

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Comparison of cerebral protection between inhalation anesthesia and total intravenous anesthesia in cardiac surgery with cardiopulmonary bypass: A Systematic Review and Meta-Analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014629
Article Type:	Research
Date Submitted by the Author:	19-Oct-2016
Complete List of Authors:	Chen, Feng Duan, You Wu, Xi Zuo, Yi Li, Hong; Xinqiao Hospital, Third Military Medical University, Anesthesiology
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Neurology
Keywords:	Anaesthesia in cardiology < ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Anaesthesia in neurology < ANAESTHETICS

SCHOLARONE™
Manuscripts

Comparison of cerebral protection between inhalation anesthesia and total intravenous anesthesia in cardiac surgery with cardiopulmonary bypass: A Systematic Review and Meta-Analysis

Feng Chen^a, Guangyou Duan^a, Zhuoxi Wu^a, Zhiyi Zuo^b, Hong Li^{*}

^a Department of Anesthesiology, Xinqiao Hospital, Third Military Medical University, Chongqing,400037, China

^bDepartment of Anesthesiology, University of Virginia, Charlottesville, Virginia,USA

* Corresponding author at: Department of Anesthesiology, Xinqiao Hospital, Third Military Medical University, Chongqing, China. Email: Lh78553@163.com

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 CMRO₂, SjvO₂%, C(a-v)O₂, O₂ER% 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

1
2
3
4 The current systematic review and meta-analysis was carried out in
5
6 accordance with the Preferred Reporting Items for Systematic Reviews
7
8 and Meta-Analyses reporting guidelines (PRISMA) for the intervention
9
10 trials^[14].
11
12

13 14 15 16 **Literature search** 17

18
19 This meta-analysis was restricted to published studies that investigated
20
21 the cerebral protection of anesthetics inpatients with CPB. Two
22
23 independent reviewers (ZW and GD) searched PubMed, EMBASE,
24
25 Science Direct/Elsevier, MEDLINE, CNKI and the Cochrane Library
26
27 from inception to August 2016, without restrictions on language or study
28
29 type. The search terms combined text words and MeSH terms. For
30
31 example, the search terms for CPB were: ‘Cardiopulmonary Bypass’,
32
33 ‘Bypass Cardiopulmonary’, ‘Bypasses Cardiopulmonary’,
34
35 ‘Cardiopulmonary Bypasses’, ‘Heart-Lung Bypass’, ‘Bypass Heart-Lung’,
36
37 ‘Bypasses Heart-Lung’, ‘Heart Lung Bypass’, ‘Heart-Lung Bypasses’.
38
39 TIVA were : ‘propofol’, ‘disoprofol’, ‘etomidate’ ‘midazolam’, ‘sodium
40
41 pentothal’, ‘thiopental’, ‘ketamine’, while those for inhalation anesthesia
42
43 were ‘halothane’, ‘sevoflurane’, ‘isoflurane’, ‘desflurane’, ‘enflurane’,
44
45 ‘methoxyflurane’. All related articles and abstracts were retrieved. In
46
47 addition, references cited within relevant reviews were retrieved by hand
48
49 and only full articles were searched in this case.
50
51
52
53
54
55
56
57
58
59
60

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 included S100B protein levels, mini-mental state examination (MMSE) scores, cerebral blood flow (CBF), cerebral metabolic rate of oxygen consumption (CMRO₂), jugular bulb oxygen saturation (SjvO₂%), arteriovenous oxygen content difference (C(a-v)O₂), cerebral oxygen extraction (O₂ER%) 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, anesthetics and 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 1485 studies were identified, without duplicate, the articles

1
2
3
4 remained 1148. After screening titles and abstracts, about 445 studies
5
6 were potentially eligible. Depend on exclusion criteria (full-text reporting
7
8 was abstract, review article, no control case, lack of outcome data, ect.),
9
10 13 studies were ultimately selected according to eligibility criteria (Figure
11
12 1). After a group discussion, all reviewers agreed to include all of the
13
14 13 papers. Although all of these randomized controlled trials (RCTs) were
15
16 regarded to have low risk of bias, 9 studies had no details on the method
17
18 about random sequence generation and allocation^[16-24]. And only one
19
20 study provided the details about the blinding of the data collection.^[25]
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

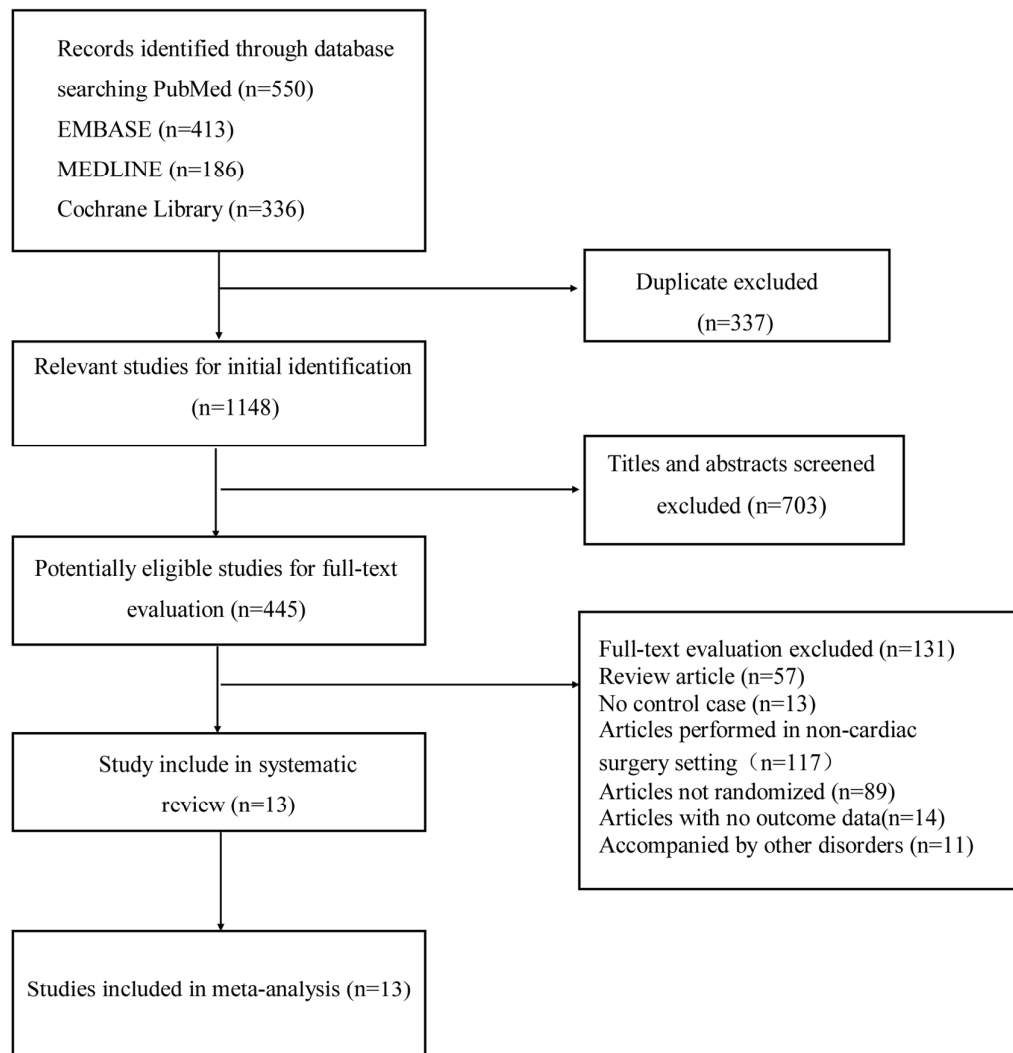


Figure1. Flow diagram of selection of eligible studies

‘Inhalation anaesthesia’ 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 anaesthetics. These studies involved a total of 549 patients, including 272 patients with inhalation anaesthesia and 277 patients with TIVA (Table 1). Patients’ age range in the 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^[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	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 ₂ ER%,SjvO ₂ %,CBP time
Thomas E1987	55.5±9.9/63.1±6.5	CPB-CABG	16/21	Isoflurane	Thiopental	CBF,CMRO ₂ ,CPP,CBP time
Gigdem Y.2014	57.37±9.8/57.33±7.2	CPB-Cardiac surgery	10/10	Sevoflurane	Midazolam	SRO ₂ ,SPO ₂ ,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)O ₂ ,O ₂ ER%,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 ₂ ER%,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
Jiyong 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, CMRO₂, D(a-j)O₂, O₂ER%, and SjvO₂% 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 (Figure 3 and 4).

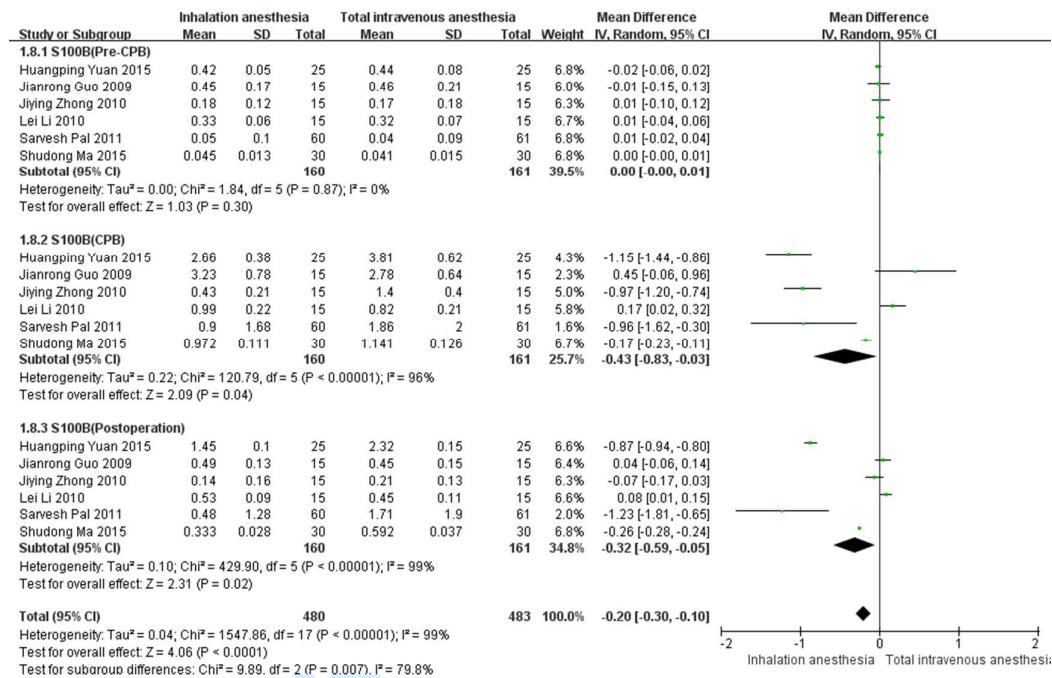


Figure 2. Forest plot showing the meta-analysis outcomes of the S100B between

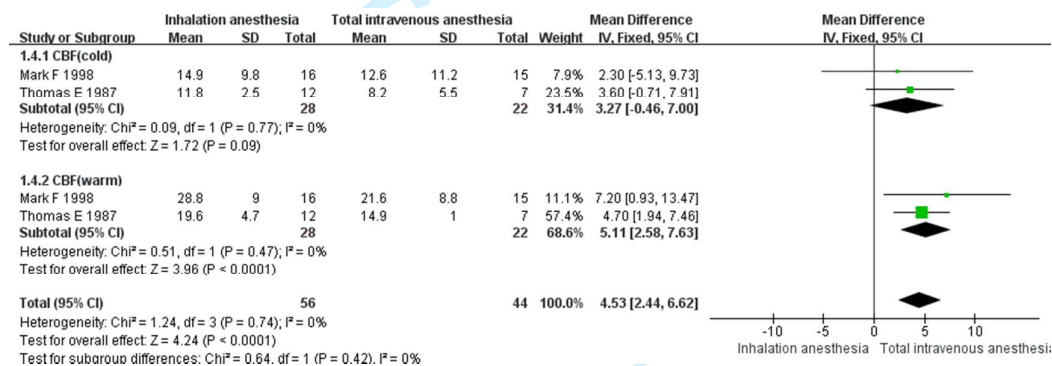


Figure 3. Forest plot showing the meta-analysis outcomes of the CBF between inhalation anesthesia and TIVA group.

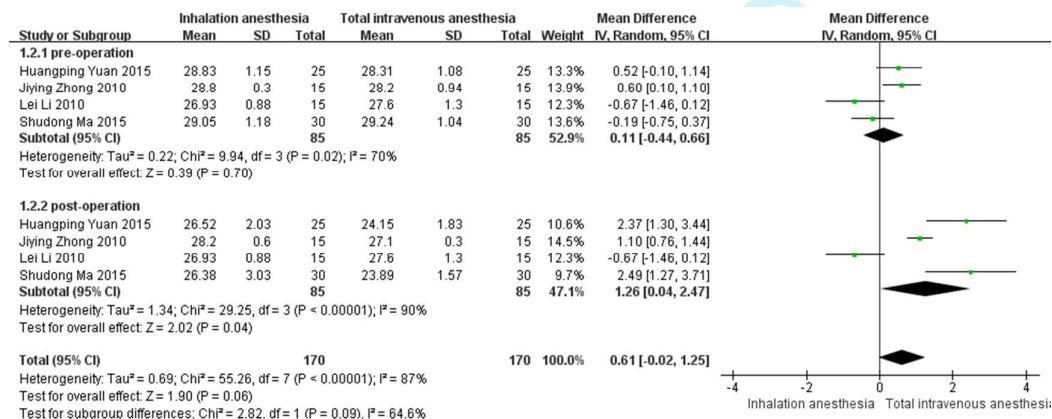


Figure 4. Forest plot showing the meta-analysis outcomes of the MMSE score between inhalation anesthesia and TIVA group.

There was no significant difference in CMRO₂, D(a-j)O₂, O₂ER%, and S_{jv}O₂% during operation between inhalation anesthesia group and TIVA group (Figure 5,6,7,8).

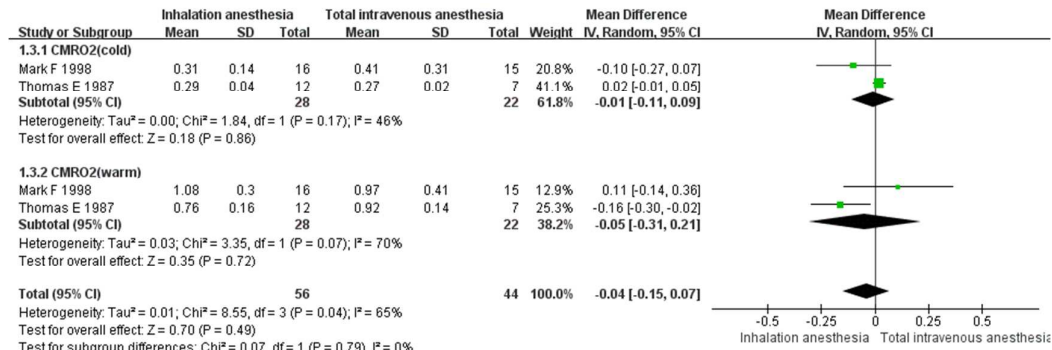


Figure 5. Forest plot showing the meta-analysis outcomes of the CMRO₂ between inhalation anesthesia and TIVA group.

