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Comparison of cerebral protection between inhalation anesthesia and total intravenous anesthesia in 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 anesthesia and total intravenous anesthesia(TIVA) may produce different cerebral protection for these patients. Therefore, a systematic literature review and meta-analysis compared the neuroprotective effects between inhalation anesthesia and TIVA.

Design: Searching in PubMed, EMBASE, Science Direct/Elsevier, CNKI and the Cochrane Library up to August 2016, we selected the related randomized controlled trials for this meta-analysis.

Result(s): A total of 1485 studies were identified, without duplicate, the articles remained 1148. After screening titles and abstracts, about 445 studies were potentially eligible. Depend on exclusion criteria(full-text

reporting was abstract, review article, no control case, lack of outcome data, ect.), 13 studies were ultimately selected according to eligibility criteria. Our results illustrated that S100B levels at CPB and postoperative 24hour in inhalation anesthesia group were significantly lower than those in TIVA group[WMD (95% CI):-0.43 (-0.83, -0.03), -0.32 (-0.59, -0.05),respectively]. The CBF and MMSE scores of inhalation anesthesia group were significantly higher than that of TIVA group [WMD (95% CI) 5.11 (2.58, 7.63), 1.26 (0.04, 2.47), respectively. However no significant difference was found in cerebral metabolic rate of $CMRO_2$, $SjvO_2$%, $C(a\text{-}v)O_2$, O_2ER% and CPB time.

Conclusion(s): The current study demonstrates that anesthesia with volatile agents appears to provide better cerebral protection for patients undergoing cardiac surgery with CPB when compared to TIVA, suggesting that inhalation anesthesia may be more suitable for patients undergoing cardiac surgery.

Key words: anesthesia; cerebral protection; cardiac surgery; cardiopulmonary bypass

Strengths and limitations of this study

1. The literature searches of our article were including six databases. Literature retrieval was comprehensive.

2. The inclusion criteria and exclusion criteria we formulate was strict.

3. This is the first systematic review and meta-analysis to compare the

neuroprotective effects between inhalation anesthesia and TIVA in cardiac surgery with cardiopulmonary bypass.

4. Neurological dysfunction remains a devastating postoperative complication after cardiopulmonary bypass, making sure which anesthetics could reduce this complication may have important significant.

5. The inherent limitations of the studies included in this analysis are the different volatile agents(sevoflurane, isoflurane, desflurane) and different intravenous anesthetics (sodium thiopental, propofol, etc.). Because of the shortage number of reported clinical trials, limited outcome data could be considered for subgroup analysis.

Introduction

Cardiopulmonary bypass (CPB) is necessary and commonly used to support the patient's circulation during cardiac surgery, but CPB can significantly increase the patients' morbidity of some postoperative complications and mortality.[1]Among these postoperative complications neurological dysfunction remains a devastating complication, and also it is one of the major causes of mortality for patients undergoing cardiac surgery[2, 3].Several factors including cerebral anoxia, embolism, excessive excitatory neurotransmitter release and systemic inflammatory response have been demonstrated to may contribute to postoperative

neurological dysfunction[4].However, at present it is lack of definitive clinical evidence to provide cerebral protection for patients undergoing cardiac surgery with CPB [5].

Early animal data supported that anesthetics can produce cerebral protection [6-8]. And many recent studies have found that anesthetic agents of general anesthesia may be neuroprotective and can produce cerebral protection for surgery patients[9, 10].However, at present the clinical studies showed that the effects of inhalation anesthesia or TIVA on neuroprotection in cardiac surgery with CPB remain controversial and much debated [11-13]. Therefore, it was unknown that which one is better in providing cerebral protection effect for patients undergoing cardiac surgery with CPB. As we know, inhalation anesthesia and TIVA are most commonly used strategy for general anesthesia, thus it is important to clarify this issue. In addition, because of the difficulty of patient inclusion and neurological dysfunction study for cardiac surgery with CPB, the sample size of these previous studies was generally small. Based on these reasons, it is necessary to systematically reviewed the available literature and performed a meta-analysis to compare the neuroprotective effects of inhalation anesthesia and TIVA.

Materials and Methods

The current systematic review and meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines (PRISMA) for the intervention trials[14].

Literature search

This meta-analysis was restricted to published studies that investigated the cerebral protection of anesthetics inpatients with CPB. Two independent reviewers (ZW and GD) searched PubMed, EMBASE, Science Direct/Elsevier, MEDLINE, CNKI and the Cochrane Library from inception to August 2016, without restrictions on language or study type. The search terms combined text words and MeSH terms. For example, the search terms for CPB were: 'Cardiopulmonary Bypass', 'Bypass Cardiopulmonary', 'Bypasses Cardiopulmonary', 'Cardiopulmonary Bypasses', 'Heart-Lung Bypass', 'Bypass Heart-Lung', 'Bypasses Heart-Lung', 'Heart Lung Bypass', 'Heart-Lung Bypasses'. TIVA were : 'propofol', 'disoprofol', 'etomidate' 'midazolam', 'sodium pentothal', 'thiopental', 'ketamine', while those for inhalation anesthesia were 'halothane', 'sevoflurane', 'isoflurane', 'desflurane', 'enflurane', 'methoxyflurane'.All related articles and abstracts were retrieved. In addition, references cited within relevant reviews were retrieved by hand and only full articles were searched in this case.

Eligibility criteria

Inclusion criteria: All patients undergoing cardiac surgery with CPB were randomly allocated to inhalation anesthesia group and TIVA group. Patients undergoing cardiac surgery with no restriction in dose and time of anesthetic administration. Outcomes includedS100B protein levels, mini-mental state examination(MMSE) scores, cerebral blood flow(CBF), cerebral metabolic rate of oxygen consumption($CMRO_2$), jugular bulb oxygen saturation($SjvO_2$%), arteriovenous oxygen content difference($C(a\text{-}v)O_2$), cerebral oxygen extraction(O_2ER%) and cardiopulmonary bypass(CPB) time.

Exclusion criteria: Studies were excluded if they were case reports, review articles, duplicate publications, or lack of outcome data. Studies involving patients with cerebrovascular disease, central nervous system disorders, psychotropic drugs, a history of alcohol or substance abuse were also excluded.

Study selection and validity assessment

Two independent reviewers (ZW and GD) screened titles and abstracts of all papers from the literature search. All relevant studies that appeared to meet inclusion criteria were retrieved. Full texts were obtained to analyze if an ambiguous decision was made based on the title and abstract. Eligible studies must be randomized controlled trial. Disagreements were resolved by consensus or a third reviewer (FC). Two

reviewers (FC and ZZ) completed the quality assessment according to the primary criteria for randomized controlled trial studies

Data extraction and statistical analysis

Data, including authors, year of publication, number and mean age of participants, setting, anestheticsand outcomes were extracted from the studies by three reviewers (ZW, GD and ZZ)**.** Disagreements were resolved by consensus. Quantitative meta-analysis was performed by two reviewers (FC and HL) with Review Manager (RevMan) software (version 5.2, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012, Copenhagen).

The weight mean differences (WMD) of outcomes in the randomized controlled trial studies and its 95% confidence intervals (95% CI) were presented. Heterogeneity was assessed by the P-value and the I-square statistic (I^2) in the pooled analyses, which represents the percentage of total variation across studies[15].If the P-value was less than 0.1 or the I^2-value was greater than 50%, the summary estimate was analyzed in a random-effects model. Otherwise, a fixed-effects model was applied. In addition, publication bias was detected by Egger's test in the meta-analysis. If the P-value was less than 0.05, publication bias existed.

Results

Characteristics of the included studies

A total of 1485studies were identified, without duplicate, the articles

remained 1148.After screening titles and abstracts, about 445 studies were potentially eligible. Depend on exclusion criteria(full-text reporting was abstract, review article, no control case, lack of outcome data, ect.), 13studies were ultimately selected according to eligibility criteria**(Figure 1).**After a group discussion, all reviewers agreed to include all of the 13papers. Although all of these randomized controlled trials (RCTs) were regarded to have low risk of bias, 9 studies had no details on the method about random sequence generation and allocation[16-24]. And only one study provided the details about the blinding of the data collection.[25]

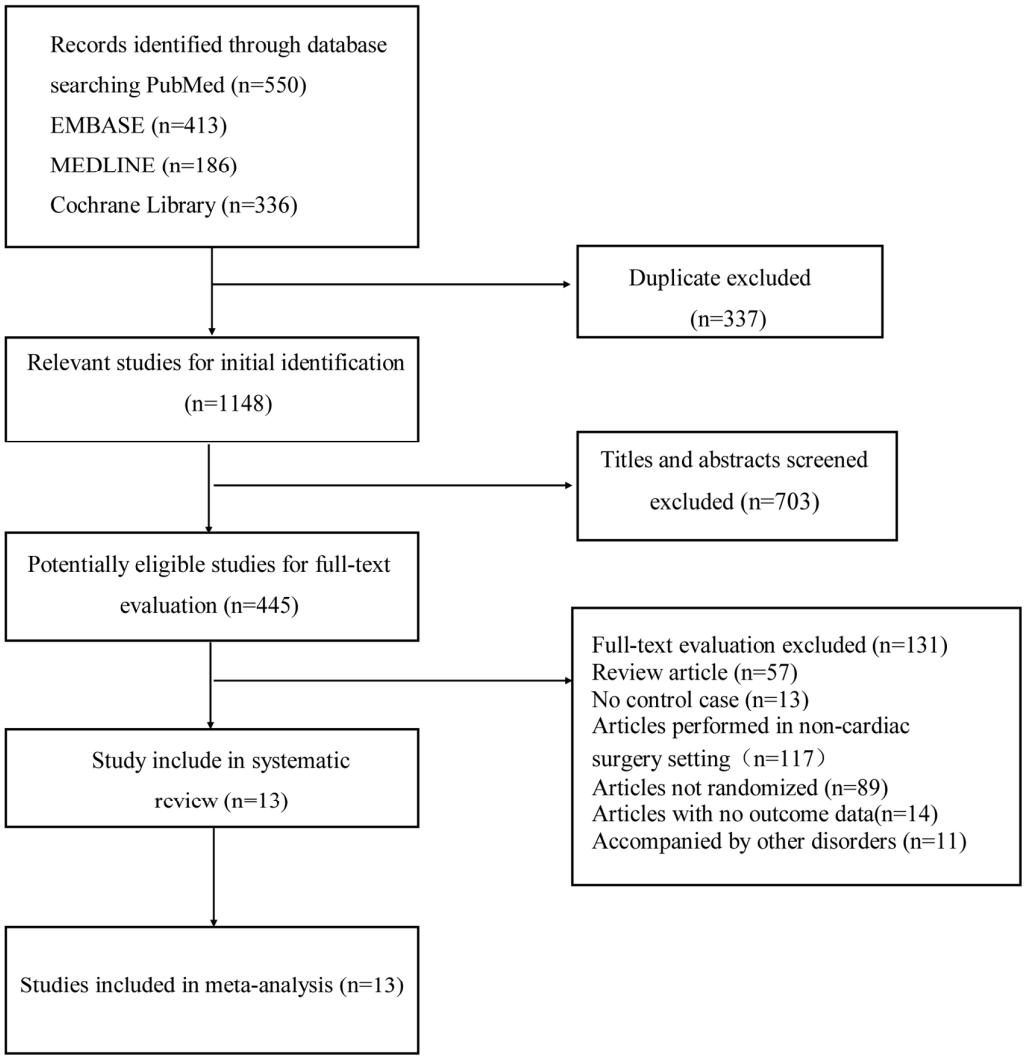

Figure1. Flow diagram of selection of eligible studies

'Inhalation anesthesia' was defined as a group receiving a volatile agent of isoflurane, sevoflurane or desflurane. And 'Total Intravenous Anaesthesia' was defined as TIVA group that not receiving volatile agents but only intravenous anesthetics. These studies involved a total of 549 patients, including 272 patients with inhalation anesthesia and 277patients with TIVA(**Table 1**). Patients' age range in the inhalation anesthesia and TIVA groups were 44 to 75 years and 43 to 74 years, respectively. The mean age of patients was unavailable for three

studies[16-18].All of the articles reported exclusion/inclusion criteria[16-28]. Of these, seven studies were isoflurane *vs.* TIVA[16, 18-20, 22, 23, 26],four studies were sevoflurane *vs.* TIVA[17, 21, 24, 25], two studies were desflurane *vs.* TIVA[27, 28].

