 1–3 indicated a low-quality study. Of the 13 included studies, 10 received scores of 1–3 and 3 received scores of 4–7 (table 2).

**Meta-analysis**

Summary estimate for S100B levels post-CPB and 24 hours postoperatively was analysed in a random-effects model because of the heterogeneity (I²=96% and I²=99%, respectively). Based on six studies from 230 patients, S100B levels assessed at the end of CPB and 24 hours postoperatively in the inhalation anaesthesia group were significantly lower than those in the TIVA group (WMD (95% CI): −0.41 (−0.81 to −0.01), −0.32 (−0.59 to −0.05), respectively, figure 2). Based on three studies from 110 patients, postoperative MMSE scores of the inhalation anaesthesia group were significantly higher than those of the TIVA group (WMD (95% CI): 1.87 (0.82 to 2.92)), figure 3). A significant heterogeneity was detected (I²=77%), and thus summary estimate was analysed in a random-effects model.

There was no significant difference in D(a-v)O₂, O₂ER and SjvO₂ assessed at cooling and rewarming during CPB between the inhalation anaesthesia group and the TIVA group (figures 4–6).

Egger’s regression test of S100B levels, MMSE scores, D(a-v)O₂, O₂ER and SjvO₂ indicated little evidence of publication bias, respectively (table 3).

Sensitivity analysis for the current meta-analysis was also performed. We omitted one study in each turn, and calculated the combined WMD for the remaining studies. The results showed that no single study significantly changed the combined results in the overall meta-analysis, indicating that the results were reliable and statistically stable (figures 7 and 8).

**DISCUSSION**

In our study, 13 published articles were included to determine the difference in the extent of cerebral protection provided by inhalation anaesthesia and TIVA during cardiac surgery with CPB. Eight out of the 13 studies suggested that inhalation anaesthesia might be superior to TIVA in terms of their cerebroprotective effect after CPB. However, the results reported in other five studies were the opposite. These results underline the existing debate on which anaesthetic approach is better for the patients. However, in the current systematic review and meta-analysis, the results of primary and secondary outcomes showed that inhalation anaesthesia might be superior to TIVA during cardiac surgery with CPB.
neuroprotection that induced by anaesthetic can be long lasting, all these effects can be expanded well beyond the immediate perioperative period. Additionally, a recent meta-analysis found that in cardiac surgery, as compared with TIVA, inhalation anaesthesia was associated with major benefits in outcome, including reduced mortality, as well as a lower incidence of pulmonary and other complications. Therefore, based on previous findings and the current meta-analysis, it is speculated that inhalation anaesthesia has the potential to serve as a preferential anaesthesia strategy for cardiac patients.

Our study has few limitations. First, the sample size of the included studies was relatively small and the total number of cases is very limited. Second, there was heterogeneity in some of our results. As trials were based in different countries and hospitals, we were unable to avoid the effects of race, age, gender and underlying disease(s) of patients in our study. Therefore, findings of the current study were limited by the overall low quality of evidence and the lack of robust data. Third, our study focused on the overall comparison between inhalation anaesthesia and TIVA, and different inhalation (isoflurane, desflurane or sevoflurane) and intravenous (sodium thiopental, propofol and so on) anaesthetics were investigated in the included studies. Because of the limited number of reported clinical trials, limited outcome data could be considered for subgroup analysis. Therefore, further studies with larger sample sizes are needed to demonstrate which anaesthetics are more beneficial for cardiac patients.

In summary, the results of this meta-analysis indicate that the cerebroprotective effect of inhalation anaesthesia is better than that of TIVA in patients undergoing cardiac surgery with CPB. Further high-quality trials with larger sample sizes are warranted to investigate the effect of anaesthetics on cerebral protection.

Contributors FC, HL and ZZ: conceived and designed the experiments. FC, GD, ZW and ZZ: performed the experiments. FC, GD and ZW: analysed the data. ZZ and HL: contributed reagents/materials/analysis tools. FC, GD, ZW, ZZ: wrote the paper. All authors: reviewed the manuscript.

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