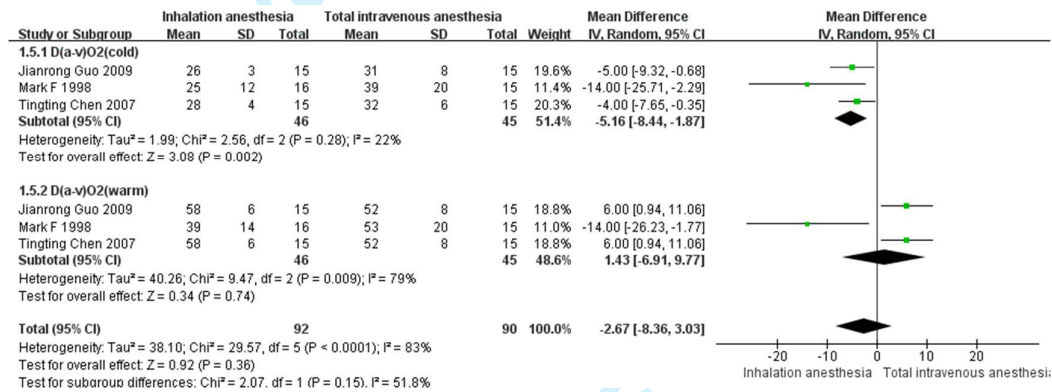


Figure 6. Forest plot showing the meta-analysis outcomes of the D(a-v)O₂ between inhalation anesthesia and TIVA group.

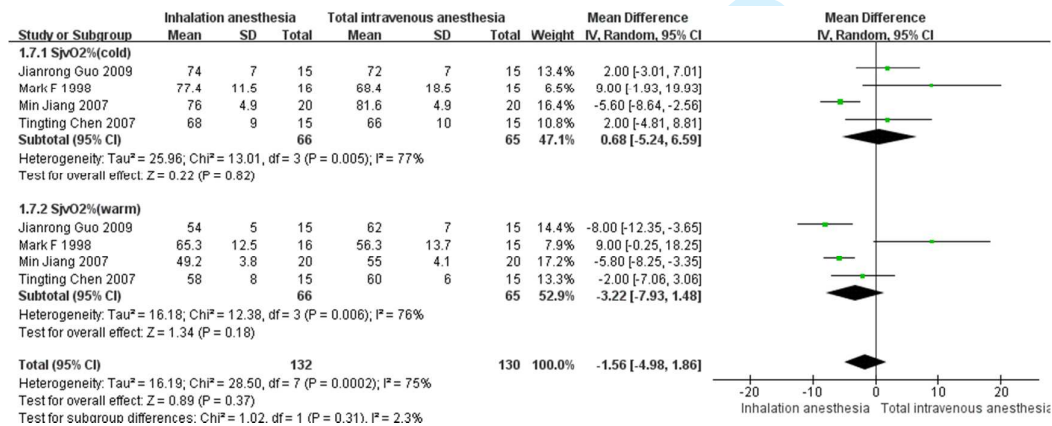


Figure 7. Forest plot showing the meta-analysis outcomes of the S_{ijv}O₂% between inhalation anesthesia and TIVA group.

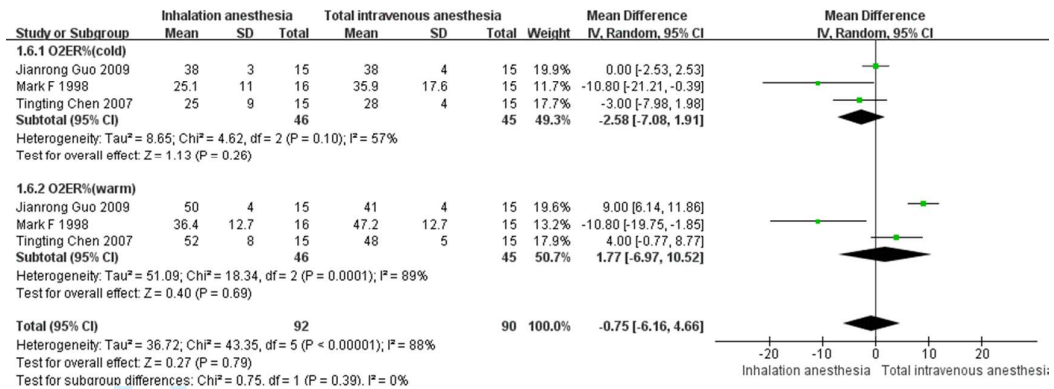


Figure 8. Forest plot showing the meta-analysis outcomes of the O₂ER% between inhalation anesthesia and TIVA group.

Egger's regression test of S100B levels, MMSE scores, CMRO₂, D(a-j)O₂, O₂ER%, and S_{ijv}O₂% 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(CMRO ₂)	-1.85	6.10	-0.30	0.79	[-28.16 24.41]
bias(D(a-j)O ₂)	186.01	99.93	1.86	0.14	[-91.44 463.46]
bias(O ₂ ER%)	13.87	6.58	3.63	0.12	[5.59 42.14]
bias(S _{ijv} O ₂ %)	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).

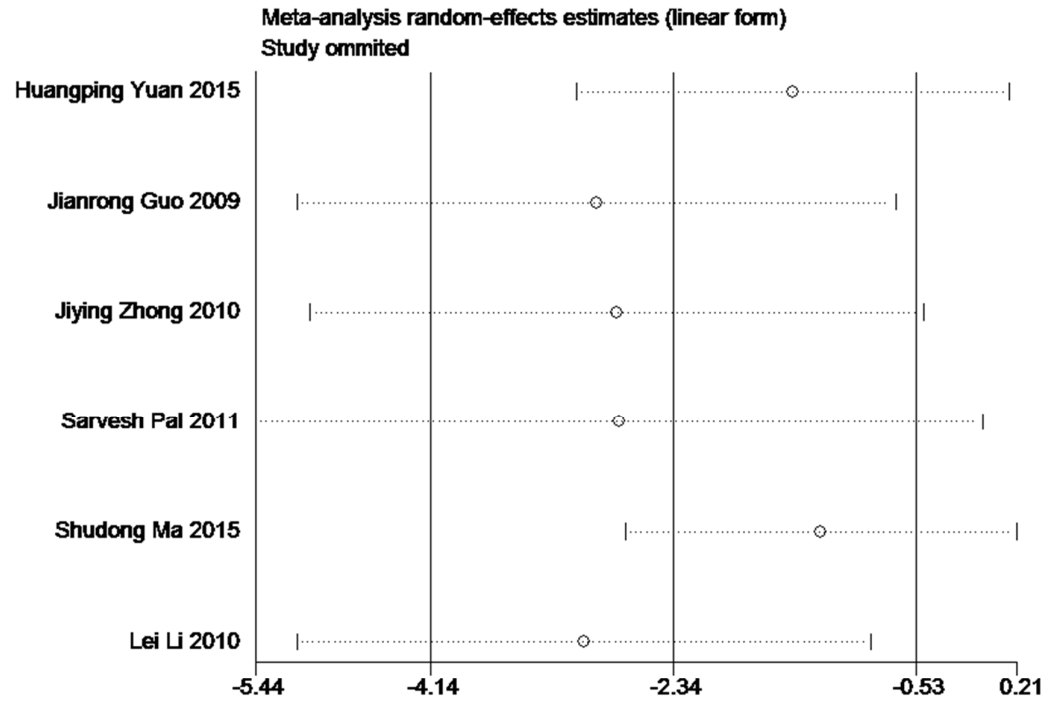


Figure 9. The plot of sensitivity analysis of S100B.

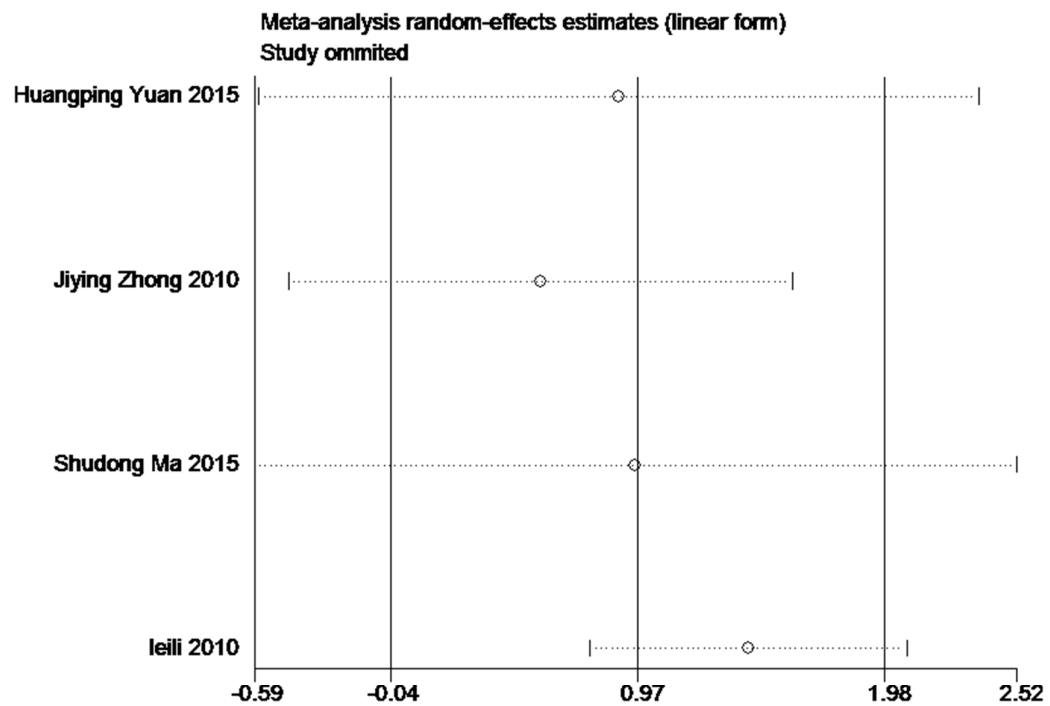


Figure 10. The plot of sensitivity analysis of MMSE score.

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 S100B has 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

1
2
3
4 postoperative MMSE score of patients in inhalation anesthesia group was
5
6 significantly higher than that of TIVA group ($P < 0.05$)^[17, 24, 28]. As we know,
7
8 although MMSE is relative simple, it is one of the most commonly used
9
10 methods for clinical evaluation of cognitive function. These results
11
12 suggest that compared to TIVA, inhalation anesthesia may maintain
13
14 better postoperative cognitive function for patients undergoing cardiac
15
16 surgery with CPB.
17
18
19

20
21 For the secondary outcomes, the meta-analysis showed that several
22
23 outcomes, such as $D(a-j)O_2$, $O_2ER\%$, $SjvO_2\%$, were not significantly
24
25 different between TIVA and inhalation anesthesia groups. However, we
26
27 found that in many studies cerebral metabolic rate of oxygen in patients
28
29 receiving inhalation anesthetics was consistently lower than that in
30
31 patients receiving TIVA. Also, the intraoperative CBF in inhalation
32
33 anesthesia group was significantly higher than that in TIVA
34
35 group ($P < 0.05$)^[19, 20]. As we know, the lower ratio of global cerebral
36
37 oxygen and adequate cerebral blood supply is an important mechanism
38
39 for interpreting the cerebral protection^[33]. The neuroprotection effects
40
41 may be mediated by favourable expression of some protective and
42
43 anti-protective proteins, to inhibit extracellular excitatory
44
45 neurotransmitter accumulation and systemic inflammatory response. Thus,
46
47 the results of $CMRO_2$ and CBF can strengthen the finding that the
48
49 inhalation anesthesia may provide better neuroprotection than TIVA.
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 Because a series of neurological complications after cardiac surgery
5 with CPB, various techniques of neurologic protection including deep
6 hypothermic cardiopulmonary bypass^[34], embolic filtering
7 device^[35], monitoring equipment (transcranial doppler and near-infrared
8 spectroscopy)^[36] and pharmacological therapy have been developed.
9
10 Meanwhile, increased attention was paid to anesthetics in neurologic
11 protection. Both of inhalation anesthesia and TIVA are reported having
12 cerebral protection for patients undergoing cardiac surgery with
13 CPB^[37-39]. However, it is still unclear which type of anesthesia can provide
14 better cerebral protection for the patients. Based on this meta-analysis, the
15 results strongly supports that inhalation anesthesia may be superior to
16 TIVA in cerebral protection.
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32

33
34 Experimental data suggest that direct positive effects of volatile
35 anesthetics may be caused by various application methods including
36 pre-conditioning and post-conditioning mechanisms^[40, 41], which
37 attenuate apoptosis and necrosis of cerebral neuron, and reduce
38 neurological dysfunction after ischaemia. Moreover, the contribution of
39 inhalation agents to preserving satisfactory haemodynamics may ensure
40 adequate perfusion and oxygenation of other organ systems^[42-45] and
41 improve the chances for recovery and survival after surgery. All these
42 effects can be expanded well beyond the immediate perioperative
43 periodon account of anesthetics-induced neuroprotection that can be long
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 lasting^[46, 47]. Additionally, a recent meta-analysis found that in cardiac
4 surgery, when compared to TIVA, inhalation anesthesia was associated
5 with major benefits in outcome, including reduced mortality, as well as
6 lower incidence of pulmonary and other complications. Therefore, based
7 on the previous findings and the current meta-analysis, it is speculated
8 that inhalation anesthesia have the potential to serve as a preferential
9 anesthesia strategy for patients.
10
11
12
13
14
15
16
17
18
19

20
21 Several limitations should be considered in our study. Firstly, the
22 sample size of the included studies was relatively small and the total
23 number of cases is very limited. Secondly, there was heterogeneity in
24 some of our results. Because of the included trials based on different
25 countries and hospitals, it was unable to avoid the effects of race, age,
26 gender and underlying disease of patients in these studies. Therefore,
27 the findings of the current study were limited by the overall low quality
28 of evidence and lack of robustness in higher-quality trials. Thirdly, the
29 current study focused on the overall comparison between inhalation
30 anesthesia and TIVA, and in the included studies different inhalation
31 anesthetics (isoflurane, desflurane, or sevoflurane) and intravenous
32 anesthetics (sodium thiopental, propofol, etc.) were studied. And because
33 of the shortage number of reported clinical trials, limited outcome data
34 could be considered for subgroup analysis. Therefore, further studies with
35 larger sample sizes are needed to demonstrate which anesthetics is the
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

Funding

This study was supported by a grant from the National Natural Science Foundation of China (No.81571870) and the Natural Science Foundation Project of Chongqing (cstc20136jjB10026).

Competing interests The authors declare no conflict of interest.

Data sharing statement No additional data are available.