Study	Mean age(inhalation/TIVA)	Setting	Case	Volatile agents	Comparator	Outcomes
Min Jiang .2007	36-62	CPB-Cardiac surgery	15/15	Isoflurane	Propofol	SjvO2%, CBP time
Huaping Yuan .2015	40-65	CPB-Cardiac valve replacement	15/15	Sevoflurane	Propofol	S100B,MMSE
Lei Li 2010	60-70	CPB-CABG	15/15	Isoflurane	Propofol	S100B,MMSE
Mark F. 1997	56±12/61±14	CPB-Cardiac valve replacement	16/15	Isoflurane	Thiopental	CBF,CMRO2,D(a-v)O2,O2ER%,SjvO2%,CBP time
Thomas E1987	55.5±9.9/63.1±6.5	CPB-CABG	16/21	Isoflurane	Thiopental	CBF,CMRO2,CPP,CBP time
Gigdem Y.2014	57.37±9.8/57.33±7.2	CPB-Cardiac surgery	10/10	Sevoflurane	Midazolam	SRO2,SPO2,HTC,CBP time
Meral kanbak .2004	56±7.6/54.5±5.9	CPB-CABG	20/20	Isoflurane	Propofol	S100B,MMSE,CBP time
Elif Dogan.2013	64.57±10.84/66.45±13.04	CPB-CABG	60/61	Desflurane	Propofol	S100B,CBP time
Sarvesh pal .2011	60.10±7.9/59.54±8.83	CPB-CABG	15/15	Sevoflurane	Midazolam	S100B,CBP time
Tingting Chen .2007	52±5/48±7	CPB-Cardiac valve replacement	20/20	Isoflurane	Propofol	S100B,D(a-v)O2,O2ER%,SjvO2%,CBP time
Jianrong Guo .2009	44±8/43±7	CPB-Cardiac valve replacement	30/30	Isoflurane	Propofol	S100B,D(a-v)O2,O2ER%,SjvO2%,CBP time
Shudong Ma .2015	49.5±2.6/49.1±2.4	CPB-Cardiac valve replacement	15/15	Sevoflurane	Propofol	S100B,MMSE
Jiying Zhong .2010	75±5/74±4	CPB-CABG	25/25	Desflurane	Ketamine	S100B,MMSE

Table 1. Study characteristics of include studies

Meta-analysis

Data of S100B levels, MMSE scores,$CMRO_2$,D(a-j)O_2,O_2ER%,and $SjvO_2$% were analyzed in a random-effects model and CBF was analyzed in a fixed-effects model.S100B levels at CPB and postoperative 24hour in inhalation anesthesia group were significantly lower than those in TIVA group[WMD (95% CI):-0.43 (-0.83, -0.03), -0.32 (-0.59, -0.05),respectively, **Figure 2**]. The CBF and MMSE scores of inhalation anesthesia group were significantly higher than that of TIVA group [WMD (95% CI) 5.11 (2.58, 7.63), 1.26 (0.04, 2.47), respectively (**Figure3 and 4**).

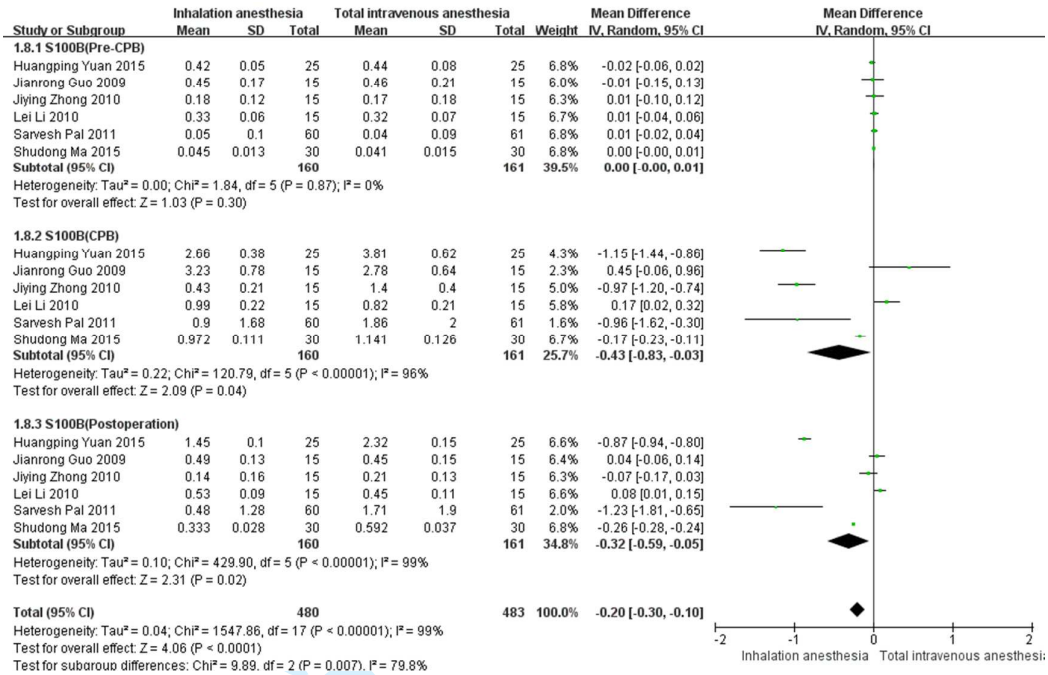

Figure 2. Forest plot showing the meta-analysis outcomes of the S100B between

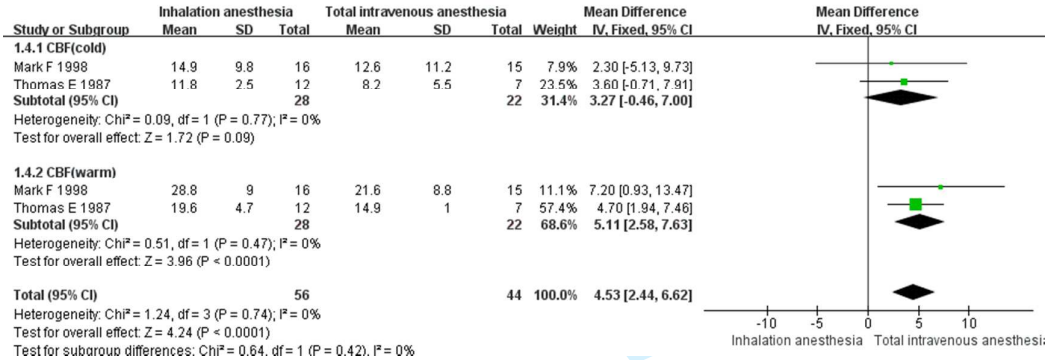

Figure 3. Forest plot showing the meta-analysis outcomes of the CBF between inhalation anesthesia and TIVA group.

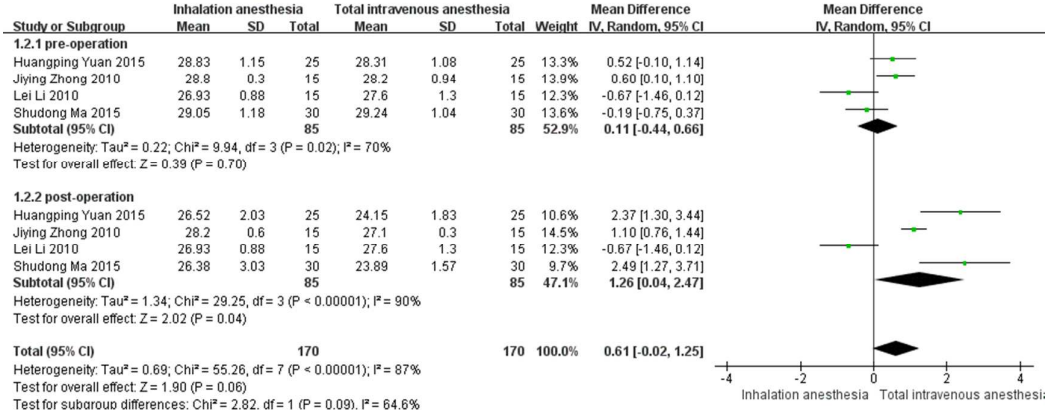

Figure 4. Forest plot showing the meta-analysis outcomes of the MMSE score between inhalation anesthesia and TIVA group.

There was no significant difference in CMRO2, D(a-j)O2, O2ER%, and SjvO2% during operation between inhalation anesthesia group and TIVA group (**Figure5,6,7,8**).

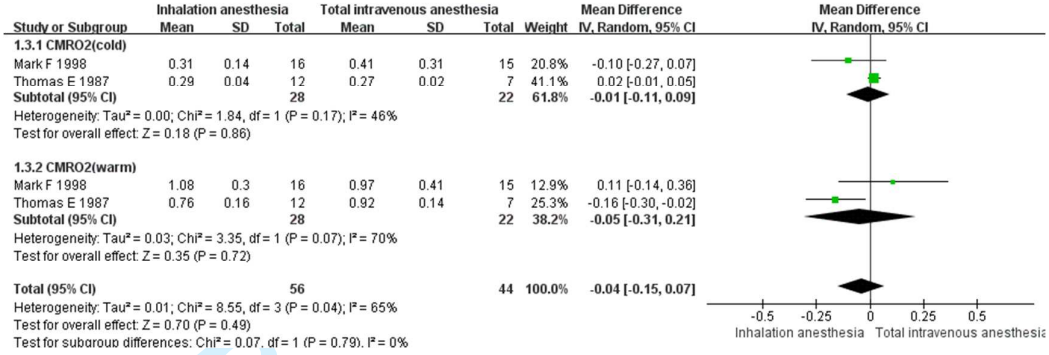

Figure 5. Forest plot showing the meta-analysis outcomes of the $CMRO_2$ between inhalation anesthesia and TIVA group.

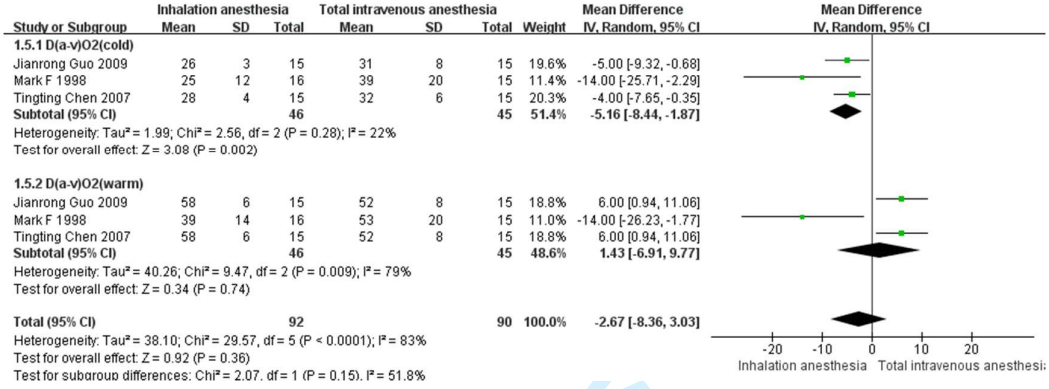

Figure 6. Forest plot showing the meta-analysis outcomes of the D(a-v)O_2between inhalation anesthesia and TIVA group.

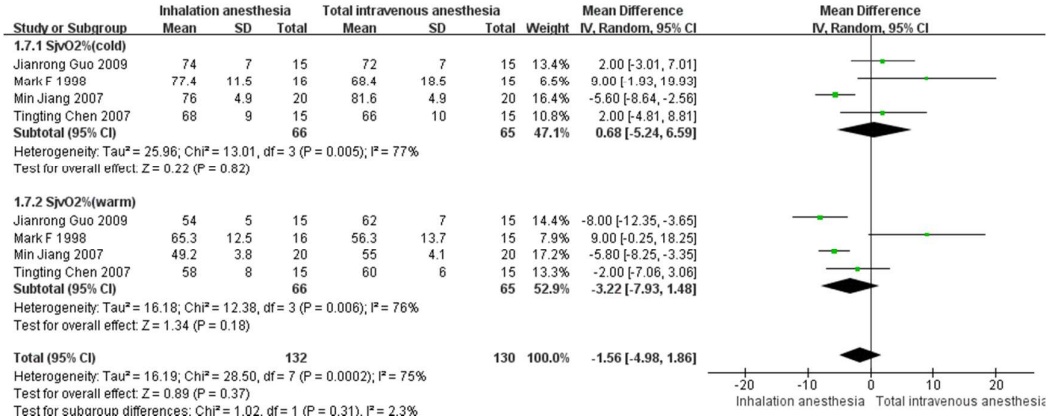

Figure 7. Forest plot showing the meta-analysis outcomes of the $SjvO_2$%between inhalation anesthesia and TIVA group.

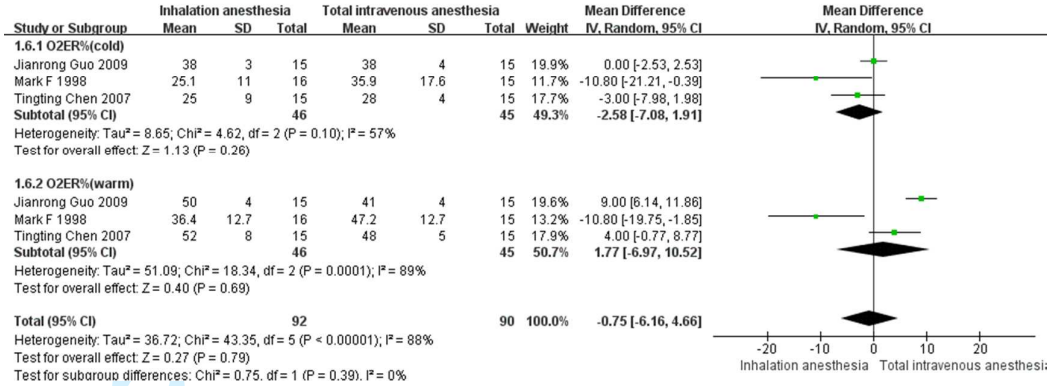

Figure 8. Forest plot showing the meta-analysis outcomes of the O_2ER%between inhalation anesthesia and TIVA group.

Egger's regression test of S100B levels, MMSE scores, CMRO2, D(a-j)O2, O2ER%, and SjvO2% indicated little evidence of publication bias, respectively (**Table2**).

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
bias(S100B)	-2.67	2.35	-1.14	0.27	[-7.65	2.32]
bias(MMSE)	2.89	5.30	0.54	0.61	[-10.08	15.85]
bias(CMRO2)	-1.85	6.10	-0.30	0.79	[-28.16	24.41]
bias(D(a-j)O2)	186.01	99.93	1.86	0.14	[-91.44	463.46]
bias(O2ER%)	13.87	6.58	3.63	0.12	[5.59	42.14]
bias(SjvO2%)	2.12	19.48	0.11	0.92	[-45.56	49.79]

Table2. The Egger's test of Publication bias

We also conduct sensitivity analysis of the meta-analysis. We omitted one study sequentially, and the calculated combined WMD for the remaining studies yielded consistent results. In the overall meta-analysis, no single study significantly changed the combined results, which indicated that the results were statistically stable and reliable (**Figure9,10**).