Reference

- [1] Gravlee GP DRFea. Cardiopulmonary Bypass Principles and Practice. *Br J Anaesth* 2008;100(5): 732.
- [2] Shroyer AL, Coombs LP, Peterson ED, et al. The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. *Ann Thorac Surg* 2003;75(6): 1856-64.
- [3] Yoon BW, Bae HJ, Kang DW, et al. Intracranial cerebral artery disease as a risk factor for central nervous system complications of coronary artery bypass graft surgery. *Stroke* 2001;32(1): 94-9.
- [4] Wimmer-Greinecker G, Matheis G, Brieden M, et al. Neuropsychological changes after cardiopulmonary bypass for coronary artery bypass grafting. *Thorac Cardiovasc Surg* 1998;46(4): 207-12.
- [5] Blumenthal JA, Mahanna EP, Madden DJ, et al. Methodological issues in the assessment of neuropsychologic function after cardiac surgery. *Ann Thorac Surg* 1995;59(5): 1345-50.
- [6] Pape M, Engelhard K, Eberspacher E, et al. The long-term effect of sevoflurane on neuronal cell damage and expression of apoptotic factors after cerebral ischemia and reperfusion in rats. *Anesth Analg* 2006;103(1): 173-9.
- [7] Sakai H, Sheng H, Yates RB, et al. Isoflurane provides long-term protection against focal cerebral ischemia in the rat. *Anesthesiology* 2007;106(1): 92-9.
- [8] Selman WR, Spetzler RF, Roessmann UR, et al. Barbiturate-induced coma therapy for focal cerebral ischemia. Effect after temporary and permanent MCA occlusion. *J Neurosurg* 1981;55(2): 220-6.
- [9] Iwata T, Inoue S, Kawaguchi M, et al. Comparison of the effects of sevoflurane and propofol on cooling and rewarming during deliberate mild hypothermia for neurosurgery. *Br J Anaesth* 2003;90(1): 32-8.
- [10] Schell RM, Cole DJ. Cerebral monitoring: jugular venous oximetry. *Anesth Analg* 2000;90(3): 559-66.
- [11] Sagara Y, Hendler S, Khoh-Reiter S, et al. Propofol hemisuccinate protects neuronal cells from oxidative injury. *J Neurochem* 1999;73(6): 2524-30.
- [12] Wang H, Lu S, Yu Q, et al. Sevoflurane preconditioning confers neuroprotection via anti-inflammatory effects. *Elite Ed* 2011;1(3): 604-15.
- [13] McAuliffe JJ, Loepke AW, Miles L, et al. Desflurane, isoflurane, and sevoflurane provide limited neuroprotection against neonatal hypoxia-ischemia in a delayed preconditioning paradigm. *Anesthesiology* 2009;111(3): 533-46.
- [14] Moher D1, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097.
- [15] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11): 1539-58.
- [16] Min J, Yanlin B. Target controlled infusion of propofol in shallow perioperative cardiopulmonary bypass for brain protection. *Int J Clin Exp Med* 2007;4(6): 120-121.
- [17] Huaping Y. Two methods of anesthesia of CPB heart valve replacement patients plasma level and the influence of cognitive function according to beta. *Shandong Med* 2015;55(15): 71-72.
- [18] Lei L, Weifu L, Jianchun F, et al. Effects of different anesthesia on cognition function in geriatric patients following off-pump coronary artery bypass grafting. *Chin J Geriatr Heart Brain Vessel Dis* 2010;12 (11): 1002-1004.
- [19] Newman MF, Croughwell ND, White WD, et al. Pharmacologic electroencephalographic suppression during cardiopulmonary bypass: a comparison of thiopental and isoflurane. *Anesth Analg* 1998;86(2): 246-51.
- [20] Woodcock TE, Murkin JM, Farrar JK, et al. Pharmacologic EEG suppression during cardiopulmonary bypass: cerebral hemodynamic and metabolic effects of thiopental or isoflurane during hypothermia and normothermia. *Anesthesiology* 1987;67(2): 218-24.
- [21] Guclu CY, Unver S, Aydinli B, et al. The effect of sevoflurane vs. TIVA on cerebral oxygen saturation during cardiopulmonary bypass--randomized trial. *Adv Clin Exp Med* 2014;23(6): 919-24.
- [22] Tingting C, Gang W, Qi Z, et al. The comparison between isoflurane and propofol with effect on cerebral

- protection in cardiac valve replacement Surgery. *Chin J ECC* 2007;5(2): 91-93+117.
- [23] Jianrong G, Donglin J, Liyuan R, et al. Isoflurane and propofol for extracorporeal circulation open-heart surgery in patients with a comparative study of perioperative cerebral protection. *Chin J Clin Pharmacol Ther* 2009;14(7): 812-817.
- [24] Shudong M, Propofol and seven halothane Anesthesia for experacorporeal circulation of brain protection effect comparison. *Chin & F Med treatment* 2015;12(9): 145-146
- [25] Singh SP, Kapoor PM, Chowdhury U, et al. Comparison of S100beta levels, and their correlation with hemodynamic indices in patients undergoing coronary artery bypass grafting with three different anesthetic techniques. *Ann Card Anaesth* 2011;14(3): 197-202.
- [26] Kanbak M, Saricaoglu F, Avci A, et al. Propofol offers no advantage over isoflurane anesthesia for cerebral protection during cardiopulmonary bypass: a preliminary study of S-100beta protein levels. *Can J Anaesth* 2004;51(7): 712-7.
- [27] Baki ED, Aldemir M, Kokulu S, et al. Comparison of the effects of desflurane and propofol anesthesia on the inflammatory response and s100beta protein during coronary artery bypass grafting. *Inflammation* 2013;36(6): 1327-33.
- [28] Jiying Z, Feng X, Xianjie W, et al. Brain protection of desflurane in old patients undergoing coronary artery bypass grafting. *Chin J New Drugs Clin Rem* 2010;29(11):847-849.
- [29] Wang DD, Bordey A. The astrocyte odyssey. *Prog Neurobiol* 2008;86(4): 342-67.
- [30] An SA, Kim J, Kim OJ, et al. Limited clinical value of multiple blood markers in the diagnosis of ischemic stroke. *Clin Biochem* 2013;46(9): 710-5.
- [31] Kuzumi E, Vuylsteke A, Guo X, et al. Serum S100 protein as a marker of cerebral damage during cardiac surgery. *Br J Anaesth* 2000;85(6): 936-7.
- [32] Rasmussen LS, Christiansen M, Eliassen K, et al. Biochemical markers for brain damage after cardiac surgery -- time profile and correlation with cognitive dysfunction. *Acta Anaesthesiol Scand* 2002;46(5): 547-51.
- [33] Goldman S, Sutter F, Ferdinand F, et al. Optimizing intraoperative cerebral oxygen delivery using noninvasive cerebral oximetry decreases the incidence of stroke for cardiac surgical patients. *Heart Surg Forum* 2004;7: 376-381.
- [34] Nathan HJ, Rodriguez R, Wozny D, et al. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: five-year follow-up of a randomized trial. *J Thorac Cardiovasc Surg* 2007;133(5): 1206-11.
- [35] Djaiani G, Fedorko L, Borger MA, et al. Continuous-flow cell saver reduces cognitive decline in elderly patients after coronary bypass surgery. *Circulation* 2007;116(17): 1888-95.
- [36] Florio P, Abella R, Marinoni E, et al. Adrenomedullin blood concentrations in infants subjected to cardiopulmonary bypass: correlation with monitoring parameters and prediction of poor neurological outcome. *Clin Chem* 2008;54(1): 202-6.
- [37] Schmid E, Krajewski S, Bachmann D, et al. The volatile anesthetic sevoflurane inhibits activation of neutrophil granulocytes during simulated extracorporeal circulation. *Int Immunopharmacol* 2012;14(2): 202-8.
- [38] Kawamura T, Kadosaki M, Nara N, et al. Effects of sevoflurane on cytokine balance in patients undergoing coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth* 2006;20(4): 503-8.
- [39] Nader ND, Karamanoukian HL, Reedy RL, et al. Inclusion of sevoflurane in cardioplegia reduces neutrophil activity during cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2006;20(1): 57-62.
- [40] McMurtrey RJ, Zuo Z. Isoflurane preconditioning and postconditioning in rat hippocampal neurons. *Brain Res* 2010;1358: 184-90.

- 1
2
3 [41] Lee JJ, Li L, Jung HH, et al. Postconditioning with isoflurane reduced ischemia-induced brain injury in rats.
4 *Anesthesiology* 2008;108(6): 1055-62.
5
6 [42] Julier K, da SR, Garcia C, et al. Preconditioning by sevoflurane decreases biochemical markers for
7 myocardial and renal dysfunction in coronary artery bypass graft surgery: a double-blinded,
8 placebo-controlled, multicenter study. *Anesthesiology* 2003;98(6): 1315-27.
9
10 [43] Kim M, Kim M, Kim N, et al. Isoflurane mediates protection from renal ischemia-reperfusion injury via
11 sphingosine kinase and sphingosine-1-phosphate-dependent pathways. *Am J Physiol Renal Physiol* 2007;
12 293(6): F1827-35.
13 [44] Lee HT, Kim M, Kim J, et al. TGF-beta1 release by volatile anesthetics mediates protection against renal
14 proximal tubule cell necrosis. *Am J Nephrol* 2007;27(4): 416-24.
15 [45] Beck-Schimmer B, Breitenstein S, Urech S, et al. A randomized controlled trial on pharmacological
16 preconditioning in liver surgery using a volatile anesthetic. *Ann Surg* 2008;248(6): 909-18.
17 [46] Li H, Yin J, Li L, et al. Isoflurane postconditioning reduces ischemia-induced nuclear factor-kappaB
18 activation and interleukin 1beta production to provide neuroprotection in rats and mice. *Neurobiol Dis* 2013;
19 1(54): 216-24.
20 [47] Zuo Z. A novel mechanism for sevoflurane preconditioning-induced neuroprotection. *Anesthesiology* 2012;
21 117(5): 942-4.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



PRISMA 2009 Checklist

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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

Page 1 of 2

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

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

For more information, visit: www.prisma-statement.org.

Page 2 of 2

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014629.R1
Article Type:	Research
Date Submitted by the Author:	27-Apr-2017
Complete List of Authors:	Chen, Feng Duan, You Wu, Xi Zuo, Yi Li, Hong; Xinqiao Hospital, Third Military Medical University, Anesthesiology
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Neurology
Keywords:	Anaesthesia in cardiology < ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Anaesthesia in neurology < ANAESTHETICS

SCHOLARONE™
Manuscripts

1
2
3
4 1
5
6 2
7
8
9 3
10
11 4
12
13
14 5
15
16 6
17
18
19 7
20
21 8
22 9
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

Feng Chen^a, Guangyou Duan^a, Zhuoxi Wu^a, Zhiyi Zuo^b, Hong Li^{*}

^a Department of Anesthesiology, Xinqiao Hospital, Third Military Medical University, Chongqing, 400037, China

^b Department of Anesthesiology, University of Virginia, Charlottesville, Virginia, USA

* Corresponding author at: Department of Anesthesiology, Xinqiao Hospital, Third Military Medical University, Chongqing, China. Email: lh78553@163.com

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

1 meta-analysis.

2 **Result(s):** A total of 1485 studies were identified. After eliminating
3 duplicate articles and screening titles and abstracts, 445 studies were
4 potentially eligible. After applying exclusion criteria (full texts reported
5 as abstracts, review article, no control case, lack of outcome data, etc.),
6 13 studies were selected for review. Our results demonstrated that the
7 primary outcome related to S100B level in the inhalation anaesthesia
8 group was significantly lower than in the TIVA group at the end of CPB
9 and 24 hours postoperatively (weighted mean difference [WMD]; 95%
10 confidence interval [CI]: -0.41 [-0.81, -0.01], -0.32 [-0.59, -0.05],
11 respectively). Among secondary outcome variables,
12 mini-mental state examination (MMSE) scores of the inhalation
13 anaesthesia group were significantly higher than those of the TIVA group
14 24 hours after operation [WMD (95%CI): 1.87 (0.82, 2.92)], cerebral
15 blood flow (CBF) in the inhalation anaesthesia group was significantly
16 higher than in the TIVA group at rewarming during CPB [WMD
17 (95%CI): 5.11 (2.58, 7.63)], and no significant difference was found in
18 cerebral metabolic rate of oxygen consumption (CMRO₂), arteriovenous
19 oxygen content difference [D(a-v)O₂], cerebral oxygen extraction ratio
20 (O₂ER), and jugular bulb venous oxygen saturation (SjvO₂), which were
21 assessed at cooling and rewarming during CPB.

22 **Conclusion(s):** This study demonstrates that anaesthesia with volatile

1 agents appears to provide better cerebral protection than TIVA for
2 patients undergoing cardiac surgery with CPB, suggesting that inhalation
3 anaesthesia may be more suitable for patients undergoing cardiac surgery.

4 **Keywords:** anaesthesia; cerebral protection; cardiac surgery;
5 cardiopulmonary bypass.

6 Strengths and limitations of this study

- 7 1. This is the first systematic review and meta-analysis to compare the
8 neuroprotective effects of inhalation anaesthesia and those of total
9 intravenous anaesthesia (TIVA) in cardiac surgery with
10 cardiopulmonary bypass (CPB).
- 11 2. This meta-analysis indicates that inhalation anaesthesia may produce
12 better cerebral protection than TIVA for patients undergoing cardiac
13 surgery with CPB.
- 14 3. The methodological quality of each study was assessed using the
15 Jadad Scale for randomised controlled trials. Meta-analysis,
16 heterogeneity test, bias assessment, sensitivity analysis, and subgroup
17 analysis were also conducted.
- 18 4. Because of the shortage of reported clinical trials, limited outcome
19 data could be considered for subgroup analysis. The strength of the
20 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

1 with CPB is unknown. Since inhalation anaesthesia and TIVA are the
2 most commonly used strategies for general anaesthesia, it is important to
3 clarify this issue. Moreover, since it is difficult to include patients in
4 neurologic dysfunction studies for cardiac surgery with CPB, the sample
5 size of these previous studies was generally small. For these reasons, it is
6 necessary to systematically review the available literature and perform a
7 meta-analysis to compare the neuroprotective effects of inhalation
8 anaesthesia and TIVA.

9 10 **Materials and Methods**

11 The current systematic review and meta-analysis was carried out in
12 accordance with the preferred reporting items for systematic reviews and
13 meta-analyses (PRISMA) reporting guidelines for intervention trials^[15].

14 15 **Literature search**

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

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

12 13 **Eligibility criteria**

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

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

1

2 **Outcomes**

3 The primary outcome of the current study was S100B protein level
4 which was detected at pre-CPB, post-CPB and 24 hours postoperatively.

5 The secondary outcomes included mini-mental state examination (MMSE)
6 scores assessed pre- and 24 hours postoperatively, and cerebral blood
7 flow (CBF), cerebral metabolic rate of oxygen consumption (CMRO₂),
8 jugular bulb venous oxygen saturation (SjvO₂), arteriovenous oxygen
9 content difference [D(a-v)O₂] and cerebral oxygen extraction ratio (O₂ER)
10 were tested at cooling and rewarming during CPB.

11

12 **Study selection and validity assessment**

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

21

22 **Data extraction and statistical analysis**

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

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

17 Results

18 Characteristics of the included studies

19 A total of 1485 studies were retrieved. Of these, 1148 remained after
20 duplicate articles were eliminated. After screening titles and abstracts,
21 445 studies were potentially eligible. Based on the exclusion criteria, 13
22 studies were ultimately selected (Fig. 1). All reviewers agreed to include

1 all 13 papers. Although all of these randomized controlled trials (RCTs)
 2 were considered to have a low risk of bias, nine studies included no
 3 details on the method of random sequence generation and allocation
 4 [17-25]. Only one study provided the details about the blinding of the data
 5 collection^[26].

6 'Inhalation anaesthesia' was defined as a group receiving a volatile
 7 agent like isoflurane, sevoflurane, or desflurane. In the included studies,
 8 patients in the 'volatile anaesthesia' group had not received propofol,
 9 thiopental, or ketamine during the surgery and CPB. The patients in the
 10 'Total Intravenous Anaesthesia' (TIVA) group had received only
 11 intravenous anaesthetics, but not volatile agents. These studies involved
 12 549 patients, including 272 patients with inhalation anaesthesia and 277
 13 patients with TIVA (Table 1). Patients' age ranges in 'inhalation
 14 anaesthesia' and 'TIVA' groups were 44 to 75 years and 43 to 74 years,
 15 respectively. The mean age of patients was unavailable for three studies
 16 [17-19]. All the articles had reported exclusion/inclusion criteria [17-29]. Of
 17 these, seven studies had used isoflurane vs. TIVA [17, 19-21, 23, 24, 27], four
 18 studies had used sevoflurane vs. TIVA [18, 22, 25, 26], and two studies had
 19 used desflurane vs. TIVA [28, 29], in patients.

20

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 ₂ ER%,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 ₂ ER%,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 ₂ ER%,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
Jiyong 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; CMRO₂, cerebral metabolic rate of oxygen consumption; D(a-v)O₂, arteriovenous oxygen content difference; O₂ER, cerebral oxygen extraction; SjvO₂, 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).

study	Jadad Score				
	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
Jiyong 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, CMRO₂, D(a-v)O₂, O₂ER, and S_{ijv}O₂ 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 CMRO₂, D(a-v)O₂, O₂ER, and S_{ijv}O₂ 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, CMRO₂, D(a-v)O₂, O₂ER, and S_{ijv}O₂ 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 ₂ ER%)	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; CMRO₂, cerebral metabolic rate of oxygen consumption; 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. 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,}

1 23, 24, 28]. These results underline the existing debate on which anaesthetic
2 approach is better for the patients. However, in the current systematic
3 review and meta-analysis, the results of primary and secondary outcomes
4 showed that inhalation anaesthesia might be superior to TIVA during
5 cardiac surgery with CPB.

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

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

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

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

22 Experimental data suggest that direct positive effects of volatile

1 anaesthetics may be caused by various pre-conditioning and
2 post-conditioning mechanisms [36, 37], which attenuate apoptosis and
3 necrosis of cerebral neurons, thereby reducing neurological dysfunction
4 after ischaemia. Moreover, the contribution of inhalation agents in
5 preserving satisfactory haemodynamics may ensure adequate perfusion
6 and oxygenation of other organ systems, [38-41] and improve the chances
7 for recovery and survival after surgery. All these effects can be expanded
8 well beyond the immediate perioperative period because of
9 anaesthetic-induced neuroprotection that can be long lasting [42, 43].
10 Additionally, a recent meta-analysis found that in cardiac surgery [44], as
11 compared to TIVA, inhalation anaesthesia was associated with major
12 benefits in outcome, including reduced mortality, as well as a lower
13 incidence of pulmonary and other complications. Therefore, based on
14 previous findings and the current meta-analysis, it is speculated that
15 inhalation anaesthesia has the potential to serve as a preferential
16 anaesthesia strategy for cardiac patients.

17 Our study has few limitations. First, the sample size of the included
18 studies was relatively small and the total number of cases is very limited.
19 Second, there was heterogeneity in some of our results. Since trials were
20 based in different countries and hospitals, we were unable to avoid the
21 effects of race, age, gender, and underlying disease(s) of patients in our
22 study. Therefore, findings of the current study

1 were limited by the overall low quality of evidence and the lack of robust
2 data. Third, our study focused on the overall comparison between
3 inhalation anaesthesia and TIVA, and different inhalation (isoflurane,
4 desflurane, or sevoflurane) and intravenous (sodium thiopental, propofol,
5 etc.) anaesthetics were investigated in the included studies. Because of
6 the limited number of reported clinical trials, limited outcome data could
7 be considered for subgroup analysis. Therefore, further studies with
8 larger sample sizes are needed to demonstrate which anaesthetics are
9 more beneficial for cardiac patients.

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

16 **Authors' contributions**

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

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

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

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

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

22 All authors have reviewed the manuscript.

Funding

This study was supported by a grant from the National Natural Science Foundation of China (No. 81571870) and the Natural Science Foundation Project of Chongqing (cstc20136jjB10026).

Competing interests: The authors declare no conflicts of interest.

Data sharing statement: No additional data are available.

References

- [1] Lamy A, Devereaux PJ, Prabhakaran D, et al. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. *N Engl J Med*. 2013. 368(13): 1179-88.
- [2] Lamy A, Devereaux PJ, Prabhakaran D, et al. Five-Year Outcomes after Off-Pump or On-Pump Coronary-Artery Bypass Grafting. *N Engl J Med*. 2016. 375(24): 2359-2368.
- [3] McKhann GM, Grega MA, Borowicz LM, et al. Stroke and encephalopathy after cardiac surgery: an update. *Stroke*. 2006. 37(2): 562-71.
- [4] Hogue CW, Palin CA, Arrowsmith JE. Cardiopulmonary bypass management and neurologic outcomes: an evidence-based appraisal of current practices. *Anesth Analg*. 2006. 103(1): 21-37.
- [5] Wimmer-Greinecker G, Matheis G, Brieden M, et al. Neuropsychological changes after cardiopulmonary bypass for coronary artery bypass grafting. *Thorac Cardiovasc Surg* 1998;46(4): 207-12.
- [6] Blumenthal JA, Mahanna EP, Madden DJ, et al. Methodological issues in the assessment of neuropsychologic function after cardiac surgery. *Ann Thorac Surg* 1995;59(5): 1345-50.
- [7] Pape M, Engelhard K, Eberspacher E, et al. The long-term effect of sevoflurane on neuronal cell damage and expression of apoptotic factors after cerebral ischemia and reperfusion in rats. *Anesth Analg* 2006;103(1): 173-9.
- [8] Sakai H, Sheng H, Yates RB, et al. Isoflurane provides long-term protection against focal cerebral ischemia in the rat. *Anesthesiology* 2007;106(1): 92-9.
- [9] Selman WR, Spetzler RF, Roessmann UR, et al. Barbiturate-induced coma therapy for focal cerebral ischemia. Effect after temporary and permanent MCA occlusion. *J Neurosurg* 1981;55(2): 220-6.
- [10] Iwata T, Inoue S, Kawaguchi M, et al. Comparison of the effects of sevoflurane and propofol on cooling and

- 1 rewarming during deliberate mild hypothermia for neurosurgery. *Br J Anaesth* 2003;90(1): 32-8.
- 2 [11] Dabrowski W, Rzecki Z, Czajkowski M, et al. Volatile anesthetics reduce biochemical markers of brain injury
3 and brain magnesium disorders in patients undergoing coronary artery bypass graft surgery. *J Cardiothorac*
4 *Vasc Anesth*. 2012. 26(3): 395-402.
- 5 [12] Sagara Y, Hendler S, Khoh-Reiter S, et al. Propofol hemisuccinate protects neuronal cells from oxidative
6 injury. *J Neurochem* 1999;73(6): 2524-30.
- 7 [13] Wang H, Lu S, Yu Q, et al. Sevoflurane preconditioning confers neuroprotection via anti-inflammatory effects.
8 *Elite Ed* 2011;1(3): 604-15.
- 9 [14] McAuliffe JJ, Loepke AW, Miles L, et al. Desflurane, isoflurane, and sevoflurane provide limited
10 neuroprotection against neonatal hypoxia-ischemia in a delayed preconditioning paradigm. *Anesthesiology*
11 2009;111(3): 533-46.
- 12 [15] Moher D1, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses:
13 the PRISMA statement. *PLoS Med* 2009;6(7):e1000097.
- 14 [16] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11): 1539-58.
- 15 [17] Min J, Yanlin B. Target controlled infusion of propofol in shallow perioperative cardiopulmonary bypass for
16 brain protection. *Int J Clin Exp Med* 2007;4(6): 120-121.
- 17 [18] Huaping Y. Two methods of anesthesia of CPB heart valve replacement patients plasma level and the
18 influence of cognitive function according to beta. *Shandong Med* 2015;55(15): 71-72.
- 19 [19] Lei L, Weifu L, Jianchun F, et al. Effects of different anesthesia on cognition function in geriatric patients
20 following off-pump coronary artery bypass grafting. *Chin J Geriatr Heart Brain Vessel Dis* 2010;12 (11):
21 1002-1004.
- 22 [20] Newman MF, Croughwell ND, White WD, et al. Pharmacologic electroencephalographic suppression during
23 cardiopulmonary bypass: a comparison of thiopental and isoflurane. *Anesth Analg* 1998;86(2): 246-51.
- 24 [21] Woodcock TE, Murkin JM, Farrar JK, et al. Pharmacologic EEG suppression during cardiopulmonary bypass:
25 cerebral hemodynamic and metabolic effects of thiopental or isoflurane during hypothermia and
26 normothermia. *Anesthesiology* 1987;67(2): 218-24.
- 27 [22] Guclu CY, Unver S, Aydinli B, et al. The effect of sevoflurane vs. TIVA on cerebral oxygen saturation during
28 cardiopulmonary bypass--randomized trial. *Adv Clin Exp Med* 2014;23(6): 919-24.
- 29 [23] Tingting C, Gang W, Qi Z, et al. The comparison between isoflurane and propofol with effect on cerebral
30 protection in cardiac valve replacement Surgery. *Chin J ECC* 2007;5(2): 91-93+117.
- 31 [24] Jianrong G, Donglin J, Liyuan R, et al. Isoflurane and propofol for extracorporeal circulation open-heart
32 surgery in patients with a comparative study of perioperative cerebral protection. *Chin J Clin Pharmacol Ther*
33 2009;14(7): 812-817.
- 34 [25] Shudong M, Propofol and seven halothane Anesthesia for experacorporeal circulation of brain protection
35 effect comparison. *Chin & F Med treatment* 2015;12(9): 145-146
- 36 [26] Singh SP, Kapoor PM, Chowdhury U, et al. Comparison of S100beta levels, and their correlation with
37 hemodynamic indices in patients undergoing coronary artery bypass grafting with three different anesthetic
38 techniques. *Ann Card Anaesth* 2011;14(3): 197-202.
- 39 [27] Kanbak M, Saricaoglu F, Avci A, et al. Propofol offers no advantage over isoflurane anesthesia for cerebral
40 protection during cardiopulmonary bypass: a preliminary study of S-100beta protein levels. *Can J Anaesth*
41 2004;51(7): 712-7.
- 42 [28] Baki ED, Aldemir M, Kokulu S, et al. Comparison of the effects of desflurane and propofol anesthesia on the
43 inflammatory response and s100beta protein during coronary artery bypass grafting. *Inflammation* 2013;36(6):
44 1327-33.

- 1 [29] Jiying Z, Feng X, Xianjie W, et al. Brain protection of desflurane in old patients undergoing coronary artery
2 bypass grafting. *Chin J New Drugs Clin Rem* 2010;29(11):847-849.
- 3 [30] Wang DD, Bordey A. The astrocyte odyssey. *Prog Neurobiol* 2008;86(4): 342-67.
- 4 [31] An SA, Kim J, Kim OJ, et al. Limited clinical value of multiple blood markers in the diagnosis of ischemic
5 stroke. *Clin Biochem* 2013;46(9): 710-5.
- 6 [32] Kuzumi E, Vuylsteke A, Guo X, et al. Serum S100 protein as a marker of cerebral damage during cardiac
7 surgery. *Br J Anaesth* 2000;85(6): 936-7.
- 8 [33] Rasmussen LS, Christiansen M, Eliassen K, et al. Biochemical markers for brain damage after cardiac surgery
9 -- time profile and correlation with cognitive dysfunction. *Acta Anaesthesiol Scand* 2002;46(5): 547-51.
- 10 [34] Svenmarker S, Engström KG, Karlsson T, et al. Influence of pericardial suction blood retransfusion on
11 memory function and release of protein S100B. *Perfusion*. 2004;19(6):337-43.
- 12 [35] Goldman S, Sutter F, Ferdinand F, et al. Optimizing intraoperative cerebral oxygen delivery using noninvasive
13 cerebral oximetry decreases the incidence of stroke for cardiac surgical patients. *Heart Surg Forum* 2004;7:
14 376-381.
- 15 [36] McMurtrey RJ, Zuo Z. Isoflurane preconditioning and postconditioning in rat hippocampal neurons. *Brain*
16 *Res* 2010;1358: 184-90.
- 17 [37] Lee JJ, Li L, Jung HH, et al. Postconditioning with isoflurane reduced ischemia-induced brain injury in rats.
18 *Anesthesiology* 2008;108(6): 1055-62.
- 19 [38] Julier K, da SR, Garcia C, et al. Preconditioning by sevoflurane decreases biochemical markers for
20 myocardial and renal dysfunction in coronary artery bypass graft surgery: a double-blinded,
21 placebo-controlled, multicenter study. *Anesthesiology* 2003;98(6): 1315-27.
- 22 [39] Kim M, Kim M, Kim N, et al. Isoflurane mediates protection from renal ischemia-reperfusion injury via
23 sphingosine kinase and sphingosine-1-phosphate-dependent pathways. *Am J Physiol Renal Physiol* 2007;
24 293(6): F1827-35.
- 25 [40] Lee HT, Kim M, Kim J, et al. TGF-beta1 release by volatile anesthetics mediates protection against renal
26 proximal tubule cell necrosis. *Am J Nephrol* 2007;27(4): 416-24.
- 27 [41] Beck-Schimmer B, Breitenstein S, Urech S, et al. A randomized controlled trial on pharmacological
28 preconditioning in liver surgery using a volatile anesthetic. *Ann Surg* 2008;248(6): 909-18.
- 29 [42] Li H, Yin J, Li L, et al. Isoflurane postconditioning reduces ischemia-induced nuclear factor-kappaB
30 activation and interleukin 1beta production to provide neuroprotection in rats and mice. *Neurobiol Dis* 2013;
31 1(54): 216-24.
- 32 [43] Zuo Z. A novel mechanism for sevoflurane preconditioning-induced neuroprotection. *Anesthesiology* 2012;
33 117(5): 942-4.
- 34 [44] Uhlig C, Bluth T, Schwarz K, et al. Effects of Volatile Anesthetics on Mortality and Postoperative Pulmonary
35 and Other Complications in Patients Undergoing Surgery: A Systematic Review and Meta-analysis. *Anesthesiology*.
36 2016. 124(6): 1230-45.
- 37