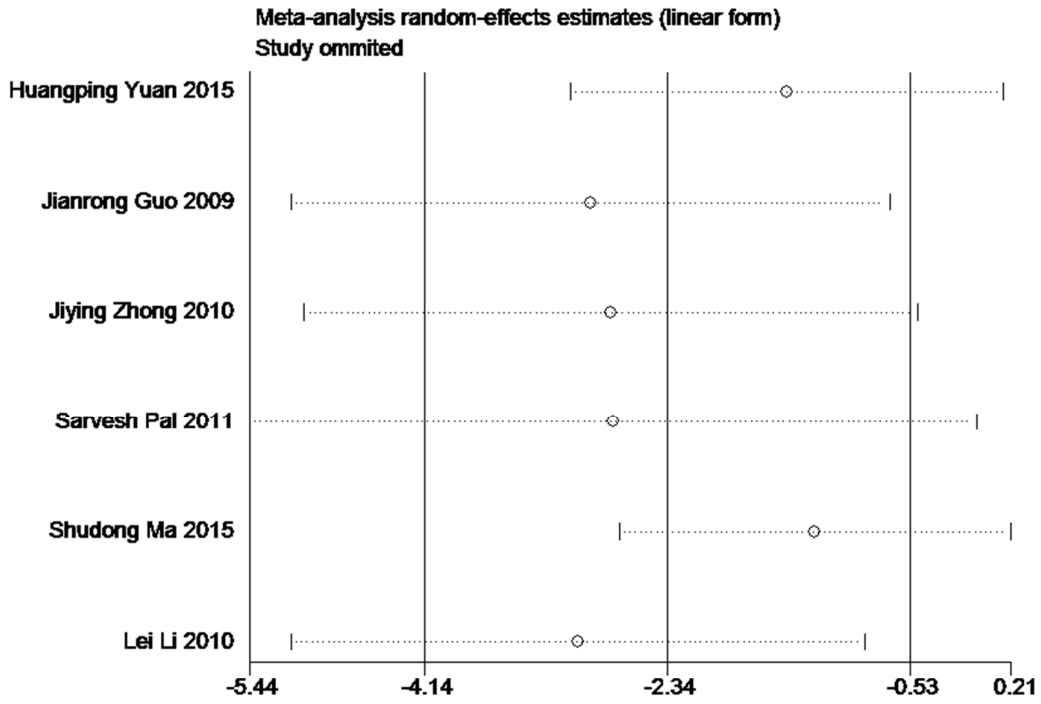

Figure 9. The plot of sensitivity analysis of S100B.

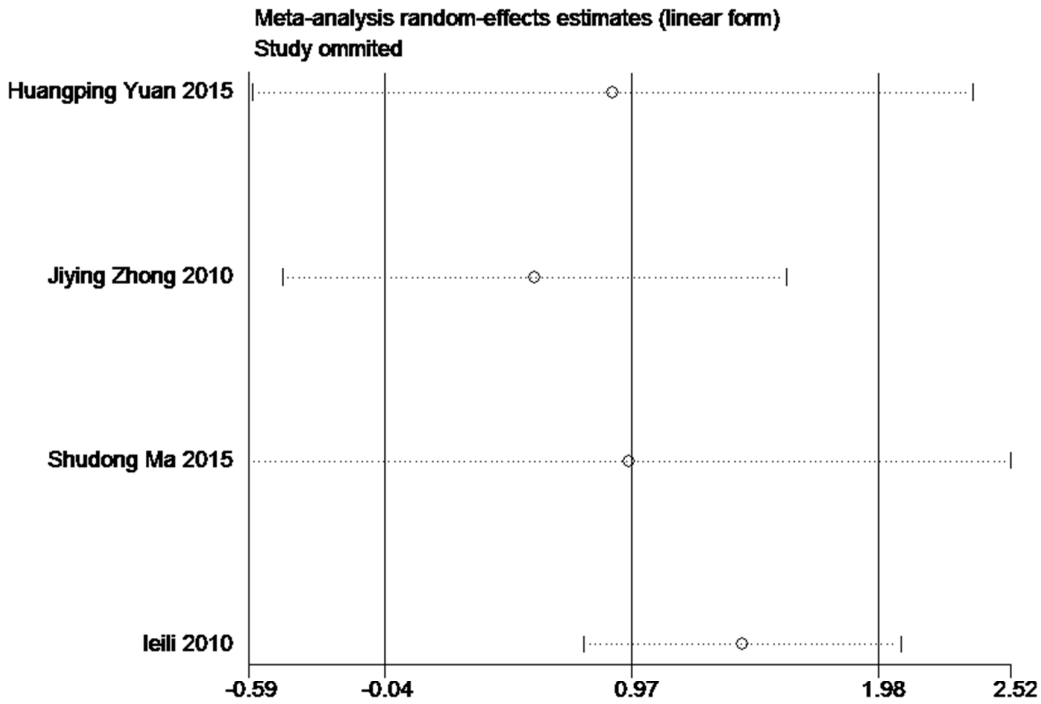

Figure 10. The plot of sensitivity analysis of MMSE score.

Discussion

In our study, thirteen published articles studied the difference of cerebral protection for patients between inhalation anesthesia and TIVA in cardiac surgery with CPB. Eight out of the thirteen papers noted that inhalation anesthesia may be superior to TIVA on cerebral protection after CPB[17, 19-21, 24-26, 28]. However, the other five studies reported opposite results[16, 18, 22, 23, 27]. These results underline the existing debate about which anesthetic approach was better for patients. However, in the current systematic review and meta-analysis, both of the results of primary and secondary outcome showed that inhalation anesthesia may be superior to TIVA in cardiac surgery with CPB.

S100B mainly expressed in the astrocytes, and blood S100B level was commonly used as an outcome parameter for evaluation the postoperative neurological dysfunction[29]. Its increase in the blood has been shown in patients after ischemic stroke and brain trauma[30]. Serum S100Bhas also been detected after adult cardiac operations complicated with neurological injury, thus it has the potential to serve as an early marker of brain damage [31, 32].In this meta-analysis, the serum level of S100B after CPB in inhalation anesthesia group was significantly lower than that in TIVA group($P<0.05$)[17, 24-26, 28], suggesting that inhalation anesthetics provide better cerebral protection against patients' brain damage compared to TIVA. Furthermore, our results also show that

postoperative MMSE score of patients in inhalation anesthesia group was significantly higher than that of TIVA group($P<0.05$)[17, 24, 28].As we know, although MMSE is relative simple, it is one of the most commonly used methods for clinical evaluation of cognitive function. These results suggest that compared to TIVA, inhalation anesthesia may maintain better postoperative cognitive function for patients undergoing cardiac surgery with CPB.

For the secondary outcomes, the meta-analysis showed that several outcomes, such as $D(a\text{-}j)O_2$, $O_2ER\%$, $SjvO_2\%$, were not significantly different between TIVA and inhalation anesthesia groups. However, we found that in many studies cerebral metabolic rate of oxygen inpatients receiving inhalation anesthetics was consistently lower than that in patients receiving TIVA. Also, the intraoperative CBF in inhalation anesthesia group was significantly higher than that in TIVA group($P<0.05$)[19, 20]. As we know, the lower ratio of global cerebral oxygen and adequate cerebral blood supply is an important mechanism for interpreting the cerebral protection[33].The neuroprotection effects may be mediated by favourable expression of some protective and anti-protective proteins, to inhibit extracellular excitatory neurotransmitter accumulation and systemic inflammatory response. Thus, the results of $CMRO_2$and CBF can strengthen the finding that the inhalation anesthesia may provide better neuroprotection than TIVA.

Because a series of neurological complications after cardiac surgery with CPB, various techniques of neurologic protection including deep hypothermic cardiopulmonary bypass[34], embolic filtering device[35],monitoring equipment (transcranial doppler and near-infrared spectroscopy)[36]and pharmacological therapy have been developed. Meanwhile, increased attention was paid to anesthetics in neurologic protection. Both of inhalation anesthesia and TIVA are reported having cerebral protection for patients undergoing cardiac surgery with CPB[37-39].However, it is still unclear which type of anesthesia can provide better cerebral protection for the patients. Based on this meta-analysis, the results strongly supports that inhalation anesthesia may be superior to TIVA in cerebral protection.

Experimental data suggest that direct positive effects of volatile anesthetics may be caused by various application methods including pre-conditioning and post-conditioning mechanisms[40, 41], which attenuate apoptosis and necrosis of cerebral neuron, and reduce neurological dysfunction after ischaemia. Moreover, the contribution of inhalation agents to preserving satisfactory haemodynamics may ensure adequate perfusion and oxygenation of other organ systems[42-45] and improve the chances for recovery and survival after surgery. All these effects can be expanded well beyond the immediate perioperative periodon account of anesthetics-induced neuroprotection that can be long

lasting[46, 47].Additionally, a recent meta-analysis found that in cardiac surgery, when compared to TIVA, inhalation anesthesia was associated with major benefits in outcome, including reduced mortality, as well as lower incidence of pulmonary and other complications. Therefore, based on the previous findings and the current meta-analysis, it is speculated that inhalation anesthesia have the potential to serve as a preferential anesthesia strategy for patients.

Several limitations should be considered in our study. Firstly, the sample size of the included studies was relatively small and the total number of cases is very limited. Secondly, there was heterogeneity in some of our results. Because of the included trials based on different countries and hospitals, it was unable to avoid the effects of race, age, gender and underlying disease of patients in these studies. Therefore, the findings of the current study were limited by the overall low quality of evidence and lack of robustness in higher-quality trials. Thirdly, the current study focused on the overall comparison between inhalation anesthesia and TIVA, and in the included studies different inhalation anesthetics (isoflurane, desflurane, or sevoflurane) and intravenous anesthetics (sodium thiopental, propofol, etc.) were studied. And because of the shortage 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 anesthetics is the

more beneficial for patients.

In summary, the results of this meta-analysis indicate that inhalation anesthesia produce better cerebral protection for patients undergoing cardiac surgery with CPB when compared to TIVA. And further higher-quality trials with large sample size to investigate the effect of anesthetics on cerebral protection are warranted in the future.

Authors' contributions

Conceived and designed the experiments: F.C, H.L, Z.Z. Performed the experiments: F.C, G.D, Z.W, Z.Z. Analyzed the data: F.C, G.D, Z.W. Contributed reagents/materials/analysis tools: Z.Z, H.L. Wrote the paper: F.C, G.D, H.L, Z.Z. All authors reviewed the manuscript.

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Competing interests The authors declare no conflict of interest.

Data sharing statement No additional data are available.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

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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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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 (CNKI), and Cochrane Library up to August 2016, we selected related randomized controlled trials for this

meta-analysis.

Result(s): 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, etc.), 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 at the end of CPB and 24 hours postoperatively (weighted mean difference [WMD]; 95% confidence interval [CI]: -0.41 [-0.81, -0.01], -0.32 [-0.59, -0.05], respectively). Among secondary outcome variables, mini-mental state examination (MMSE) 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, 2.92)], cerebral blood flow **(**CBF) in the inhalation anaesthesia group was significantly higher than in the TIVA group at rewarming during CPB [WMD (95%CI): 5.11 (2.58, 7.63)], and no significant difference was found in cerebral metabolic rate of oxygen consumption ($CMRO_2$), arteriovenous oxygen content difference [$D(a\text{-}v)O_2$], cerebral oxygen extraction ratio (O_2ER), and jugular bulb venous oxygen saturation ($SjvO_2$), which were assessed at cooling and rewarming during CPB.

Conclusion(s): 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.

Keywords: anaesthesia; cerebral protection; cardiac surgery; cardiopulmonary bypass.

Strengths and limitations of this study

1. This is the first systematic review and meta-analysis to compare the neuroprotective effects of inhalation anaesthesia and those of total intravenous anaesthesia (TIVA) in cardiac surgery with cardiopulmonary bypass (CPB).
2. This meta-analysis indicates that inhalation anaesthesia may produce better cerebral protection than TIVA for patients undergoing cardiac surgery with CPB.
3. The methodological quality of each study was assessed using the Jadad Scale for randomised controlled trials. Meta-analysis, heterogeneity test, bias assessment, sensitivity analysis, and subgroup analysis were also conducted.
4. Because of the shortage of reported clinical trials, limited outcome data could be considered for subgroup analysis. The strength of the conclusion is limited by the quality and number of studies.

Introduction

Cardiopulmonary bypass (CPB) is a necessary and common procedure to support the patient's circulation during cardiac surgery. Although previous studies [1,2] reported that CPB does not increase the postoperative morbidity and mortality in patients undergoing coronary artery bypass graft (CABG) 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 [5]. However, at present, there is no definitive clinical evidence regarding cerebral protection for patients undergoing cardiac surgery with CPB [6]. Previous studies on animals support the hypothesis that anaesthetics can produce cerebral protection [7-9]. Many recent studies have found that anaesthetic agents may be neuroprotective and may provide cerebral protection to surgery patients [10, 11]. 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 devbated [12-14]. Therefore, which option provides better cerebral protection to patients undergoing cardiac surgery

with CPB is unknown. Since inhalation anaesthesia and TIVA are the most commonly used strategies for general anaesthesia, it is important to clarify this issue. Moreover, since it is difficult to include patients in neurologic 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 carried out in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) reporting guidelines for intervention trials [15].

Literature search

This meta-analysis was restricted to published studies that investigated the cerebral protective effects of anaesthetics in patients with CPB. Two independent reviewers searched PubMed, EMBASE, Science Direct/Elsevier, MEDLINE, CNKI, and the Cochrane Library from inception to August 2016, without restrictions on language or study type. The search terms combined text words and medical subject headings (MeSH) terms. For example, the search terms for CPB were:

'Cardiopulmonary Bypass' and 'Heart Lung Bypass'. Those for TIVA were: 'propofol', 'disoprofol', 'etomidate' 'midazolam', 'sodium pentothal', 'thiopental', and 'ketamine', while those for inhalation anaesthesia were 'halothane', 'sevoflurane', 'isoflurane', 'desflurane', 'enflurane', and 'methoxyflurane'. (The MEDLINE search strategy is provided in the online supplementary appendix, and the finalised MEDLINE search strategy will be adapted to the syntax and subject headings specifications of the other databases.). All relevant articles and abstracts were retrieved. In addition, references cited within relevant reviews were retrieved manually and only full articles were searched in this case.

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

The primary outcome of the current study was S100B protein level which was detected at pre-CPB, post-CPB and 24 hours postoperatively. The secondary outcomes included mini-mental state examination (MMSE) scores assessed pre- and 24 hours postoperatively, and cerebral blood flow (CBF), cerebral metabolic rate of oxygen consumption ($CMRO_2$), jugular bulb venous oxygen saturation ($SjvO_2$), arteriovenous oxygen content difference [$D(a\text{-}v)O_2$] and cerebral oxygen extraction ratio (O_2ER) were tested at cooling and rewarming during CPB.

Study selection and validity assessment

Two independent reviewers screened titles and abstracts of all papers from the literature search. All relevant studies that appeared to meet the inclusion criteria were retrieved. Full texts were obtained to check if an ambiguous decision was made based on the title and the abstract. Only randomized controlled trials were included in the analysis. Disagreements were resolved through consensus or by a third reviewer. Two reviewers completed the quality assessment according to the primary criteria for randomized controlled trial studies

Data extraction and statistical analysis

Data on authors, year of publication, number and mean age of participants, anaesthetics, and study setting and outcomes were extracted by three reviewers**.** Disagreements between reviewers were resolved by consensus. Quantitative meta-analysis was performed by two reviewers with Review Manager (RevMan) software (version 5.2, Nordic Cochrane Centre, Cochrane Collaboration, 2012, Copenhagen).

The weighted mean differences (WMD) of outcomes in randomized controlled trials and their 95% confidence intervals (CI) were presented. Heterogeneity was assessed using the P-value and the I-square statistic (I^2) in the pooled analysis, which represents the percentage of total variation across studies [16]. If the *P*-value was less than 0.1 or the I^2 value was greater than 50%, the summary estimate was analysed in a random-effects model. Otherwise, a fixed-effects model was applied. In addition, publication bias was detected using Egger's test in the meta-analysis. If the *P*-value was less than 0.05, publication bias was assumed existed.

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 (Fig. 1). All reviewers agreed to include

all 13 papers. Although all of these randomized controlled trials (RCTs) were considered to have a low risk of bias, nine studies included no details on the method of random sequence generation and allocation [17-25].Only one study provided the details about the blinding of the data collection[26].

'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 'Total Intravenous Anaesthesia' (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 to 75 years and 43 to 74 years, respectively. The mean age of patients was unavailable for three studies [17-19]. All the articles had reported exclusion/inclusion criteria [17-29]. Of these, seven studies had used isoflurane *vs.* TIVA [17, 19-21, 23, 24, 27], four studies had used sevoflurane *vs.* TIVA [18, 22, 25, 26], and two studies had used desflurane *vs.* TIVA [28, 29], in patients.

Study	Mean age(inhalation/TIVA)	Setting	Case	Volatile agents	Comparator	Outcomes
Min Jiang .2007	36-62	CPB-Cardiac surgery	15/15	Isoflurane	Propofol	$SjvO_2$%, CBP time
Huaping Yuan .2015	40-65	CPB-Cardiac valve replacement	15/15	Sevoflurane	Propofol	S100B,MMSE

Lei Li 2010	60-70	CPB-CABG	15/15	Isoflurane	Propofol	S100B,MMSE
Mark F. 1997	56±12/61±14	CPB-Cardiac valve replacement	16/15	Isoflurane	Thiopental	CBF,$CMRO_2$,D(a-v)O_2,O_2ER%,SjvO_2%,CBP time
Thomas E1987	55.5±9.9/63.1±6.5	CPB-CABG	16/21	Isoflurane	Thiopental	CBF,$CMRO_2$, CBP time
Gigdem Y.2014	57.37±9.8/57.33±7.2	CPB-Cardiac surgery	10/10	Sevoflurane	Midazolam	CBP time
Meral kanbak .2004	56±7.6/54.5±5.9	CPB-CABG	20/20	Isoflurane	Propofol	S100B, CBP time
Elif Dogan.2013	64.57±10.84/66.45±13.04	CPB-CABG	60/61	Desflurane	Propofol	S100B,CBP time
Sarvesh pal .2011	60.10±7.9/59.54±8.83	CPB-CABG	15/15	Sevoflurane	Midazolam	S100B,CBP time
Tingting Chen .2007	52±5/48±7	CPB-Cardiac valve replacement	20/20	Isoflurane	Propofol	S100B,D(a-v)O_2,O_2ER%,SjvO_2%,CBP time
Jianrong Guo .2009	44±8/43±7	CPB-Cardiac valve replacement	30/30	Isoflurane	Propofol	S100B,D(a-v)O_2,O_2ER%,SjvO_2%,CBP time
Shudong Ma .2015	49.5±2.6/49.1±2.4	CPB-Cardiac valve replacement	15/15	Sevoflurane	Propofol	S100B,MMSE
Jiying Zhong .2010	75±5/74±4	CPB-CABG	25/25	Desflurane	Ketamine	S100B,MMSE

Table 1. Study characteristics of the included studies

(n) TIVA, total intravenous anaesthesia; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; MMSE, mini-mental state examination; CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen consumption; D(a-v)O_2, arteriovenous oxygen content difference; O_2ER, cerebral oxygen extraction; SjvO_2, jugular bulb venous oxygen saturation

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 three received scores of 4-7 (Table 2).

	Jadad Score				
study	Randomization	Allocaion concealment	Blinding	Attrition	Score
Min Jiang .2007	1	0	1	0	2
Huaping Yuan .2015	1	0	0	0	1
Lei Li 2010	1	0	1	0	2
Mark F. 1997	1	0	0	0	1
Thomas E1987	1	0	0	0	1
Gigdem Y.2014	1	0	1	0	1
Meral kanbak .2004	1	2	1	0	4
Elif Dogan.2013	1	2	1	0	4
Sarvesh pal .2011	2	2	1	0	5
Tingting Chen .2007	1	0	0	0	1

Jianrong Guo .2009	1	0	0	0	1
Shudong Ma .2015	1	0	0	0	1
Jiying Zhong .2010	2	0	1	0	3

Table 2. Methodology quality of the included randomized controlled trials (RCTs)

Meta-analysis

Data on S100B levels, MMSE scores, $CMRO_2$, $D(a\text{-}v)O_2$, O_2ER, and $SjvO_2$ were analysed in a random-effects model and, CBF was analysed in a fixed-effects model. S100B levels assessed at the end of CPB and 24 hours postoperatively in inhalation anaesthesia group were significantly lower than those in TIVA group [WMD (95% CI): -0.41 (-0.81, -0.01), -0.32 (-0.59, -0.05), respectively, Fig. 2]. The postoperative MMSE scores of the inhalation anaesthesia group were significantly higher than those of the TIVA group[WMD (95%CI): 1.87 (0.82, 2.92)], Fig. 3]. The CBF assessed at rewarming during CPB was significantly higher in the inhalation anaesthesia group than in the TIVA group [WMD (95% CI): 5.11 (2.58, 7.63), Fig. 4].

There was no significant difference in $CMRO_2$, $D(a\text{-}v)O_2$, O_2ER, and $SjvO_2$ assessed at cooling and rewarming during CPB between the inhalation anaesthesia group and the TIVA group (Fig. 5, 6, 7, 8).

Egger's regression test of S100B levels, MMSE scores, $CMRO_2$, $D(a\text{-}v)O_2$, O_2ER, and $SjvO_2$ indicated little evidence of publication bias, respectively (Table 3).

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
bias(S100B)	-2.67	2.35	-1.14	0.27	[-7.65	2.32]
bias(MMSE)	2.89	5.30	0.54	0.61	[-10.08	15.85]
bias($CMRO_2$)	-1.85	6.10	-0.30	0.79	[-28.16	24.41]
bias(D(a-v)O_2)	186.01	99.93	1.86	0.14	[-91.44	463.46]
bias(O_2ER%)	13.87	6.58	3.63	0.12	[5.59	42.14]
bias($SjvO_2$%)	2.12	19.48	0.11	0.92	[-45.56	49.79]

Table 3. Egger's test of Publication bias

(n) MMSE, mini-mental state examination; CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen consumption; D(a-v)O_2, arteriovenous oxygen content difference; O_2ER, cerebral oxygen extraction; $SjvO_2$, jugular bulb venous oxygen saturation

We conducted sensitivity analysis of the meta-analysis. We omitted one study sequentially, and calculated the combined WMD for the remaining studies, which yielded consistent results. In the overall meta-analysis, no single study significantly changed the combined results, which indicated that the results were statistically stable and reliable (Fig. 9, 10).

Discussion

In our study, thirteen 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 thirteen studies suggested that inhalation anaesthesia might be superior to TIVA in terms of their cerebroprotective effect after CPB [18, 20-22, 25-27, 29]. However, the results reported in other five studies were the opposite [17, 19,

[23, 24, 28]. 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.

S100B is mainly expressed in the astrocytes, and blood S100B level is commonly used as an outcome parameter for evaluating the postoperative neurological dysfunction [30]. Its level in the blood has been shown to increase in patients after ischemic stroke and brain trauma [31]. Serum S100B has also been detected after cardiac surgery complicated by neurological injury in adults; thus, it has the potential to serve as an early marker of brain damage [32, 33]. In this meta-analysis, the serum level of S100B after CPB in the inhalation anaesthesia group was found to be significantly lower than that in the TIVA group ($P<0.05$) [18, 25-27, 29], suggesting that inhalation anaesthetics provide better cerebral protection than TIVA against brain damage.

As reported by Svenmarker et al[34], it is inevitable that S100B contamination will occur due to the pericardial suction blood, which is often re-transfused or processed in the cell saver and then re-transfused during CPB. However, a strict control of clinical procedures may decrease its potential effect on the difference of S100B detection between the two groups. In the included studies, the use of re-transfusion and cell

salvage were not mentioned. Therefore, the possible effect of re-transfusion and cell salvage should not be neglected, and this is a potential limitation of the current study.

Among the secondary outcomes, the MMSE is one of the most commonly used parameters for the clinical evaluation of cognitive function. Our results show that postoperative MMSE scores of patients in the inhalation anaesthesia group were significantly higher than those in the TIVA group ($P<0.05$) [18, 25, 29]. These results suggest that inhalation anaesthesia is better than TIVA in terms of protecting the postoperative cognitive function of patients undergoing cardiac surgery with CPB. The meta-analysis also showed that the other outcomes such as $D(a\text{-}v)O_2$, O_2ER, and $SjvO_2$, were not significantly different for TIVA and inhalation anaesthesia groups. However, we found that in many studies, the cerebral oxygen metabolic rate in patients receiving inhalation anaesthetics was consistently lower than that in patients receiving TIVA. Additionally, the intraoperative CBF in the inhalation anaesthesia group was significantly higher than that in the TIVA group ($P<0.05$) [20, 21]. A low ratio of global cerebral oxygen and adequate cerebral blood supply is an important parameter for evaluating cerebral protection [35]. Thus, the results based on $CMRO_2$ and CBF can strengthen the finding that inhalation anaesthesia may provide better neuroprotection than TIVA.

Experimental data suggest that direct positive effects of volatile

anaesthetics may be caused by various pre-conditioning and post-conditioning mechanisms [36, 37], which attenuate apoptosis and necrosis of cerebral neurons, thereby reducing neurological dysfunction after ischaemia. Moreover, the contribution of inhalation agents in preserving satisfactory haemodynamics may ensure adequate perfusion and oxygenation of other organ systems, [38-41] and improve the chances for recovery and survival after surgery. All these effects can be expanded well beyond the immediate perioperative period because of anaesthetic-induced neuroprotection that can be long lasting [42, 43]. Additionally, a recent meta-analysis found that in cardiac surgery [44], as compared to 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. Since 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, etc.) 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.

Authors' contributions

Conception and design of experiments: F.C, H.L, Z.Z.

Performed the experiments: F.C, G.D, Z.W, Z.Z.

Analysis of data: F.C, G.D, Z.W.

Contribution of reagents/materials/analysis tools: Z.Z, H.L.

Paper written by: F.C, G.D, H.L, Z.Z.

All authors have reviewed the manuscript.

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Competing interests: The authors declare no conflicts of interest.

Data sharing statement: No additional data are available.