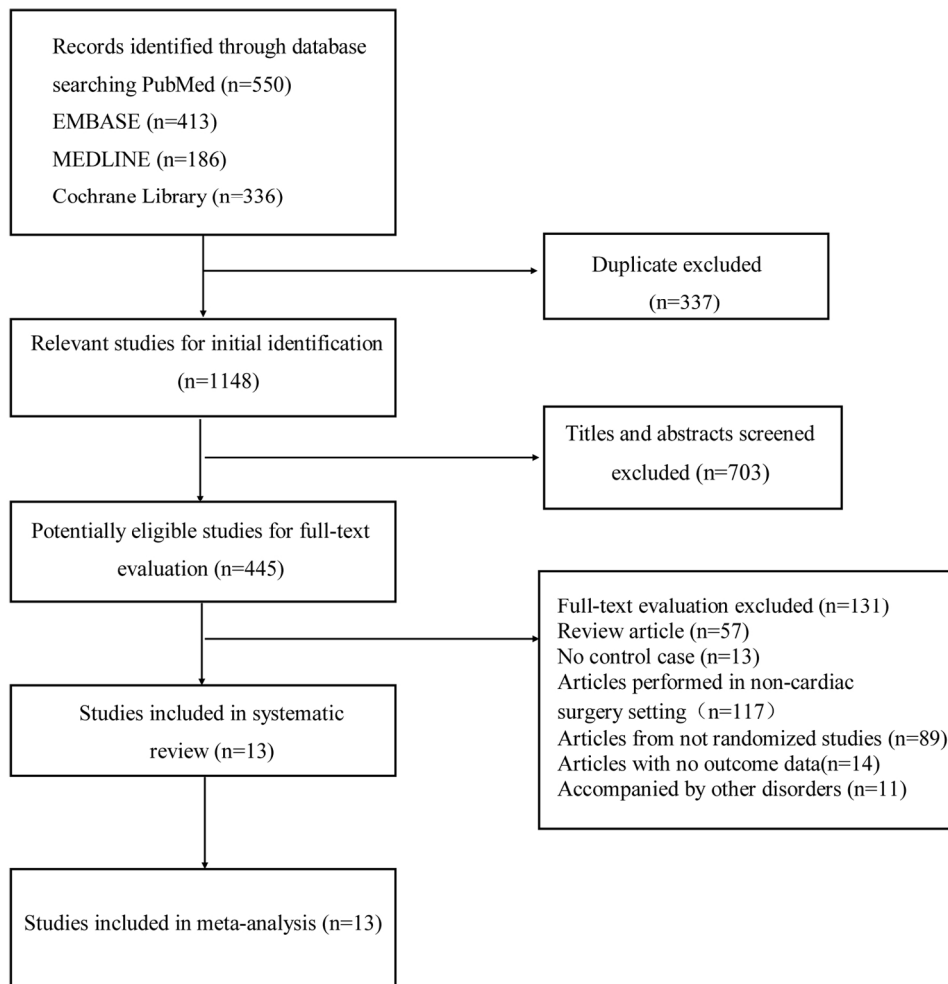


Fig. 1 Flow diagram for the selection of eligible studies

160x160mm (300 x 300 DPI)



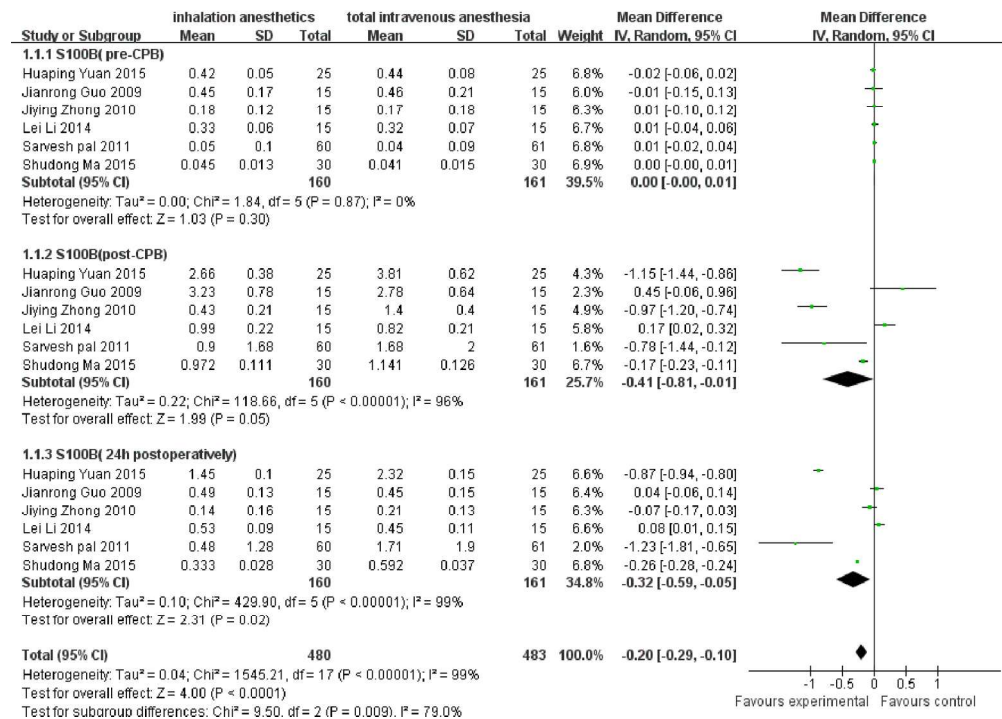


Fig. 2 Forest plot showing the meta-analysis outcomes of the difference in S100B levels of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x113mm (300 x 300 DPI)

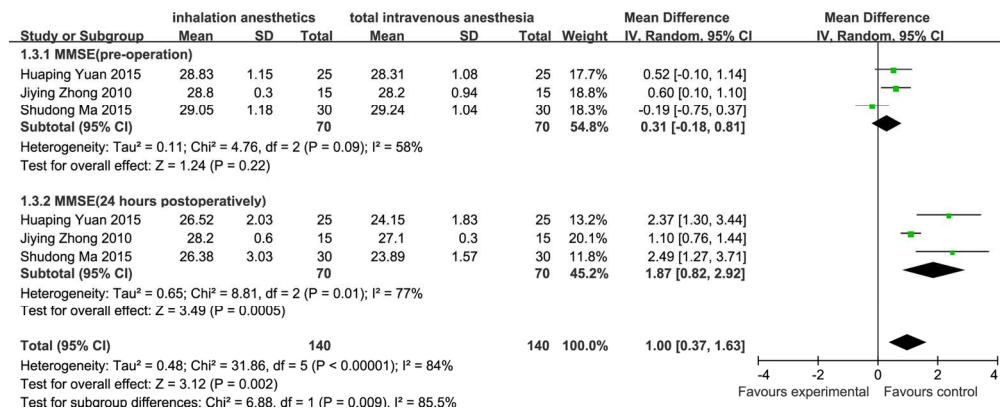


Fig. 3 Forest plot showing the meta-analysis outcomes of the difference in mini-mental state examination (MMSE) scores of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x64mm (300 x 300 DPI)

Peer review only

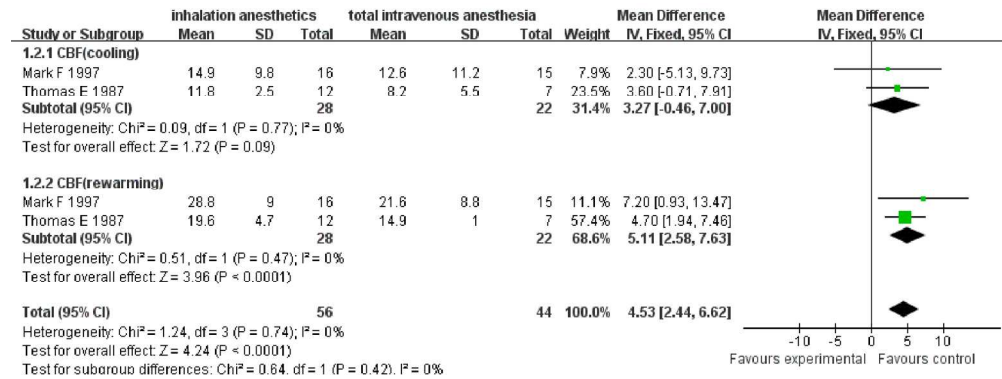


Fig. 4 Forest plot showing the meta-analysis outcomes of the difference in cerebral blood flow (CBF) of the inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x59mm (300 x 300 DPI)

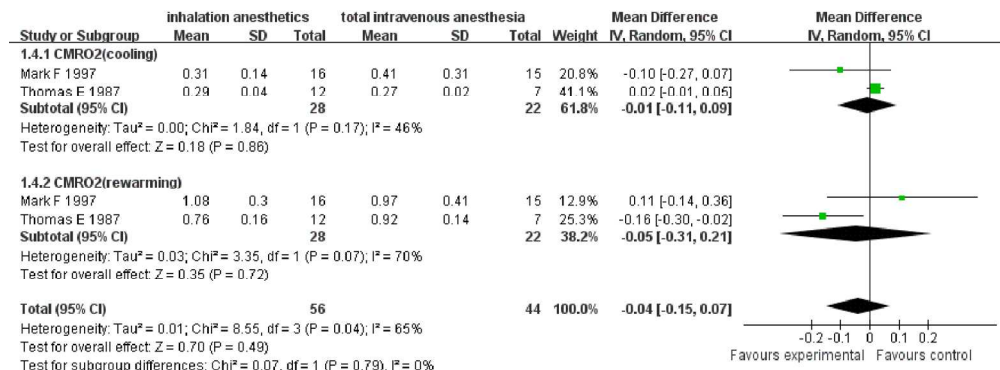


Fig. 5 Forest plot showing the meta-analysis outcomes of the difference in cerebral metabolic rate of oxygen consumption (CMRO2) of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x58mm (300 x 300 DPI)

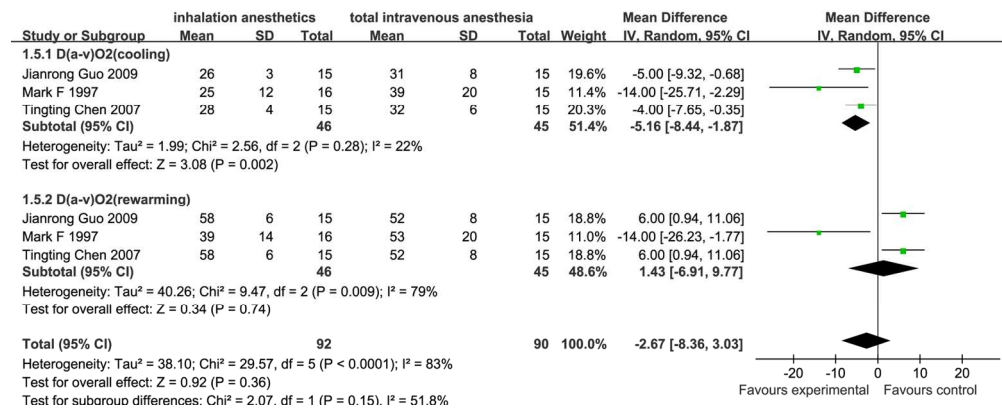


Fig. 6 Forest plot showing the meta-analysis outcomes of the difference in arteriovenous oxygen content difference [D(a-v) O₂] of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x63mm (300 x 300 DPI)

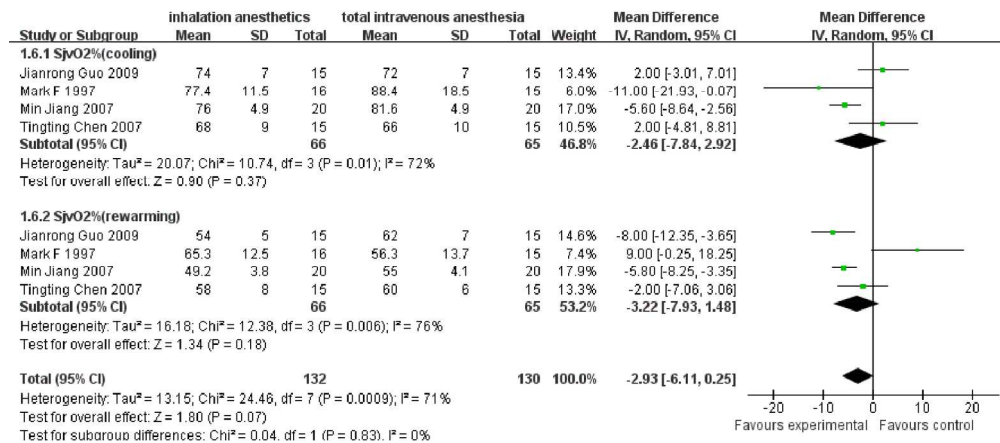


Fig. 7 Forest plot showing the meta-analysis outcomes of the difference in jugular bulb venous oxygen saturation (SjvO2) of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x69mm (300 x 300 DPI)

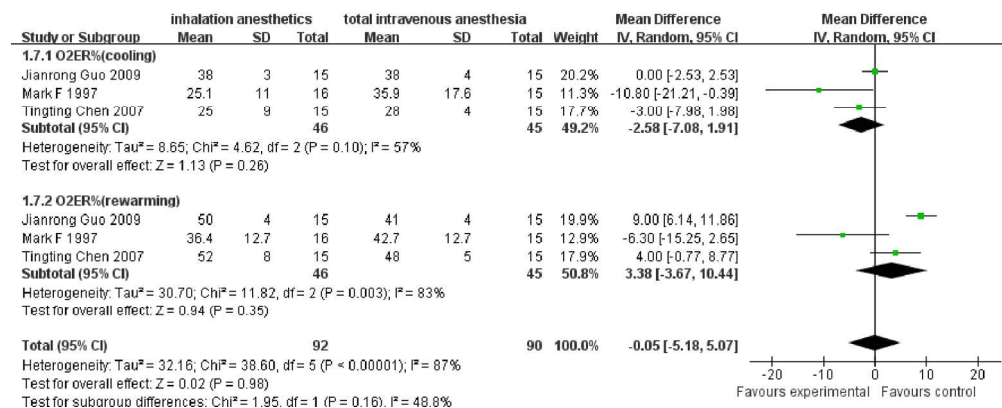


Fig. 8 Forest plot showing the meta-analysis outcomes of the difference in cerebral oxygen extraction ratio (O2ER) between inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x63mm (300 x 300 DPI)

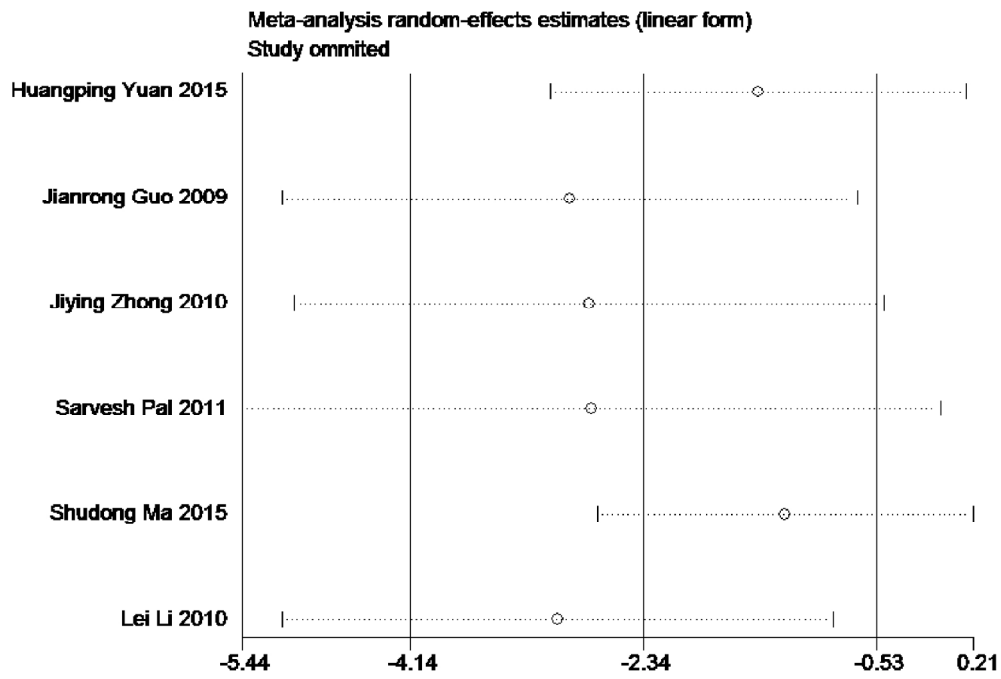


Fig. 9 The plot of sensitivity analysis of S100B levels

160x119mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

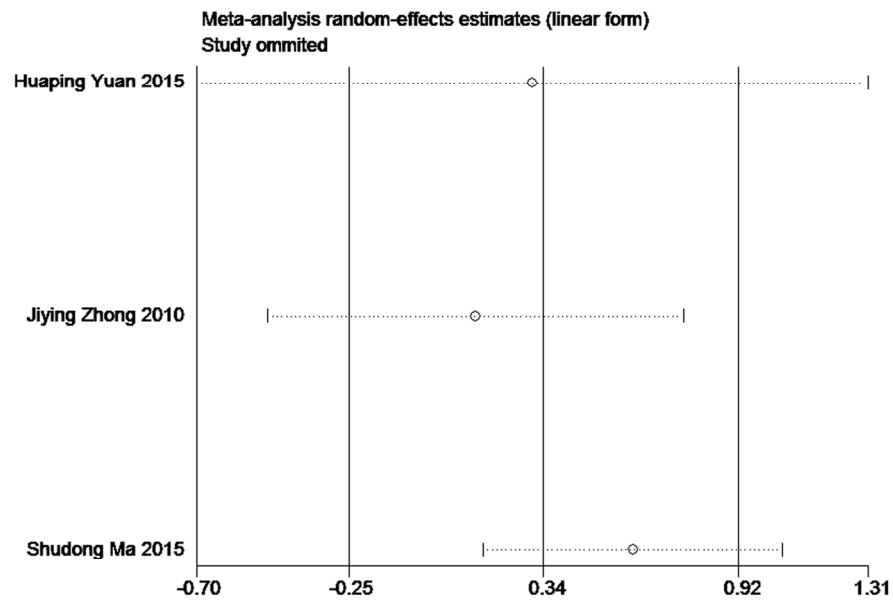


Fig. 10 The plot of sensitivity analysis of mini-mental state examination (MMSE) scores

160x106mm (300 x 300 DPI)

view only

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

1
2
3
4 Thiopentobarbital OR Thiopentone OR Bomathal OR Pentothal Sodico

5
6
7 #14 Ketamine[MeSH] OR Calypsol OR Kalips

8
9 #15 Midazolam[MeSH] OR Hydrochloride, Midazolam OR Maleate,
10
11 Midazolam

12
13 #16 OR/#10-#15

14
15
16
17 #17 randomized controlled trial [pt]

18
19
20 #18 controlled clinical trial [pt]

21
22
23 #19 randomized [tiab]

24
25
26 #20 placebo [tiab]

27
28 #21 drug therapy [sh]

29
30
31 #22 randomly [tiab]

32
33
34 #23 trial [tiab]

35
36
37 #24 groups [tiab]

38
39
40 #25 OR/#17-#24

41
42 #26 animals [mh] NOT humans [mh]

43
44
45 #27 #25 NOT #26

46
47 #28 #1 AND #5 AND #9 AND #16 AND #27
48
49
50
51
52
53
54
55
56
57
58
59
60



PRISMA 2009 Checklist

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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

Page 1 of 2

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

For more information, visit: www.prisma-statement.org.

Page 2 of 2

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014629.R2
Article Type:	Research
Date Submitted by the Author:	09-Jun-2017
Complete List of Authors:	Chen, Feng Duan, You Wu, Xi Zuo, Yi Li, Hong; Xinqiao Hospital, Third Military Medical University, Anesthesiology
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Neurology
Keywords:	Anaesthesia in cardiology < ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Anaesthesia in neurology < ANAESTHETICS

SCHOLARONE™
Manuscripts

1
2
3
4 1
5
6 2
7
8
9 3
10
11 4
12
13
14 5
15
16
17 6
18
19 7
20
21 8
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

Feng Chen^a, Guangyou Duan^a, Zhuoxi Wu^a, Zhiyi Zuo^b, Hong Li^{*}

^a Department of Anesthesiology, Xinqiao Hospital, Third Military Medical University, Chongqing, 400037, China

^b Department of Anesthesiology, University of Virginia, Charlottesville, Virginia, USA

* Corresponding author at: Department of Anesthesiology, Xinqiao Hospital, Third Military Medical University, Chongqing, China. Email: lh78553@163.com

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

1 meta-analysis.

2 **Result(s):** A total of 1485 studies were identified. After eliminating
3 duplicate articles and screening titles and abstracts, 445 studies were
4 potentially eligible. After applying exclusion criteria (full texts reported
5 as abstracts, review article, no control case, lack of outcome data, etc.),
6 13 studies were selected for review. Our results demonstrated that the
7 primary outcome related to S100B level in the inhalation anaesthesia
8 group was significantly lower than in the TIVA group after CPB and 24
9 hours postoperatively (weighted mean difference [WMD]; 95%
10 confidence interval [CI]: -0.41 [-0.81, -0.01], -0.32 [-0.59, -0.05],
11 respectively). Among secondary outcome variables,
12 mini-mental state examination (MMSE) scores of the inhalation
13 anaesthesia group were significantly higher than those of the TIVA group
14 24 hours after operation [WMD (95%CI): 1.87 (0.82, 2.92)], but no
15 significant difference was found in arteriovenous oxygen content
16 difference [D(a-v)O₂], cerebral oxygen extraction ratio (O₂ER), and
17 jugular bulb venous oxygen saturation (SjvO₂), which were assessed at
18 cooling and rewarming during CPB.

19 **Conclusion(s):** This study demonstrates that anaesthesia with volatile
20 agents appears to provide better cerebral protection than TIVA for
21 patients undergoing cardiac surgery with CPB, suggesting that inhalation
22 anaesthesia may be more suitable for patients undergoing cardiac surgery.

1
2
3
4 **Keywords:** anaesthesia; cerebral protection; cardiac surgery;
5
6 cardiopulmonary bypass.
7

8 Strengths and limitations of this study

- 9
10
11 1. This is the first systematic review and meta-analysis to compare the
12
13 neuroprotective effects of inhalation anaesthesia and those of total
14
15 intravenous anaesthesia (TIVA) in cardiac surgery with
16
17 cardiopulmonary bypass (CPB).
18
19
20
21 2. This study focused on the overall comparison between inhalation
22
23 anaesthesia and TIVA, different inhalation and intravenous
24
25 anaesthetics were investigated in the included studies.
26
27
28
29 3. The methodological quality of each study was assessed using the
30
31 Jadad Scale for randomised controlled trials. Meta-analysis,
32
33 heterogeneity test, bias assessment, sensitivity analysis, and subgroup
34
35 analysis were also conducted.
36
37
38
39 4. Because of the shortage of reported clinical trials, limited outcome
40
41 data could be considered for subgroup analysis. The strength of the
42
43 conclusion is limited by the quality and number of studies.
44
45
46
47
48
49
50
51

52 Introduction

53
54 Cardiopulmonary bypass (CPB) is a necessary and common
55
56 procedure to support the patient's circulation during cardiac surgery.
57
58
59
60

1
2
3
4 1 Although previous studies ^[1,2] reported that CPB does not increase the
5
6 2 postoperative morbidity and mortality in patients undergoing coronary
7
8 3 artery bypass graft (CABG) surgery, it was demonstrated that the
9
10 4 incidence of some postoperative complications for these patients remains
11
12 5 high. Neurological dysfunction is one of the most commonly reported
13
14 6 postoperative complications in patients undergoing cardiac surgery ^[3,4].
15
16 7 Several factors including cerebral anoxia, embolism, excessive excitatory
17
18 8 neurotransmitter release, and systemic inflammatory response have been
19
20 9 demonstrated to contribute to postoperative neurological dysfunction ^[5].
21
22 10 However, at present, there is no definitive clinical evidence regarding
23
24 11 cerebral protection for patients undergoing cardiac surgery with CPB ^[6].
25
26 12 Previous studies on animals support the hypothesis that anaesthetics can
27
28 13 produce cerebral protection ^[7-9]. Many recent studies have found that
29
30 14 anaesthetic agents may be neuroprotective and may provide cerebral
31
32 15 protection to surgery patients ^[10, 11]. However, clinical studies show that
33
34 16 the relative effects of inhalation anaesthesia or total intravenous
35
36 17 anaesthesia (TIVA) on neuroprotection in cardiac surgery with CPB
37
38 18 remain controversial and much debated ^[12-14]. Therefore, which option
39
40 19 provides better cerebral protection to patients undergoing cardiac surgery
41
42 20 with CPB is unknown. Since inhalation anaesthesia and TIVA are the
43
44 21 most commonly used strategies for general anaesthesia, it is important to
45
46 22 clarify this issue. Moreover, since it is difficult to include patients in
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 neurologic dysfunction studies for cardiac surgery with CPB, the sample
2 size of these previous studies was generally small. For these reasons, it is
3 necessary to systematically review the available literature and perform a
4 meta-analysis to compare the neuroprotective effects of inhalation
5 anaesthesia and TIVA.

7 **Materials and Methods**

8 The current systematic review and meta-analysis was carried out in
9 accordance with the preferred reporting items for systematic reviews and
10 meta-analyses (PRISMA) reporting guidelines for intervention trials ^[15].

12 **Literature search**

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

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

10 Eligibility criteria

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

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

21 Outcomes

22 In the included studies, S100B levels in serum were detected before

1 CPB (pre-CPB), after CPB (post-CPB) and 24 hours postoperatively. And
2 the primary outcomes were protein S100B levels in serum post-CPB and
3 24 hours postoperatively. The secondary outcomes included
4 mini-mental state examination (MMSE) scores assessed preoperatively
5 and 24 hours postoperatively, the jugular bulb venous oxygen saturation
6 (SjvO₂), arteriovenous oxygen content difference [D(a-v)O₂] and cerebral
7 oxygen extraction ratio (O₂ER) were tested at cooling and rewarming
8 during CPB.

10 **Study selection and validity assessment**

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

20 **Data extraction and statistical analysis**

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

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

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

15 Results

16 Characteristics of the included studies

17 A total of 1485 studies were retrieved. Of these, 1148 remained after
18 duplicate articles were eliminated. After screening titles and abstracts,
19 445 studies were potentially eligible. Based on the exclusion criteria, 13
20 studies were ultimately selected (Fig. 1). All reviewers agreed to include
21 all 13 papers. Although all of these randomized controlled trials (RCTs)
22 were considered to have a low risk of bias, nine studies included no

1 details on the method of random sequence generation and allocation
 2 [17-25]. Only one study provided the details about the blinding of the data
 3 collection^[26].

4 'Inhalation anaesthesia' was defined as a group receiving a volatile
 5 agent like isoflurane, sevoflurane, or desflurane. In the included studies,
 6 patients in the 'volatile anaesthesia' group had not received propofol,
 7 thiopental, or ketamine during the surgery and CPB. The patients in the
 8 'Total Intravenous Anaesthesia' (TIVA) group had received only
 9 intravenous anaesthetics, but not volatile agents. These studies involved
 10 549 patients, including 272 patients with inhalation anaesthesia and 277
 11 patients with TIVA (Table 1). Patients' age ranges in 'inhalation
 12 anaesthesia' and 'TIVA' groups were 44 to 75 years and 43 to 74 years,
 13 respectively. The mean age of patients was unavailable for three studies
 14 [17-19]. All the articles had reported exclusion/inclusion criteria [17-29]. Of
 15 these, seven studies had used isoflurane vs. TIVA [17, 19-21, 23, 24, 27], four
 16 studies had used sevoflurane vs. TIVA [18, 22, 25, 26], and two studies had
 17 used desflurane vs. TIVA [28, 29], in patients.

18

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 ₂ ER%,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 ₂ ER%,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 ₂ ER%,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
Jiyong 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; CMRO₂, cerebral metabolic rate of oxygen consumption; D(a-v)O₂, arteriovenous oxygen content difference; O₂ER, cerebral oxygen extraction; SjvO₂, 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).

study	Jadad Score				Score
	Randomization	Allocaion concealment	Blinding	Attrition	
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
Jiyong Zhong .2010	2	0	1	0	3

16

1
2
3 **Table 2. Methodology quality of the included randomized controlled trials**
4 **(RCTs)**
5
6
7
8

9 **Meta-analysis**

10 Summary estimate for S100B levels post-CPB and 24 hours
11 postoperatively were analysed in a random-effects model because of the
12 heterogeneity ($I^2=96%$ and $I^2=99%$, respectively). Based on 6 studies
13 from 230 patients, S100B levels assessed at the end of CPB and 24 hours
14 postoperatively in inhalation anaesthesia group were significantly lower
15 than those in TIVA group [WMD (95% CI): -0.41 (-0.81, -0.01), -0.32
16 (-0.59, -0.05), respectively, Fig. 2]. Based on 3 studies from 110 patients,
17 postoperative MMSE scores of the inhalation anaesthesia group were
18 significantly higher than those of the TIVA group [WMD (95%CI): 1.87
19 (0.82, 2.92)], Fig. 3]. A significant heterogeneity was detected ($I^2=77%$),
20 and thus summary estimate was analysed in a random-effects model.

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

24 Egger's regression test of S100B levels, MMSE scores, $D(a-v)O_2$,
25 O_2ER , and $SjvO_2$ indicated little evidence of publication bias,
26 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 ₂ ER%)	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

1
2
3
4 1 showed that inhalation anaesthesia might be superior to TIVA during
5
6 2 cardiac surgery with CPB.
7

8
9 3 S100B is mainly expressed in the astrocytes, and blood S100B level
10
11 4 is commonly used as an outcome parameter for evaluating the
12
13 5 postoperative neurological dysfunction^[30]. Its level in the blood has been
14
15 6 shown to increase in patients after ischemic stroke and brain trauma^[31].
16
17 7 Serum S100B has also been detected after cardiac surgery complicated by
18
19 8 neurological injury in adults; thus, it has the potential to serve as an early
20
21 9 marker of brain damage^[32, 33]. In this meta-analysis, the serum level of
22
23 10 S100B after CPB in the inhalation anaesthesia group was found to be
24
25 11 significantly lower than that in the TIVA group ($P < 0.05$)^[18, 25-27, 29],
26
27 12 suggesting that inhalation anaesthetics provide better cerebral protection
28
29 13 than TIVA against brain damage.
30
31
32
33
34
35

36 14 As reported by Svenmarker et al^[34], it is inevitable that S100B
37
38 15 contamination will occur due to the pericardial suction blood, which is
39
40 16 often re-transfused or processed in the cell saver and then re-transfused
41
42 17 during CPB. However, a strict control of clinical procedures may
43
44 18 decrease its potential effect on the difference of S100B detection between
45
46 19 the two groups. In the included studies, the use of re-transfusion and cell
47
48 20 salvage were not mentioned. Therefore, the possible effect of
49
50 21 re-transfusion and cell salvage should not be neglected, and this is a
51
52 22 potential limitation of the current study.
53
54
55
56
57
58
59
60

1
2
3
4 1 Among the secondary outcomes, the MMSE is one of the most
5
6 2 commonly used parameters for the clinical evaluation of cognitive
7
8 3 function. Our results show that postoperative MMSE scores of patients in
9
10 4 the inhalation anaesthesia group were significantly higher than those in
11
12 5 the TIVA group ($P < 0.05$) [18, 25, 29]. These results suggest that inhalation
13
14 6 anaesthesia is better than TIVA in terms of protecting the postoperative
15
16 7 cognitive function of patients undergoing cardiac surgery with CPB. The
17
18 8 meta-analysis also showed that the other outcomes such as $D(a-v)O_2$,
19
20 9 O_2ER , and $SjvO_2$, were not significantly different for TIVA and
21
22 10 inhalation anaesthesia groups. However, we found that in some studies,
23
24 11 the cerebral oxygen metabolic rate ($CMRO_2$) in patients receiving
25
26 12 inhalation anaesthetics assessed at cooling and rewarming during CPB
27
28 13 was consistently lower than that in patients receiving TIVA [20, 21].
29
30 14 Additionally, the intraoperative cerebral blood flow (CBF) assessed at
31
32 15 cooling and rewarming during CPB in the inhalation anaesthesia group
33
34 16 was significantly higher than that in the TIVA group [20, 21]. A low ratio of
35
36 17 global cerebral oxygen and adequate cerebral blood supply is an
37
38 18 important parameter for evaluating cerebral protection [35]. Thus, these
39
40 19 results based on $CMRO_2$ and CBF can strengthen the finding that
41
42 20 inhalation anaesthesia may provide better neuroprotection than TIVA.
43
44
45
46
47
48
49
50
51
52

53 21 Experimental data suggest that direct positive effects of volatile
54
55 22 anaesthetics may be caused by various pre-conditioning and
56
57
58
59
60

1
2
3
4 1 post-conditioning mechanisms ^[36, 37], which attenuate apoptosis and
5
6 2 necrosis of cerebral neurons, thereby reducing neurological dysfunction
7
8
9 3 after ischaemia. Moreover, the contribution of inhalation agents in
10
11 4 preserving satisfactory haemodynamics may ensure adequate perfusion
12
13 5 and oxygenation of other organ systems, ^[38-41] and improve the chances
14
15 6 for recovery and survival after surgery. All these effects can be expanded
16
17 7 well beyond the immediate perioperative period because of
18
19 8 anaesthetic-induced neuroprotection that can be long lasting ^[42, 43].
20
21 9 Additionally, a recent meta-analysis found that in cardiac surgery ^[44], as
22
23 10 compared to TIVA, inhalation anaesthesia was associated with major
24
25 11 benefits in outcome, including reduced mortality, as well as a lower
26
27 12 incidence of pulmonary and other complications. Therefore, based on
28
29 13 previous findings and the current meta-analysis, it is speculated that
30
31 14 inhalation anaesthesia has the potential to serve as a preferential
32
33 15 anaesthesia strategy for cardiac patients.