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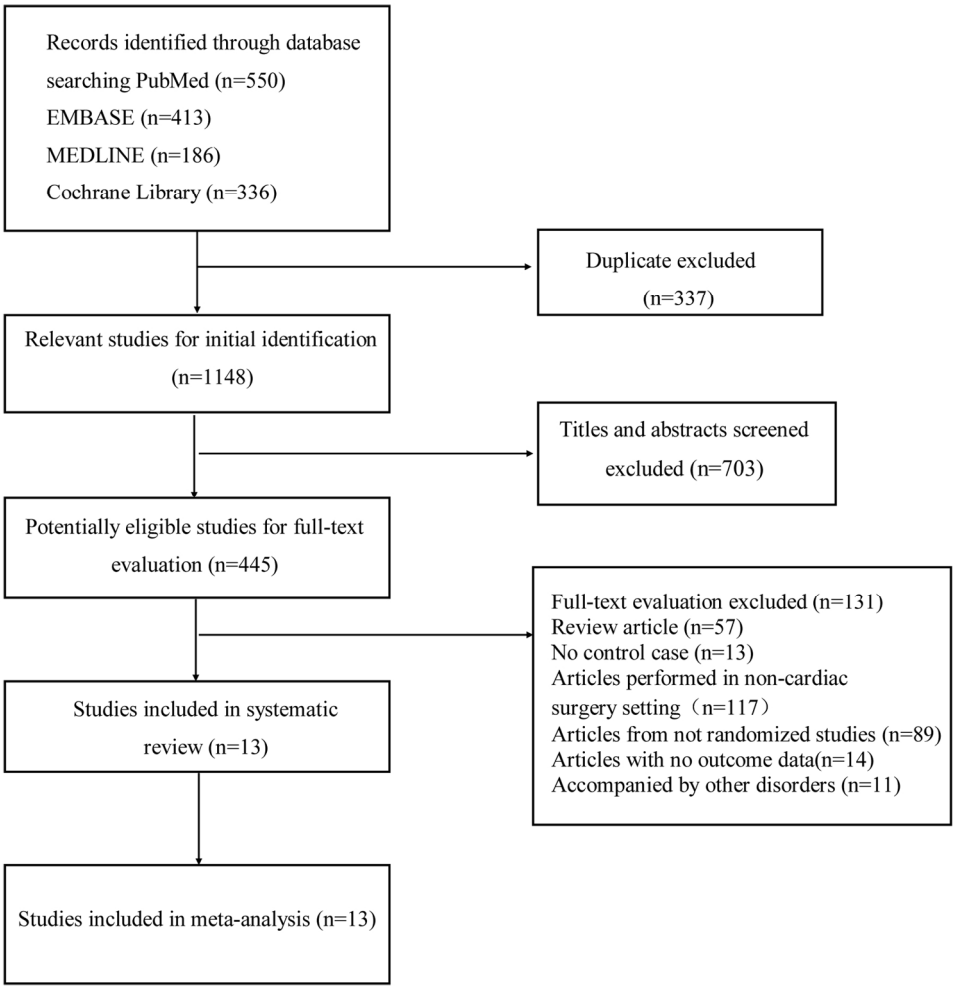

Fig. 1 Flow diagram for the selection of eligible studies

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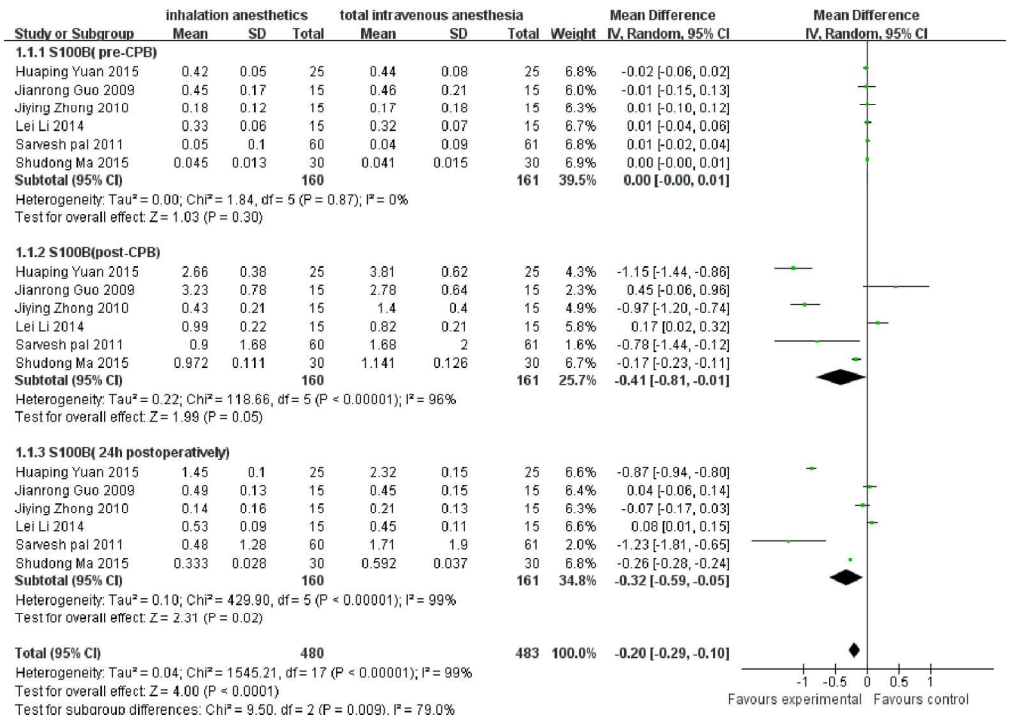

Fig. 2 Forest plot showing the meta-analysis outcomes of the difference in S100B levels of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x113mm (300 x 300 DPI)

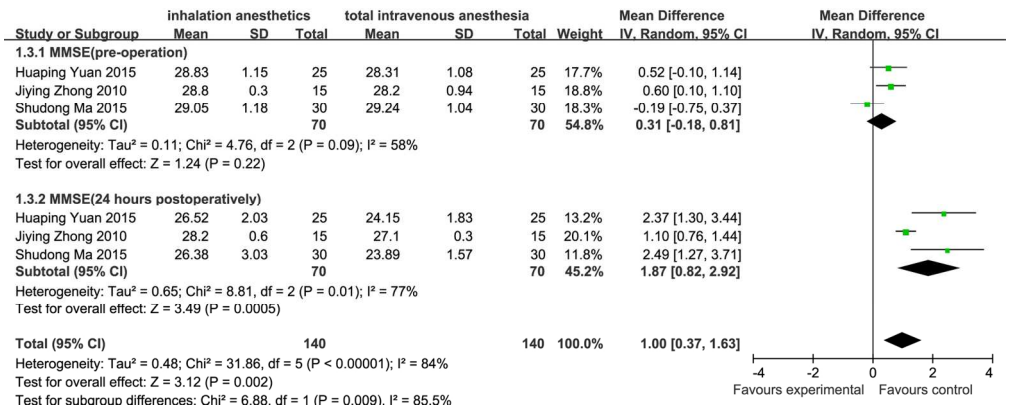

Fig. 3 Forest plot showing the meta-analysis outcomes of the difference in mini-mental state examination (MMSE) scores of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x64mm (300 x 300 DPI)

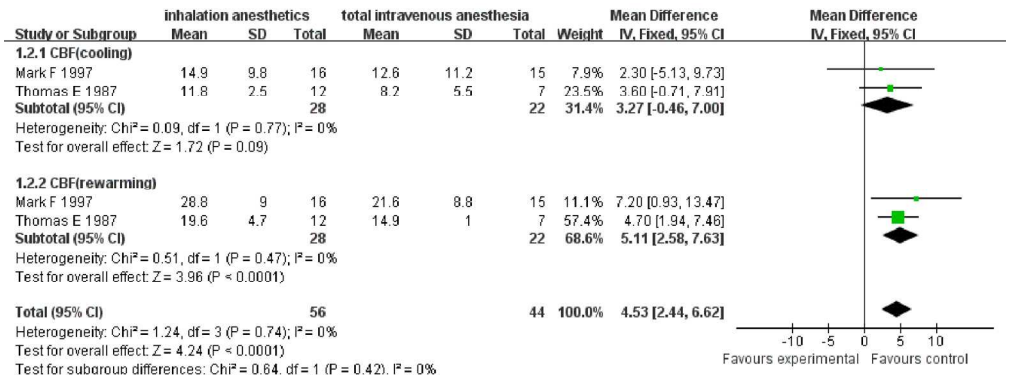

Fig. 4 Forest plot showing the meta-analysis outcomes of the difference in cerebral blood flow (CBF) of the inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

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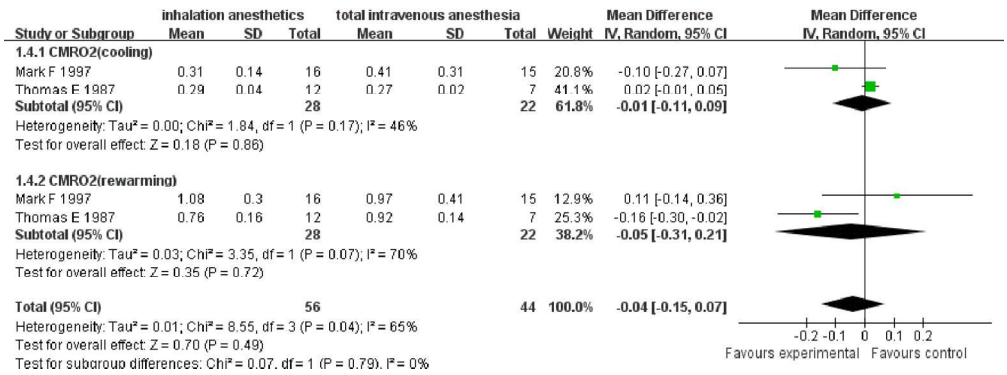

Fig. 5 Forest plot showing the meta-analysis outcomes of the difference in cerebral metabolic rate of oxygen consumption (CMRO2) of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x58mm (300 x 300 DPI)

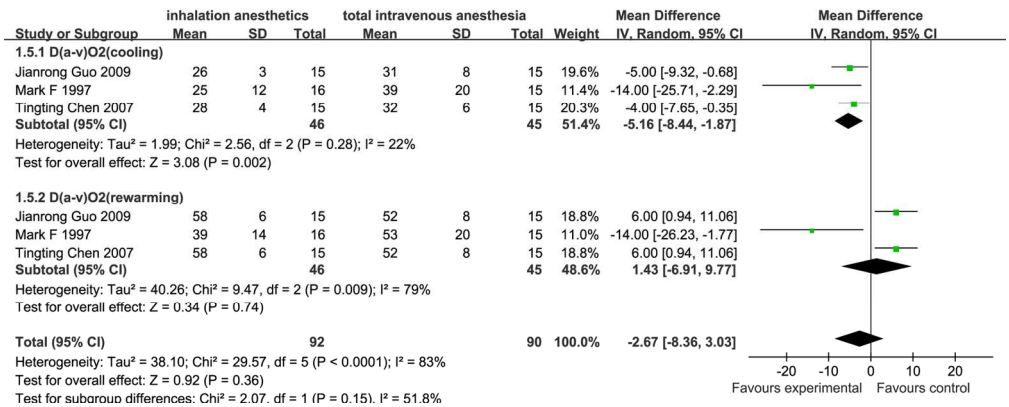

Fig. 6 Forest plot showing the meta-analysis outcomes of the difference in arteriovenous oxygen content difference [D(a-v) O2] of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x63mm (300 x 300 DPI)

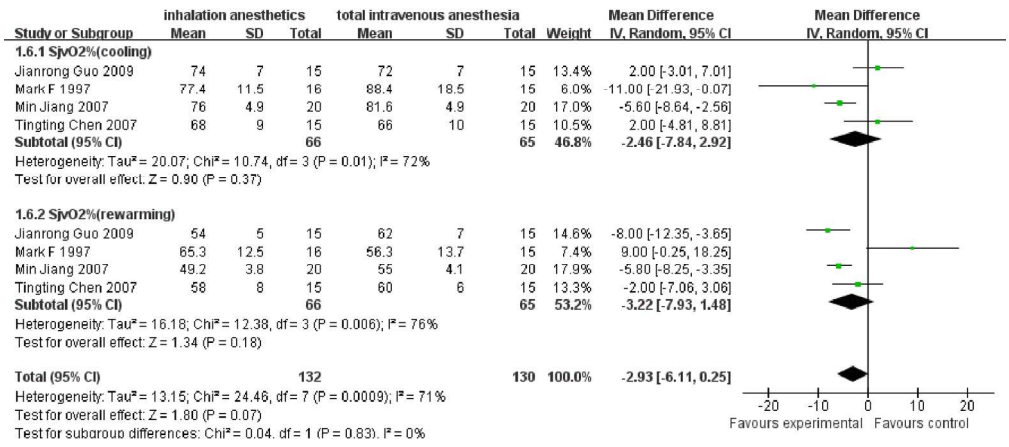

Fig. 7 Forest plot showing the meta-analysis outcomes of the difference in jugular bulb venous oxygen saturation (SjvO2) of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x69mm (300 x 300 DPI)

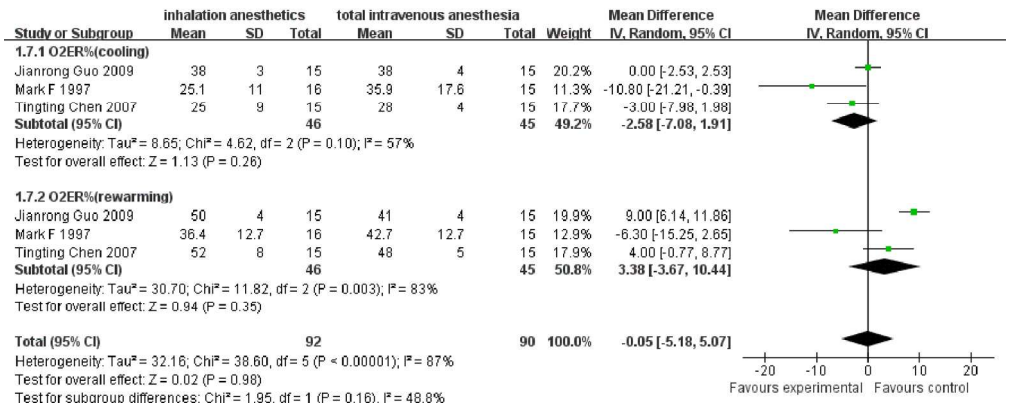

Fig. 8 Forest plot showing the meta-analysis outcomes of the difference in cerebral oxygen extraction ratio (O2ER) between inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x63mm (300 x 300 DPI)

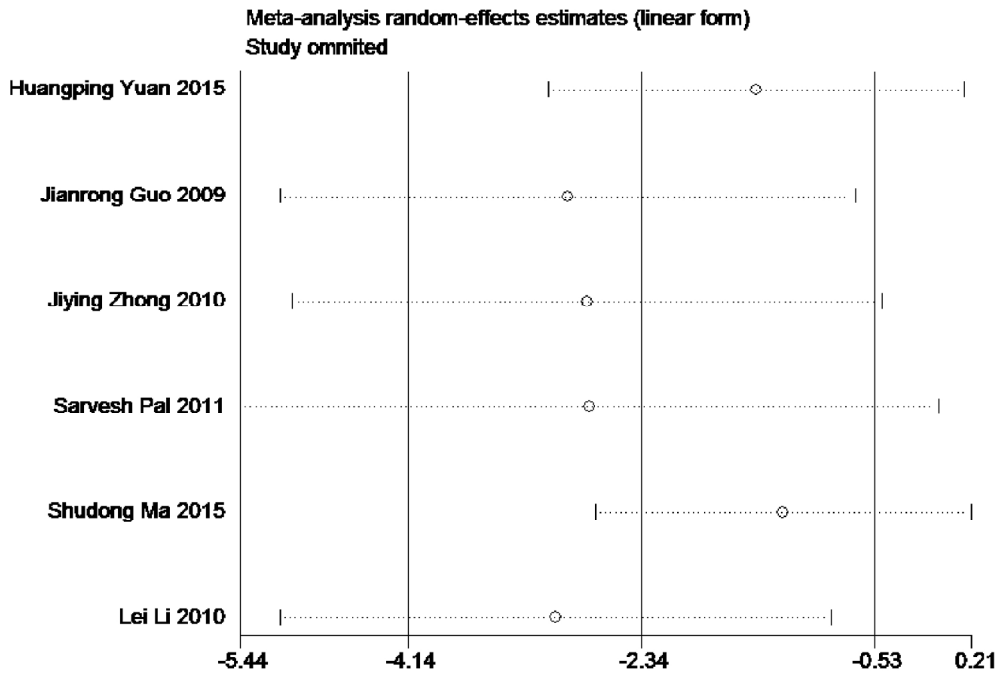

Fig. 9 The plot of sensitivity analysis of S100B levels

160x119mm (300 x 300 DPI)

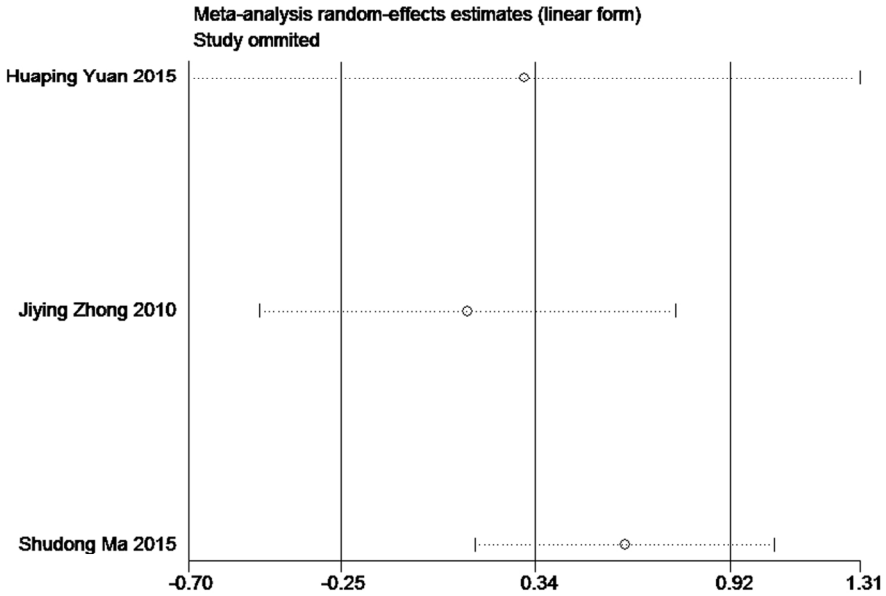

Fig. 10 The plot of sensitivity analysis of mini-mental state examination (MMSE) scores

160x106mm (300 x 300 DPI)

Appendix. MEDLINE search strategy

#1 Heart surgery[MeSH] OR heart operation or cardiac surgery, valve replacement[MeSH] or Coronary artery bypass surgery[MeSH]

#2 Extracorporeal Circulation[MeSH] OR Circulation, Extracorporeal OR Circulations, Extracorporeal OR Extracorporeal Circulations

#3 Cardiopulmonary Bypass[MeSH] OR Bypass, Cardiopulmonary OR Bypasses, Cardiopulmonary OR Cardiopulmonary Bypasses

#4 Heart-Lung Bypass[MeSH] OR Bypass, Heart-Lung OR Bypasses, Heart-Lung OR Heart Lung Bypass OR Heart-Lung Bypasses

#5 #2 OR #3 OR #4

#6 cerebral protection[MeSH] OR Brain protection[MeSH] OR neuroprotection[MeSH]

#7 Anesthesia, Inhalation[MeSH] OR Inhalation Anesthesia OR Anesthesia, Insufflation

#8 Isoflurane OR Sevoflurane OR Enflurane OR Desflurane OR Halothane OR Nitrous Oxide OR Xenon

#9 #7 OR #8

#10 Anesthesia, Intravenous[MeSH] OR Anesthesias, Intravenous OR Intravenous Anesthesia OR Intravenous Anesthesias

#11 Propofol[MeSH] OR Disoprofol

#12 Etomidate[MeSH] OR Ethomidate;

13 Thiopental[MeSH] OR Penthiobarbital OR Thiomebumal OR

Thiopentobarbital OR Thiopentone OR Bomathal OR Pentothal Sodico

#14 Ketamine[MeSH] OR Calypsol OR Kalips

#15 Midazolam[MeSH] OR Hydrochloride, Midazolam OR Maleate, Midazolam

#16 OR/#10-#15

#17 randomized controlled trial [pt]

#18 controlled clinical trial [pt]

#19 randomized [tiab]

#20 placebo [tiab]

#21 drug therapy [sh]

#22 randomly [tiab]

#23 trial [tiab]

#24 groups [tiab]

#25 OR/#17-#24

#26 animals [mh] NOT humans [mh]

#27 #25 NOT #26

#28 #1 AND #5 AND #9 AND #16 AND #27

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

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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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Neurology
Keywords:	Anaesthesia in cardiology < ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Anaesthesia in neurology < ANAESTHETICS

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 (CNKI), and Cochrane Library up to August 2016, we selected related randomized controlled trials for this

meta-analysis.

Result(s): 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, etc.), 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% confidence interval [CI]: -0.41 [-0.81, -0.01], -0.32 [-0.59, -0.05], respectively). Among secondary outcome variables, mini-mental state examination (MMSE) 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, 2.92)], but no significant difference was found in arteriovenous oxygen content difference [D(a-v)O_2], cerebral oxygen extraction ratio (O_2ER), and jugular bulb venous oxygen saturation (SjvO_2), which were assessed at cooling and rewarming during CPB.

Conclusion(s): 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.

Keywords: anaesthesia; cerebral protection; cardiac surgery; cardiopulmonary bypass.

Strengths and limitations of this study

1. This is the first systematic review and meta-analysis to compare the neuroprotective effects of inhalation anaesthesia and those of total intravenous anaesthesia (TIVA) in cardiac surgery with cardiopulmonary bypass (CPB).
2. This study focused on the overall comparison between inhalation anaesthesia and TIVA, different inhalation and intravenous anaesthetics were investigated in the included studies.
3. The methodological quality of each study was assessed using the Jadad Scale for randomised controlled trials. Meta-analysis, heterogeneity test, bias assessment, sensitivity analysis, and subgroup analysis were also conducted.
4. Because of the shortage of reported clinical trials, limited outcome data could be considered for subgroup analysis. The strength of the conclusion is limited by the quality and number of studies.

Introduction

Cardiopulmonary bypass (CPB) is a necessary and common procedure to support the patient's circulation during cardiac surgery.

Although previous studies [1,2] reported that CPB does not increase the postoperative morbidity and mortality in patients undergoing coronary artery bypass graft (CABG) 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 [5]. However, at present, there is no definitive clinical evidence regarding cerebral protection for patients undergoing cardiac surgery with CPB [6]. Previous studies on animals support the hypothesis that anaesthetics can produce cerebral protection [7-9]. Many recent studies have found that anaesthetic agents may be neuroprotective and may provide cerebral protection to surgery patients [10, 11]. 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 [12-14]. Therefore, which option provides better cerebral protection to patients undergoing cardiac surgery with CPB is unknown. Since inhalation anaesthesia and TIVA are the most commonly used strategies for general anaesthesia, it is important to clarify this issue. Moreover, since it is difficult to include patients in

neurologic 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 carried out in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) reporting guidelines for intervention trials [15].

Literature search

This meta-analysis was restricted to published studies that investigated the cerebral protective effects of anaesthetics in patients with CPB. Two independent reviewers searched PubMed, EMBASE, Science Direct/Elsevier, MEDLINE, CNKI, and the Cochrane Library from inception to August 2016, without restrictions on language or study type. The search terms combined text words and medical subject headings (MeSH) terms. For example, the search terms for CPB were: 'Cardiopulmonary Bypass' and 'Heart Lung Bypass'. Those for TIVA were: 'propofol', 'disoprofol', 'etomidate' 'midazolam', 'sodium pentothal', 'thiopental', and 'ketamine', while those for inhalation

anaesthesia were ‘halothane’, ‘sevoflurane’, ‘isoflurane’, ‘desflurane’, ‘enflurane’, and ‘methoxyflurane’. (The MEDLINE search strategy is provided in the online supplementary appendix, and the finalised MEDLINE search strategy will be adapted to the syntax and subject headings specifications of the other databases.). All relevant articles and abstracts were retrieved. In addition, references cited within relevant reviews were retrieved manually and only full articles were searched in this case.

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. And 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 ($SjvO_2$), arteriovenous oxygen content difference [$D(a\text{-}v)O_2$] and cerebral oxygen extraction ratio (O_2ER) were tested at cooling and rewarming during CPB.

Study selection and validity assessment

Two independent reviewers screened titles and abstracts of all papers from the literature search. All relevant studies that appeared to meet the inclusion criteria were retrieved. Full texts were obtained to check if an ambiguous decision was made based on the title and the abstract. Only randomized controlled trials were included in the analysis. Disagreements were resolved through consensus or by a third reviewer. Two reviewers completed the quality assessment according to the primary criteria for randomized controlled trial studies

Data extraction and statistical analysis

Data on authors, year of publication, number and mean age of participants, anaesthetics, and study setting and outcomes were extracted

by three reviewers. Disagreements between reviewers were resolved by consensus. Quantitative meta-analysis was performed by two reviewers with Review Manager (RevMan) software (version 5.2, Nordic Cochrane Centre, Cochrane Collaboration, 2012, Copenhagen).

The weighted mean differences (WMD) of outcomes in randomized controlled trials and their 95% confidence intervals (CI) were presented. Heterogeneity was assessed using the P-value and the I-square statistic (I^2) in the pooled analysis, which represents the percentage of total variation across studies [16]. If the *P*-value was less than 0.1 or the I^2 value was greater than 50%, the summary estimate was analysed in a random-effects model. Otherwise, a fixed-effects model was applied. In addition, publication bias was detected using Egger's test in the meta-analysis. If the *P*-value was less than 0.05, publication bias was assumed existed.

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 (Fig. 1). All reviewers agreed to include all 13 papers. Although all of these randomized controlled trials (RCTs) were considered to have a low risk of bias, nine studies included no

details on the method of random sequence generation and allocation [17-25].Only one study provided the details about the blinding of the data collection[26].

'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 'Total Intravenous Anaesthesia' (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 to 75 years and 43 to 74 years, respectively. The mean age of patients was unavailable for three studies [17-19]. All the articles had reported exclusion/inclusion criteria [17-29]. Of these, seven studies had used isoflurane *vs.* TIVA [17, 19-21, 23, 24, 27], four studies had used sevoflurane *vs.* TIVA [18, 22, 25, 26], and two studies had used desflurane *vs.* TIVA [28, 29], in patients.