34
35
36
37
38
39
40
41 16 Our study has few limitations. First, the sample size of the included
42
43 17 studies was relatively small and the total number of cases is very limited.
44
45 18 Second, there was heterogeneity in some of our results. Since trials were
46
47 19 based in different countries and hospitals, we were unable to avoid the
48
49 20 effects of race, age, gender, and underlying disease(s) of patients in our
50
51 21 study. Therefore, findings of the current study
52
53 22 were limited by the overall low quality of evidence and the lack of robust
54
55
56
57
58
59
60

1 data. Third, our study focused on the overall comparison between
2 inhalation anaesthesia and TIVA, and different inhalation (isoflurane,
3 desflurane, or sevoflurane) and intravenous (sodium thiopental, propofol,
4 etc.) anaesthetics were investigated in the included studies. Because of
5 the limited number of reported clinical trials, limited outcome data could
6 be considered for subgroup analysis. Therefore, further studies with
7 larger sample sizes are needed to demonstrate which anaesthetics are
8 more beneficial for cardiac patients.

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

14 **Authors' contributions**

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

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

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

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

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

20 All authors have reviewed the manuscript.

21
22

1 Funding

2 This study was supported by a grant from the National Natural Science
3 Foundation of China (No. 81571870) and the Natural Science Foundation
4 Project of Chongqing (cstc20136jjB10026).

6 **Competing interests:** The authors declare no conflicts of interest.

8 **Data sharing statement:** No additional data are available.

11 References

- 13 [1] Lamy A, Devereaux PJ, Prabhakaran D, et al. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. *N Engl J Med*. 2013. 368(13): 1179-88.
- 15 [2] Lamy A, Devereaux PJ, Prabhakaran D, et al. Five-Year Outcomes after Off-Pump or On-Pump Coronary-Artery Bypass Grafting. *N Engl J Med*. 2016. 375(24): 2359-2368.
- 17 [3] McKhann GM, Grega MA, Borowicz LM, et al. Stroke and encephalopathy after cardiac surgery: an update. *Stroke*. 2006. 37(2): 562-71.
- 19 [4] Hogue CW, Palin CA, Arrowsmith JE. Cardiopulmonary bypass management and neurologic outcomes: an evidence-based appraisal of current practices. *Anesth Analg*. 2006. 103(1): 21-37.
- 21 [5] Wimmer-Greinecker G, Matheis G, Brieden M, et al. Neuropsychological changes after cardiopulmonary bypass for coronary artery bypass grafting. *Thorac Cardiovasc Surg* 1998;46(4): 207-12.
- 23 [6] Blumenthal JA, Mahanna EP, Madden DJ, et al. Methodological issues in the assessment of neuropsychologic function after cardiac surgery. *Ann Thorac Surg* 1995;59(5): 1345-50.
- 25 [7] Pape M, Engelhard K, Eberspacher E, et al. The long-term effect of sevoflurane on neuronal cell damage and expression of apoptotic factors after cerebral ischemia and reperfusion in rats. *Anesth Analg* 2006;103(1): 173-9.
- 28 [8] Sakai H, Sheng H, Yates RB, et al. Isoflurane provides long-term protection against focal cerebral ischemia in the rat. *Anesthesiology* 2007;106(1): 92-9.
- 30 [9] Selman WR, Spetzler RF, Roessmann UR, et al. Barbiturate-induced coma therapy for focal cerebral ischemia. Effect after temporary and permanent MCA occlusion. *J Neurosurg* 1981;55(2): 220-6.
- 32 [10] Iwata T, Inoue S, Kawaguchi M, et al. Comparison of the effects of sevoflurane and propofol on cooling and rewarming during deliberate mild hypothermia for neurosurgery. *Br J Anaesth* 2003;90(1): 32-8.
- 34 [11] Dabrowski W, Rzecki Z, Czajkowski M, et al. Volatile anesthetics reduce biochemical markers of brain injury

- 1 and brain magnesium disorders in patients undergoing coronary artery bypass graft surgery. *J Cardiothorac*
2 *Vasc Anesth.* 2012. 26(3): 395-402.
- 3 [12] Sagara Y, Hendler S, Khoh-Reiter S, et al. Propofol hemisuccinate protects neuronal cells from oxidative
4 injury. *J Neurochem* 1999;73(6): 2524-30.
- 5 [13] Wang H, Lu S, Yu Q, et al. Sevoflurane preconditioning confers neuroprotection via anti-inflammatory effects.
6 *Elite Ed* 2011;1(3): 604-15.
- 7 [14] McAuliffe JJ, Loepeke AW, Miles L, et al. Desflurane, isoflurane, and sevoflurane provide limited
8 neuroprotection against neonatal hypoxia-ischemia in a delayed preconditioning paradigm. *Anesthesiology*
9 2009;111(3): 533-46.
- 10 [15] Moher D1, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses:
11 the PRISMA statement. *PLoS Med* 2009;6(7):e1000097.
- 12 [16] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11): 1539-58.
- 13 [17] Min J, Yanlin B. Target controlled infusion of propofol in shallow perioperative cardiopulmonary bypass for
14 brain protection. *Int J Clin Exp Med* 2007;4(6): 120-121.
- 15 [18] Huaping Y. Two methods of anesthesia of CPB heart valve replacement patients plasma level and the
16 influence of cognitive function according to beta. *Shandong Med* 2015;55(15): 71-72.
- 17 [19] Lei L, Weifu L, Jianchun F, et al. Effects of different anesthesia on cognition function in geriatric patients
18 following off-pump coronary artery bypass grafting. *Chin J Geriatr Heart Brain Vessel Dis* 2010;12 (11):
19 1002-1004.
- 20 [20] Newman MF, Croughwell ND, White WD, et al. Pharmacologic electroencephalographic suppression during
21 cardiopulmonary bypass: a comparison of thiopental and isoflurane. *Anesth Analg* 1998;86(2): 246-51.
- 22 [21] Woodcock TE, Murkin JM, Farrar JK, et al. Pharmacologic EEG suppression during cardiopulmonary bypass:
23 cerebral hemodynamic and metabolic effects of thiopental or isoflurane during hypothermia and
24 normothermia. *Anesthesiology* 1987;67(2): 218-24.
- 25 [22] Guclu CY, Unver S, Aydinli B, et al. The effect of sevoflurane vs. TIVA on cerebral oxygen saturation during
26 cardiopulmonary bypass--randomized trial. *Adv Clin Exp Med* 2014;23(6): 919-24.
- 27 [23] Tingting C, Gang W, Qi Z, et al. The comparison between isoflurane and propofol with effect on cerebral
28 protection in cardiac valve replacement Surgery. *Chin J ECC* 2007;5(2): 91-93+117.
- 29 [24] Jianrong G, Donglin J, Liyuan R, et al. Isoflurane and propofol for extracorporeal circulation open-heart
30 surgery in patients with a comparative study of perioperative cerebral protection. *Chin J Clin Pharmacol Ther*
31 2009;14(7): 812-817.
- 32 [25] Shudong M, Propofol and seven halothane Anesthesia for experacorporeal circulation of brain protection
33 effect comparison. *Chin & F Med treatment* 2015;12(9): 145-146
- 34 [26] Singh SP, Kapoor PM, Chowdhury U, et al. Comparison of S100beta levels, and their correlation with
35 hemodynamic indices in patients undergoing coronary artery bypass grafting with three different anesthetic
36 techniques. *Ann Card Anaesth* 2011;14(3): 197-202.
- 37 [27] Kanbak M, Saricaoglu F, Avci A, et al. Propofol offers no advantage over isoflurane anesthesia for cerebral
38 protection during cardiopulmonary bypass: a preliminary study of S-100beta protein levels. *Can J Anaesth*
39 2004;51(7): 712-7.
- 40 [28] Baki ED, Aldemir M, Kokulu S, et al. Comparison of the effects of desflurane and propofol anesthesia on the
41 inflammatory response and s100beta protein during coronary artery bypass grafting. *Inflammation* 2013;36(6):
42 1327-33.
- 43 [29] Jiying Z, Feng X, Xianjie W, et al. Brain protection of desflurane in old patients undergoing coronary artery
44 bypass grafting. *Chin J New Drugs Clin Rem* 2010;29(11):847-849.

- 1 [30] Wang DD, Bordey A. The astrocyte odyssey. *Prog Neurobiol* 2008;86(4): 342-67.
- 2 [31] An SA, Kim J, Kim OJ, et al. Limited clinical value of multiple blood markers in the diagnosis of ischemic
3 stroke. *Clin Biochem* 2013;46(9): 710-5.
- 4 [32] Kuzumi E, Vuylsteke A, Guo X, et al. Serum S100 protein as a marker of cerebral damage during cardiac
5 surgery. *Br J Anaesth* 2000;85(6): 936-7.
- 6 [33] Rasmussen LS, Christiansen M, Eliassen K, et al. Biochemical markers for brain damage after cardiac surgery
7 -- time profile and correlation with cognitive dysfunction. *Acta Anaesthesiol Scand* 2002;46(5): 547-51.
- 8 [34] Svenmarker S, Engström KG, Karlsson T, et al. Influence of pericardial suction blood retransfusion on
9 memory function and release of protein S100B. *Perfusion*. 2004;19(6):337-43.
- 10 [35] Goldman S, Sutter F, Ferdinand F, et al. Optimizing intraoperative cerebral oxygen delivery using noninvasive
11 cerebral oximetry decreases the incidence of stroke for cardiac surgical patients. *Heart Surg Forum* 2004;7:
12 376-381.
- 13 [36] McMurtrey RJ, Zuo Z. Isoflurane preconditioning and postconditioning in rat hippocampal neurons. *Brain*
14 *Res* 2010;1358: 184-90.
- 15 [37] Lee JJ, Li L, Jung HH, et al. Postconditioning with isoflurane reduced ischemia-induced brain injury in rats.
16 *Anesthesiology* 2008;108(6): 1055-62.
- 17 [38] Julier K, da SR, Garcia C, et al. Preconditioning by sevoflurane decreases biochemical markers for
18 myocardial and renal dysfunction in coronary artery bypass graft surgery: a double-blinded,
19 placebo-controlled, multicenter study. *Anesthesiology* 2003;98(6): 1315-27.
- 20 [39] Kim M, Kim M, Kim N, et al. Isoflurane mediates protection from renal ischemia-reperfusion injury via
21 sphingosine kinase and sphingosine-1-phosphate-dependent pathways. *Am J Physiol Renal Physiol* 2007;
22 293(6): F1827-35.
- 23 [40] Lee HT, Kim M, Kim J, et al. TGF-beta1 release by volatile anesthetics mediates protection against renal
24 proximal tubule cell necrosis. *Am J Nephrol* 2007;27(4): 416-24.
- 25 [41] Beck-Schimmer B, Breitenstein S, Urech S, et al. A randomized controlled trial on pharmacological
26 preconditioning in liver surgery using a volatile anesthetic. *Ann Surg* 2008;248(6): 909-18.
- 27 [42] Li H, Yin J, Li L, et al. Isoflurane postconditioning reduces ischemia-induced nuclear factor-kappaB
28 activation and interleukin 1beta production to provide neuroprotection in rats and mice. *Neurobiol Dis* 2013;
29 1(54): 216-24.
- 30 [43] Zuo Z. A novel mechanism for sevoflurane preconditioning-induced neuroprotection. *Anesthesiology* 2012;
31 117(5): 942-4.
- 32 [44] Uhlig C, Bluth T, Schwarz K, et al. Effects of Volatile Anesthetics on Mortality and Postoperative Pulmonary
33 and Other Complications in Patients Undergoing Surgery: A Systematic Review and Meta-analysis. *Anesthesiology*.
34 2016. 124(6): 1230-45.