Study	Mean age(inhalation/TIVA)	Setting	Case	Volatile agents	Comparator	Outcomes
Min Jiang .2007	36-62	CPB-Cardiac surgery	15/15	Isoflurane	Propofol	$SjvO_2$%, CBP time
Huaping Yuan .2015	40-65	CPB-Cardiac valve replacement	15/15	Sevoflurane	Propofol	S100B,MMSE
Lei Li 2010	60-70	CPB-CABG	15/15	Isoflurane	Propofol	S100B
Mark F. 1997	56±12/61±14	CPB-Cardiac valve replacement	16/15	Isoflurane	Thiopental	CBF,$CMRO_2$,D(a-v)O_2,O_2ER%,$SjvO_2$%,CBP time
Thomas E1987	55.5±9.9/63.1±6.5	CPB-CABG	16/21	Isoflurane	Thiopental	CBF,$CMRO_2$, CBP time
Gigdem Y.2014	57.37±9.8/57.33±7.2	CPB-Cardiac surgery	10/10	Sevoflurane	Midazolam	CBP time

Meral kanbak .2004	56±7.6/54.5±5.9	CPB-CABG	20/20	Isoflurane	Propofol	S100B, CBP time
Elif Dogan.2013	64.57±10.84/66.45±13.04	CPB-CABG	60/61	Desflurane	Propofol	S100B,CBP time
Sarvesh pal .2011	60.10±7.9/59.54±8.83	CPB-CABG	15/15	Sevoflurane	Midazolam	S100B,CBP time
Tingting Chen .2007	52±5/48±7	CPB-Cardiac valve replacement	20/20	Isoflurane	Propofol	S100B,D(a-v)O_2,O_2ER%,SjvO_2%,CBP time
Jianrong Guo .2009	44±8/43±7	CPB-Cardiac valve replacement	30/30	Isoflurane	Propofol	S100B,D(a-v)O_2,O_2ER%,SjvO_2%,CBP time
Shudong Ma .2015	49.5±2.6/49.1±2.4	CPB-Cardiac valve replacement	15/15	Sevoflurane	Propofol	S100B,MMSE
Jiying Zhong .2010	75±5/74±4	CPB-CABG	25/25	Desflurane	Ketamine	S100B,MMSE

Table 1. Study characteristics of the included studies

(n) TIVA, total intravenous anaesthesia; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; MMSE, mini-mental state examination; CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen consumption; D(a-v)O_2, arteriovenous oxygen content difference; O_2ER, cerebral oxygen extraction; SjvO_2, jugular bulb venous oxygen saturation

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 three received scores of 4-7 (Table 2).

	Jadad Score				
study	Randomization	Allocaion concealment	Blinding	Attrition	Score
Min Jiang .2007	1	0	1	0	2
Huaping Yuan .2015	1	0	0	0	1
Lei Li 2010	1	0	1	0	2
Mark F. 1997	1	0	0	0	1
Thomas E1987	1	0	0	0	1
Gigdem Y.2014	1	0	1	0	1
Meral kanbak .2004	1	2	1	0	4
Elif Dogan.2013	1	2	1	0	4
Sarvesh pal .2011	2	2	1	0	5
Tingting Chen .2007	1	0	0	0	1
Jianrong Guo .2009	1	0	0	0	1
Shudong Ma .2015	1	0	0	0	1
Jiying Zhong .2010	2	0	1	0	3

Table 2. Methodology quality of the included randomized controlled trials (RCTs)

Meta-analysis

Summary estimate for S100B levels post-CPB and 24 hours postoperatively were analysed in a random-effects model because of the heterogeneity (I^2=96% and I^2=99%, respectively). Based on 6 studies from 230 patients, S100B levels assessed at the end of CPB and 24 hours postoperatively in inhalation anaesthesia group were significantly lower than those in TIVA group [WMD (95% CI): -0.41 (-0.81, -0.01), -0.32 (-0.59, -0.05), respectively, Fig. 2]. Based on 3 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, 2.92)], Fig. 3]. A significant heterogeneity was detected (I^2=77%), and thus summary estimate was analysed in a random-effects model.

There was no significant difference in D(a-v)O_2, O_2ER, and SjvO_2 assessed at cooling and rewarming during CPB between the inhalation anaesthesia group and the TIVA group (Fig. 4, 5, 6).

Egger's regression test of S100B levels, MMSE scores, D(a-v)O_2, O_2ER, and SjvO_2 indicated little evidence of publication bias, respectively (Table 3).

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]	
bias(S100B)	-2.67	2.35	-1.14	0.27	[-7.65	2.32]
bias(MMSE)	2.89	5.30	0.54	0.61	[-10.08	15.85]
bias(D(a-v)O_2)	186.01	99.93	1.86	0.14	[-91.44	463.46]

bias(O_2ER%)	13.87	6.58	3.63	0.12	[5.59	42.14]
bias($SjvO_2$%)	2.12	19.48	0.11	0.92	[-45.56	49.79]

Table 3. Egger's test of Publication bias

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

We conducted sensitivity analysis of the meta-analysis. We omitted one study sequentially, and calculated the combined WMD for the remaining studies, which yielded consistent results. In the overall meta-analysis, no single study significantly changed the combined results, which indicated that the results were statistically stable and reliable (Fig. 7, 8).

Discussion

In our study, thirteen 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 thirteen studies suggested that inhalation anaesthesia might be superior to TIVA in terms of their cerebroprotective effect after CPB [18, 20-22, 25-27, 29]. However, the results reported in other five studies were the opposite [17, 19, 23, 24, 28]. 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.

S100B is mainly expressed in the astrocytes, and blood S100B level is commonly used as an outcome parameter for evaluating the postoperative neurological dysfunction [30]. Its level in the blood has been shown to increase in patients after ischemic stroke and brain trauma [31]. Serum S100B has also been detected after cardiac surgery complicated by neurological injury in adults; thus, it has the potential to serve as an early marker of brain damage [32, 33]. In this meta-analysis, the serum level of S100B after CPB in the inhalation anaesthesia group was found to be significantly lower than that in the TIVA group ($P<0.05$) [18, 25-27, 29], suggesting that inhalation anaesthetics provide better cerebral protection than TIVA against brain damage.

As reported by Svenmarker et al[34], it is inevitable that S100B contamination will occur due to the pericardial suction blood, which is often re-transfused or processed in the cell saver and then re-transfused during CPB. However, a strict control of clinical procedures may decrease its potential effect on the difference of S100B detection between the two groups. In the included studies, the use of re-transfusion and cell salvage were not mentioned. Therefore, the possible effect of re-transfusion and cell salvage should not be neglected, and this is a potential limitation of the current study.

Among the secondary outcomes, the MMSE is one of the most commonly used parameters for the clinical evaluation of cognitive function. Our results show that postoperative MMSE scores of patients in the inhalation anaesthesia group were significantly higher than those in the TIVA group ($P<0.05$) [18, 25, 29]. These results suggest that inhalation anaesthesia is better than TIVA in terms of protecting the postoperative cognitive function of patients undergoing cardiac surgery with CPB. The meta-analysis also showed that the other outcomes such as $D(a\text{-}v)O_2$, O_2ER, and $SjvO_2$, were not significantly different for TIVA and inhalation anaesthesia groups. However, we found that in some studies, the cerebral oxygen metabolic rate ($CMRO_2$) in patients receiving inhalation anaesthetics assessed at cooling and rewarming during CPB was consistently lower than that in patients receiving TIVA[20, 21]. Additionally, the intraoperative cerebral blood flow (CBF) assessed at cooling and rewarming during CPB in the inhalation anaesthesia group was significantly higher than that in the TIVA group [20, 21]. A low ratio of global cerebral oxygen and adequate cerebral blood supply is an important parameter for evaluating cerebral protection [35]. Thus, these results based on $CMRO_2$ and CBF can strengthen the finding that inhalation anaesthesia may provide better neuroprotection than TIVA.

Experimental data suggest that direct positive effects of volatile anaesthetics may be caused by various pre-conditioning and

post-conditioning mechanisms [36, 37], which attenuate apoptosis and necrosis of cerebral neurons, thereby reducing neurological dysfunction after ischaemia. Moreover, the contribution of inhalation agents in preserving satisfactory haemodynamics may ensure adequate perfusion and oxygenation of other organ systems, [38-41] and improve the chances for recovery and survival after surgery. All these effects can be expanded well beyond the immediate perioperative period because of anaesthetic-induced neuroprotection that can be long lasting [42, 43]. Additionally, a recent meta-analysis found that in cardiac surgery [44], as compared to 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. Since 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, etc.) 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.

Authors' contributions

Conception and design of experiments: F.C, H.L, Z.Z.

Performed the experiments: F.C, G.D, Z.W, Z.Z.

Analysis of data: F.C, G.D, Z.W.

Contribution of reagents/materials/analysis tools: Z.Z, H.L.

Paper written by: F.C, G.D, H.L, Z.Z.

All authors have reviewed the manuscript.

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Figure legends

Fig. 1 Flow diagram for the selection of eligible studies

Fig. 2 Forest plot showing the meta-analysis outcomes of the difference in S100B levels of inhalation anaesthesia and total intravenous

anaesthesia (TIVA) groups

Fig. 3 Forest plot showing the meta-analysis outcomes of the difference in mini-mental state examination (MMSE) scores of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

Fig 4. Forest plot showing the meta-analysis outcomes of the difference in arteriovenous oxygen content difference [D(a-v)O2] of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups.

Fig 5. Forest plot showing the meta-analysis outcomes of the difference in jugular bulb venous oxygen saturation (SjvO2) of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups.

Fig 6. Forest plot showing the meta-analysis outcomes of the difference in cerebral oxygen extraction ratio (O2ER) of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups.

Fig. 7 The plot of sensitivity analysis of S100B levels

Fig. 8 The plot of sensitivity analysis of mini-mental state examination (MMSE) scores

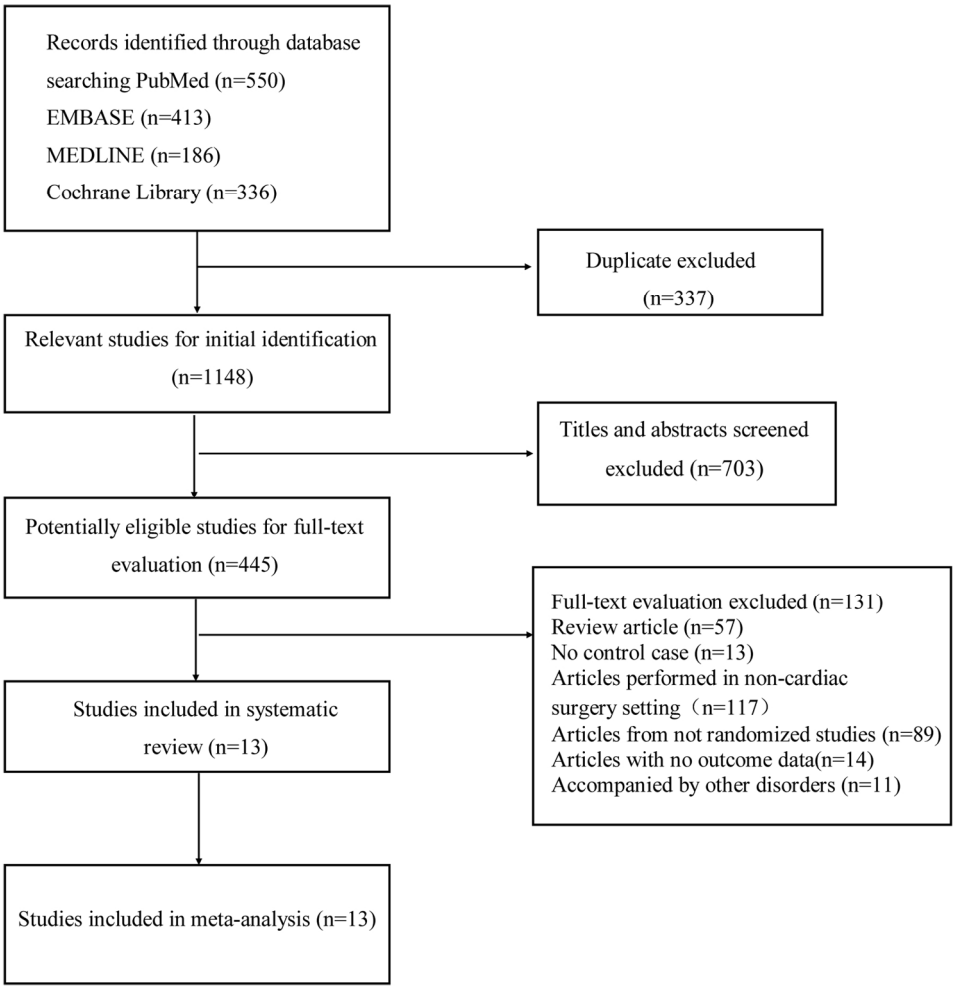

Fig. 1 Flow diagram for the selection of eligible studies

160x160mm (300 x 300 DPI)

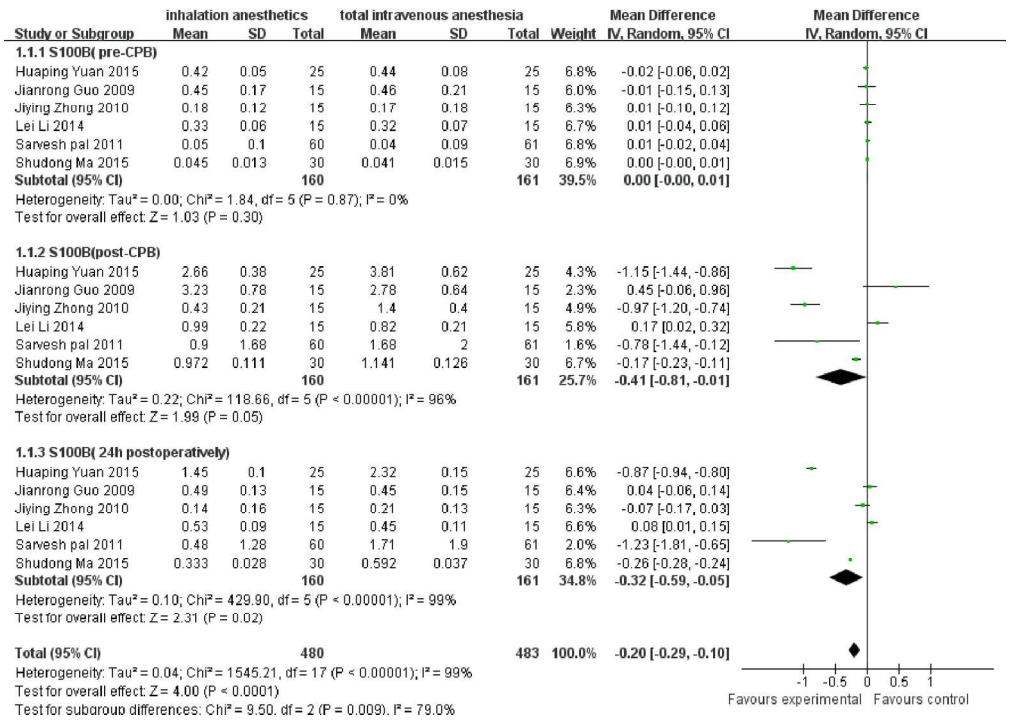

Fig. 2 Forest plot showing the meta-analysis outcomes of the difference in S100B levels of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x113mm (300 x 300 DPI)

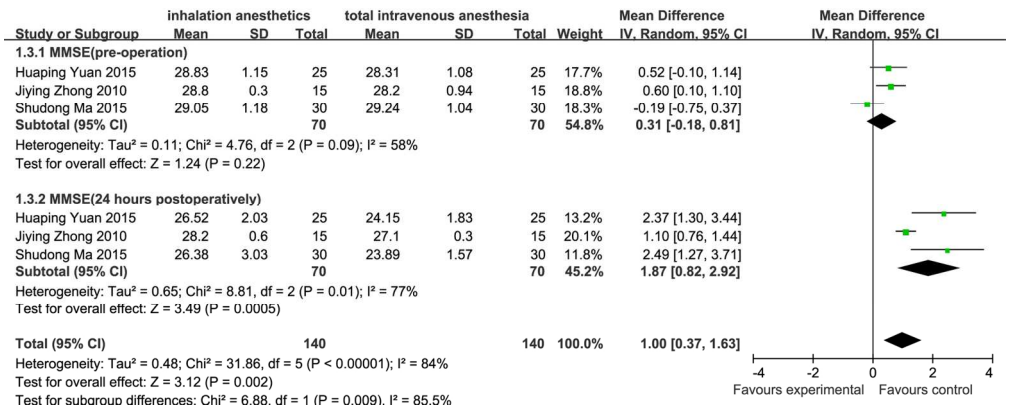

Fig. 3 Forest plot showing the meta-analysis outcomes of the difference in mini-mental state examination (MMSE) scores of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x64mm (300 x 300 DPI)

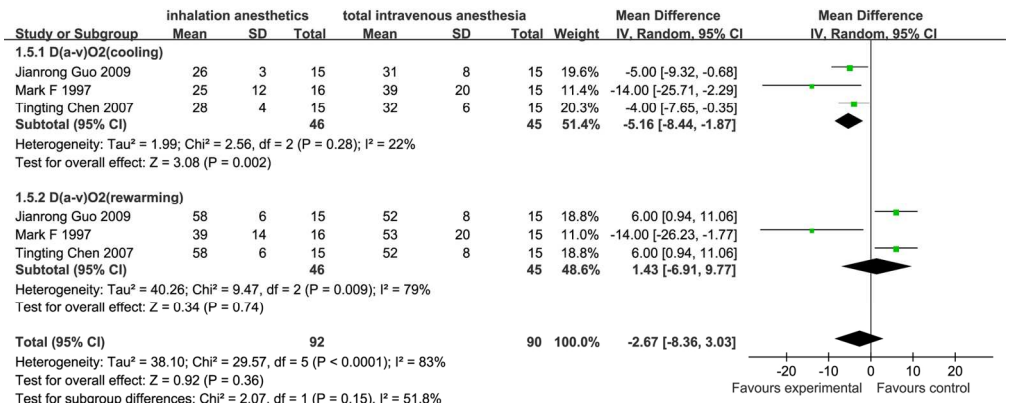

Fig 4. Forest plot showing the meta-analysis outcomes of the difference in arteriovenous oxygen content difference [D(a-v)O2] of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups.

160x63mm (299 x 299 DPI)

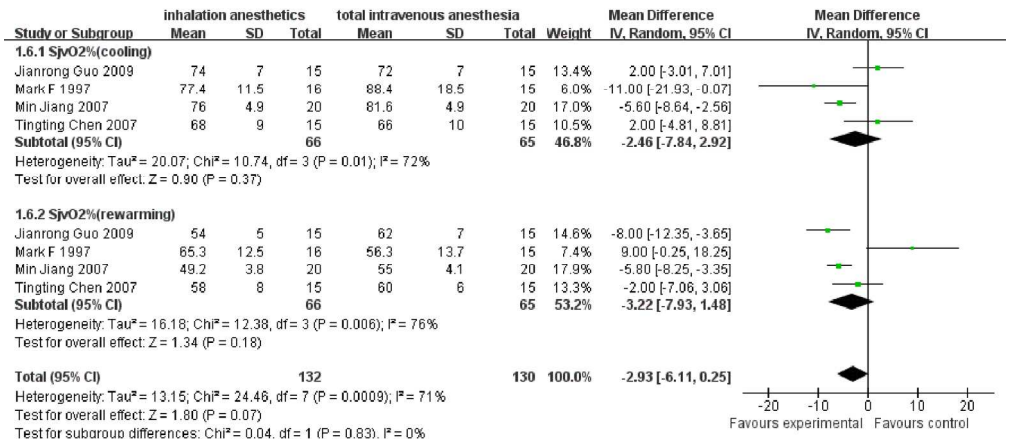

Fig 5. Forest plot showing the meta-analysis outcomes of the difference in jugular bulb venous oxygen saturation (SjvO2) of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups.

160x69mm (299 x 299 DPI)

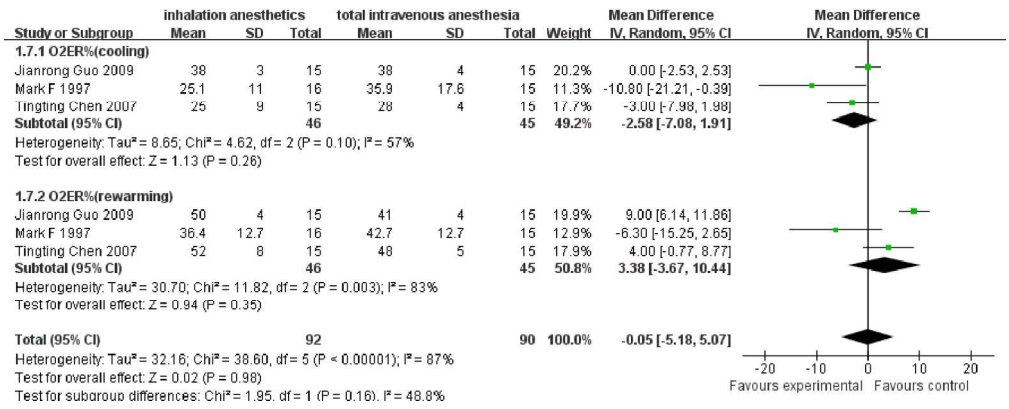

Fig 6. Forest plot showing the meta-analysis outcomes of the difference in cerebral oxygen extraction ratio (O2ER) of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups.

160x63mm (299 x 299 DPI)

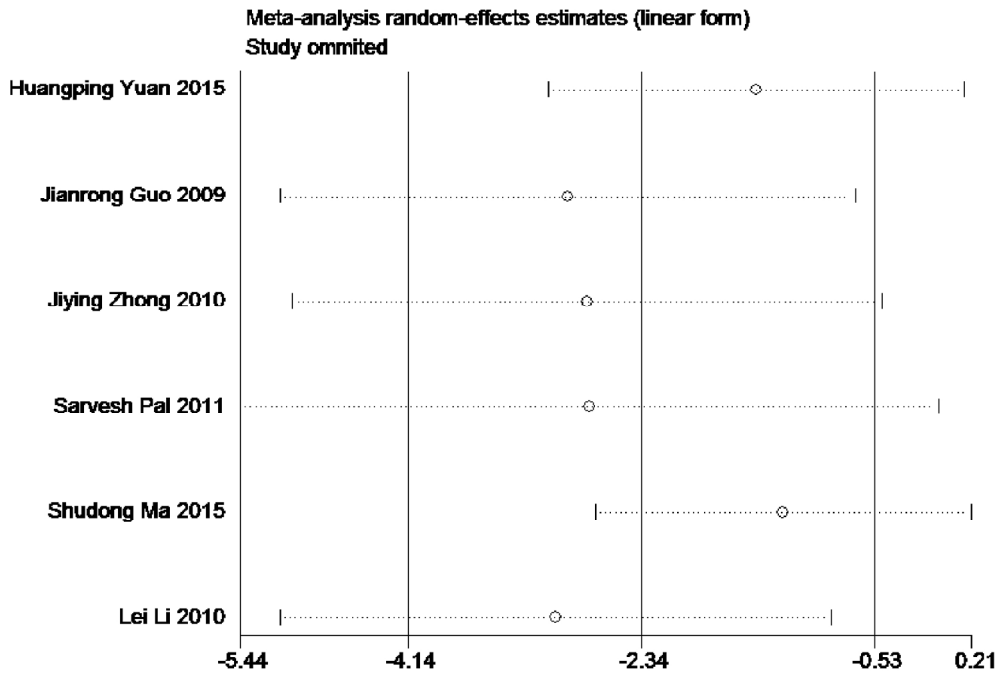

Fig. 7 The plot of sensitivity analysis of S100B levels

160x119mm (300 x 300 DPI)

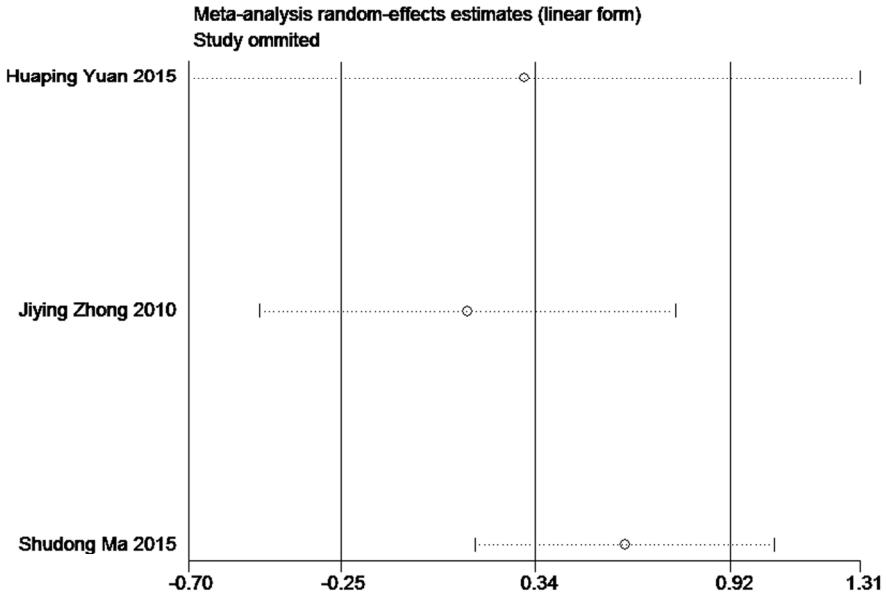

Fig. 8 The plot of sensitivity analysis of mini-mental state examination (MMSE) scores

160x106mm (299 x 299 DPI)

Appendix. MEDLINE search strategy

#1 Heart surgery[MeSH] OR heart operation or cardiac surgery, valve replacement[MeSH] or Coronary artery bypass surgery[MeSH]

#2 Extracorporeal Circulation[MeSH] OR Circulation, Extracorporeal OR Circulations, Extracorporeal OR Extracorporeal Circulations

#3 Cardiopulmonary Bypass[MeSH] OR Bypass, Cardiopulmonary OR Bypasses, Cardiopulmonary OR Cardiopulmonary Bypasses

#4 Heart-Lung Bypass[MeSH] OR Bypass, Heart-Lung OR Bypasses, Heart-Lung OR Heart Lung Bypass OR Heart-Lung Bypasses

#5 #2 OR #3 OR #4

#6 cerebral protection[MeSH] OR Brain protection[MeSH] OR neuroprotection[MeSH]

#7 Anesthesia, Inhalation[MeSH] OR Inhalation Anesthesia OR Anesthesia, Insufflation

#8 Isoflurane OR Sevoflurane OR Enflurane OR Desflurane OR Halothane OR Nitrous Oxide OR Xenon

#9 #7 OR #8

#10 Anesthesia, Intravenous[MeSH] OR Anesthesias, Intravenous OR Intravenous Anesthesia OR Intravenous Anesthesias

#11 Propofol[MeSH] OR Disoprofol

#12 Etomidate[MeSH] OR Ethomidate;

13 Thiopental[MeSH] OR Penthiobarbital OR Thiomebumal OR

Thiopentobarbital OR Thiopentone OR Bomathal OR Pentothal Sodico

#14 Ketamine[MeSH] OR Calypsol OR Kalips

#15 Midazolam[MeSH] OR Hydrochloride, Midazolam OR Maleate, Midazolam

#16 OR/#10-#15

#17 randomized controlled trial [pt]

#18 controlled clinical trial [pt]

#19 randomized [tiab]

#20 placebo [tiab]

#21 drug therapy [sh]

#22 randomly [tiab]

#23 trial [tiab]

#24 groups [tiab]

#25 OR/#17-#24

#26 animals [mh] NOT humans [mh]

#27 #25 NOT #26

#28 #1 AND #5 AND #9 AND #16 AND #27

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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