37 Figure legends

38 Fig. 1 Flow diagram for the selection of eligible studies

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

1 anaesthesia (TIVA) groups

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

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

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

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

14 Fig. 7 The plot of sensitivity analysis of S100B levels

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

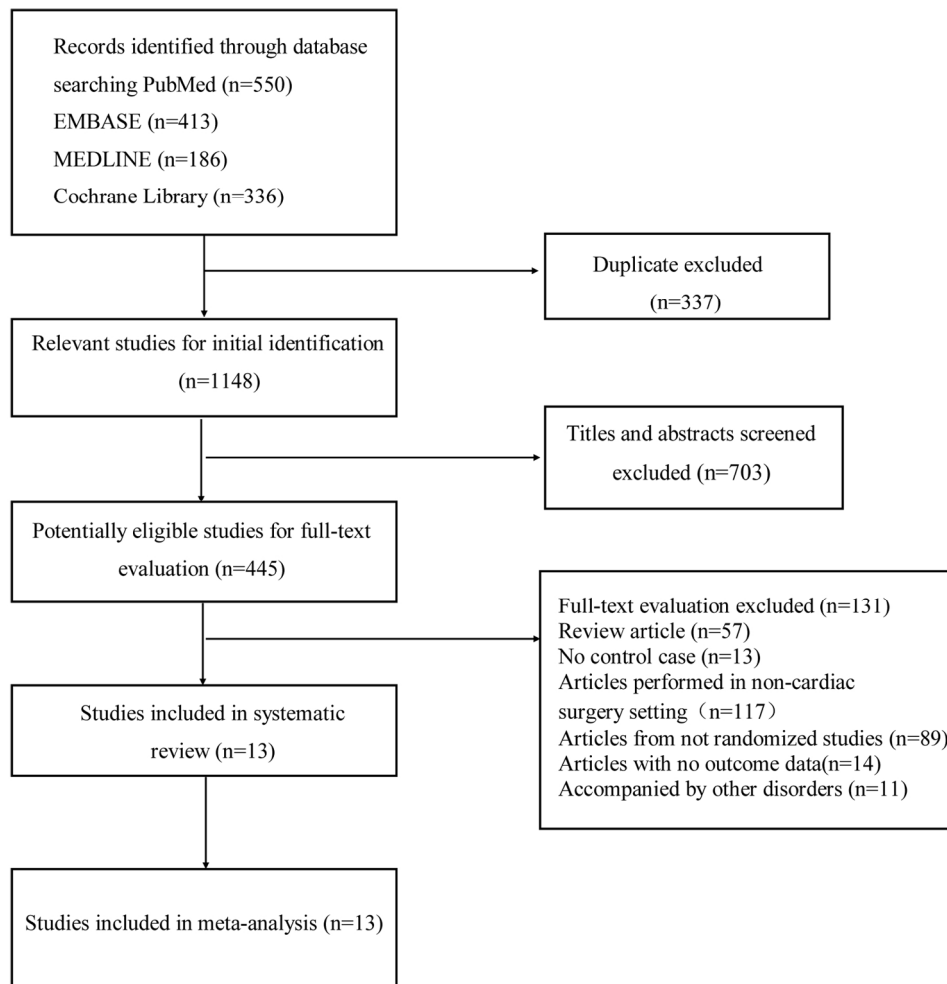


Fig. 1 Flow diagram for the selection of eligible studies

160x160mm (300 x 300 DPI)

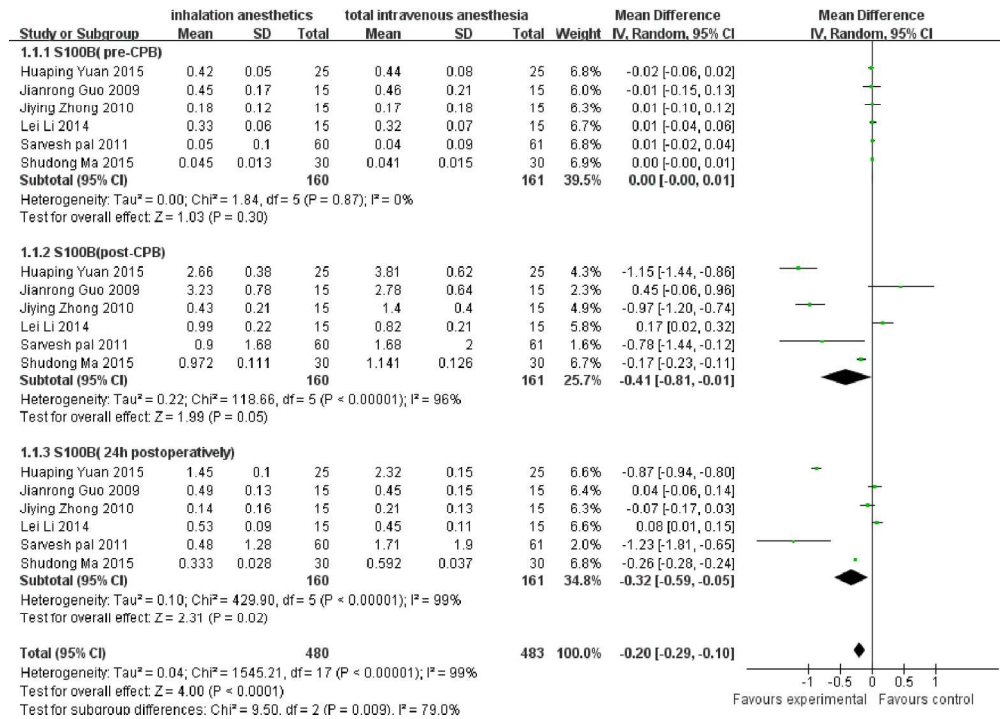


Fig. 2 Forest plot showing the meta-analysis outcomes of the difference in S100B levels of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x113mm (300 x 300 DPI)

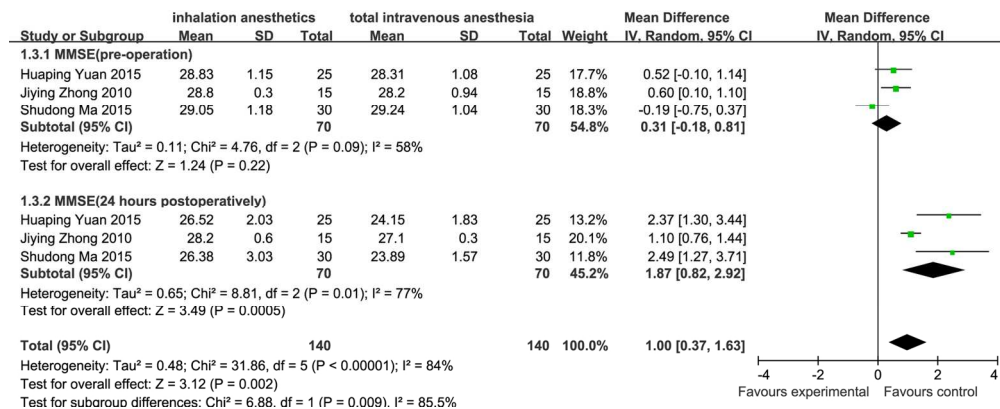


Fig. 3 Forest plot showing the meta-analysis outcomes of the difference in mini-mental state examination (MMSE) scores of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups

160x64mm (300 x 300 DPI)

Peer review only

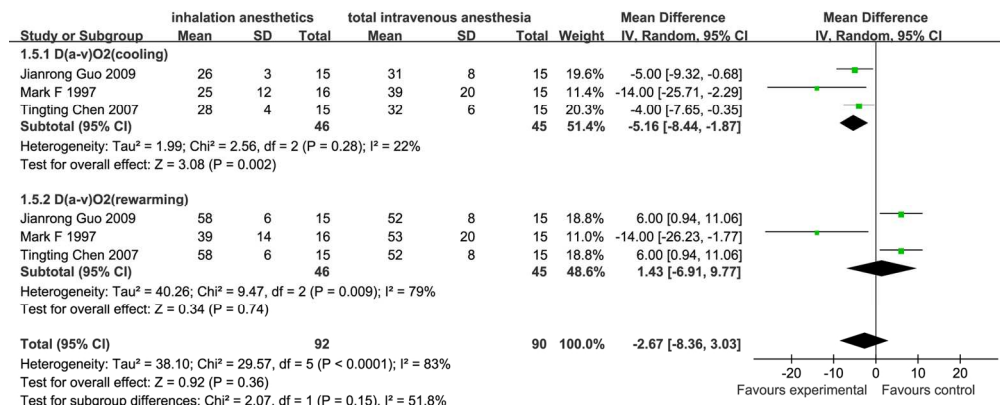


Fig 4. Forest plot showing the meta-analysis outcomes of the difference in arteriovenous oxygen content difference [D(a-v)O₂] of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups.

160x63mm (299 x 299 DPI)

Peer review only

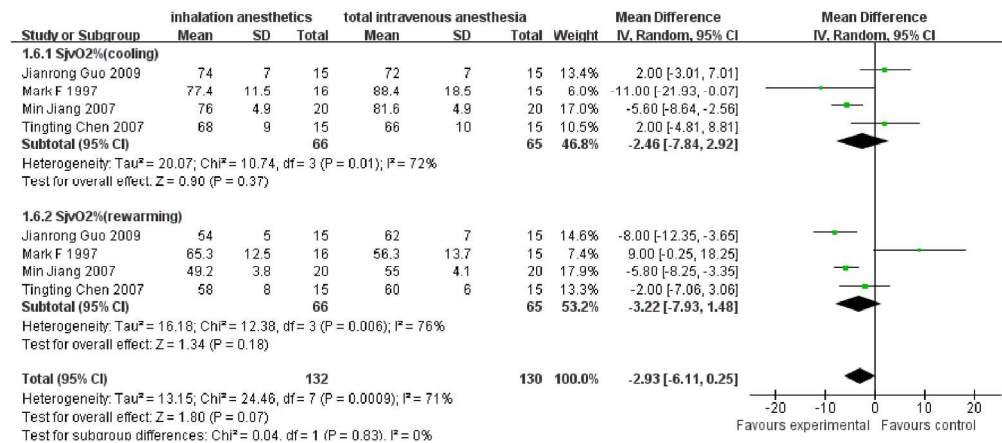


Fig 5. Forest plot showing the meta-analysis outcomes of the difference in jugular bulb venous oxygen saturation (SjvO₂) of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups.

160x69mm (299 x 299 DPI)

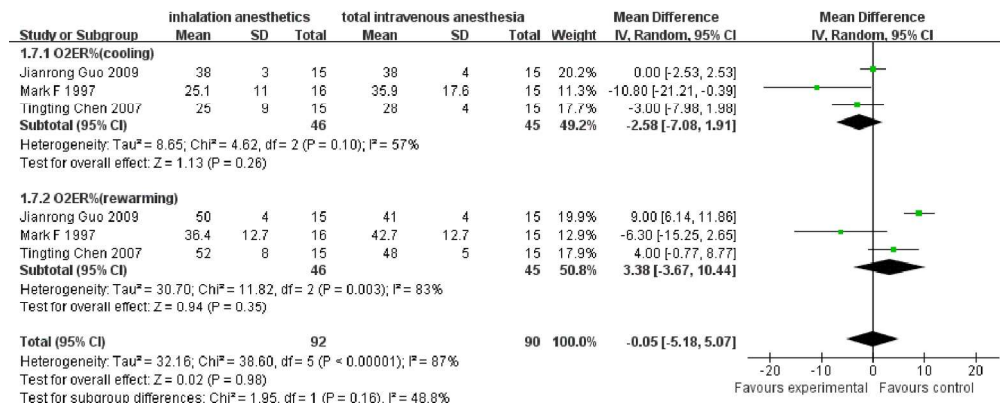


Fig 6. Forest plot showing the meta-analysis outcomes of the difference in cerebral oxygen extraction ratio (O2ER) of inhalation anaesthesia and total intravenous anaesthesia (TIVA) groups.

160x63mm (299 x 299 DPI)

Peer review only

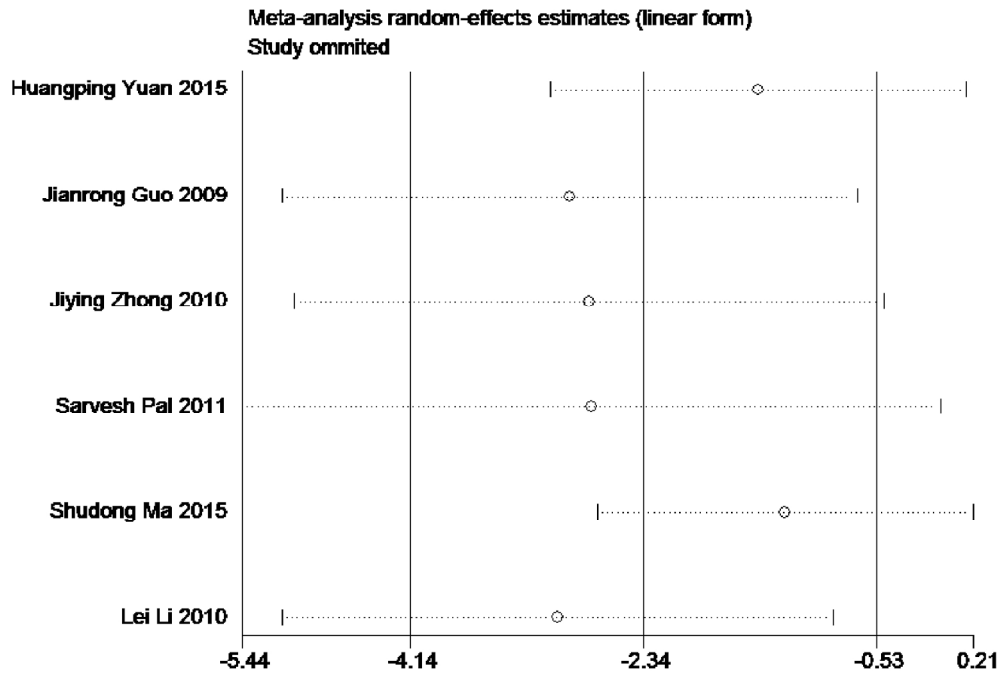


Fig. 7 The plot of sensitivity analysis of S100B levels

160x119mm (300 x 300 DPI)

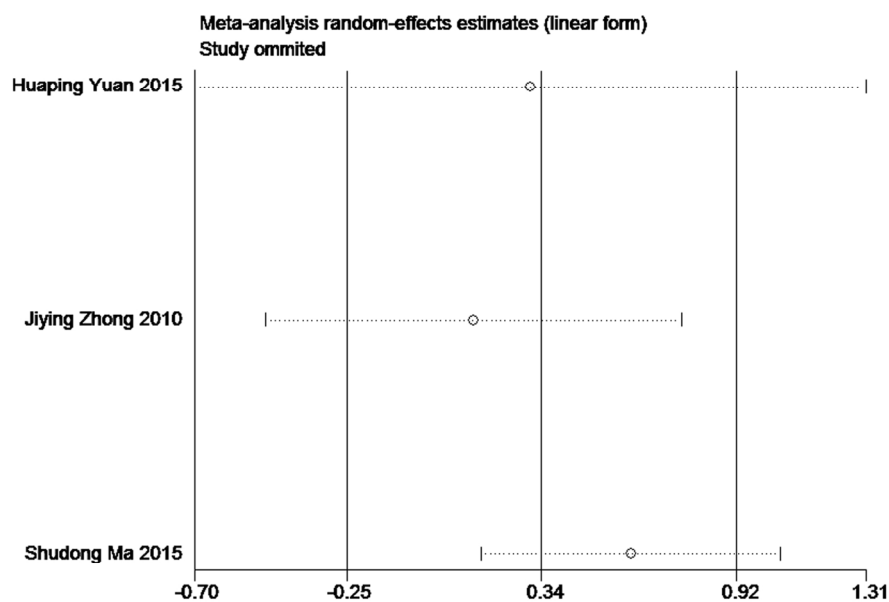


Fig. 8 The plot of sensitivity analysis of mini-mental state examination (MMSE) scores

160x106mm (299 x 299 DPI)

view only

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

1
2
3
4 Thiopentobarbital OR Thiopentone OR Bomathal OR Pentothal Sodico
5
6

7 #14 Ketamine[MeSH] OR Calypsol OR Kalips
8

9 #15 Midazolam[MeSH] OR Hydrochloride, Midazolam OR Maleate,
10
11 Midazolam
12

13
14 #16 OR/#10-#15
15

16
17 #17 randomized controlled trial [pt]
18

19
20 #18 controlled clinical trial [pt]
21

22
23 #19 randomized [tiab]
24

25
26 #20 placebo [tiab]
27

28
29 #21 drug therapy [sh]
30

31
32 #22 randomly [tiab]
33

34
35 #23 trial [tiab]
36

37
38 #24 groups [tiab]
39

40
41 #25 OR/#17-#24
42

43
44 #26 animals [mh] NOT humans [mh]
45

46
47 #27 #25 NOT #26
48

49
50 #28 #1 AND #5 AND #9 AND #16 AND #27
51
52
53
54
55
56
57
58
59
60



PRISMA 2009 Checklist

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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

Page 1 of 2

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

For more information, visit: www.prisma-statement.org.

Page 2 of 2

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>