Meta-analysis of protective effect of sevoflurane on myocardium during cardiac surgery

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Abstract. – BACKGROUND: This study aims to evaluate the effect of sevoflurane anesthesia on myocardium in cardiac surgery and provide evidence for clinical anesthesia practice.

MATERIALS AND METHODS: Literature about the protective effect of sevoflurane anesthesia on myocardium in cardiac surgery published before March, 2012 was retrieved from the database of PubMed and EMBASE. The quality of inclusive randomized controlled trials was evaluated and screened according to the Jadad scale. Finally, meta-analysis was performed by using the RevMan5.0 software.

RESULTS: In this research, there were totally 17 articles in accordance with the inclusive criteria and all of them were in English with the study sites being abroad. Each article was more than 3 points in Jadad scale. Compared with total intravenous anesthesia group, postoperative 12h CO and CI of patients have been significantly improved in the sevoflurane anesthesia group; and concentration of postoperative 24 h cTnI in the sevoflurane anesthesia group has been reduced, as well as assisted respiratory time and ICU stay after operation. There is no significant difference in hospitalization stay between both groups; postoperative usage of vasoactive drugs in sevoflurane anesthesia group is less than in total intravenous anesthesia group. There is no significant difference in postoperative appearance of atrial fibrillation, recurrence rate of angina pectoris and mortality of patients after operation between both groups.

CONCLUSIONS: Sevoflurane can better protect myocardium in the cardiac surgery.

Key Words:
  Sevoflurane, Cardiac surgery, Meta-analysis.

myocardial ischemic injury [1]. Today, sevoflurane is one of the most widely used halogen fluoride volatile anesthetics and it has advantages of rapid induction, less stimulus, quicker recovery and no significant side effects[2,3]. It has been proven by a large number of *in vitro* and *in vivo* animal experiments that sevoflurane can protect ischemic myocardium. Lately some studies find that the myocardial damage marker after operation is less and the cardiac function when the operation is better if sevoflurane is provided in the full course rather than just before ischemia or after coronary artery anastomosis. Coronary artery bypass grafting proves that the one-year cardiovascular disease prevalence of patients provided with sevoflurane anesthesia is lower than that of control group[4]. Study of off-pump cardiac bypass grafting also reports that sevoflurane has a better protective effect on myocardium[5].

Meta-analysis is a statistical analysis technique that can provide a method to settle controversial and uncertain problems through qualitative analysis of several dependent clinical researches that can be comprehensively combined. Published literature about randomized controlled trials of protection of sevoflurane anesthesia on myocardium in cardiac surgery was retrieved, evaluated and screened here. And a meta-analysis was conducted for final inclusive literature. This systematical evaluation on the protective effect of sevoflurane anesthesia on myocardium during cardiac surgery may provide an evidence-based medicine for clinical practice.

Introduction

Volatile anesthetic preconditioning has a similar mechanism with ischemic preconditioning, both of which can provide a protective effect on

Materials and methods

Literature about the protective effect of sevoflurane anesthesia on myocardium in cardiac surgery published before March, 2012 was re-

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trieved in the database of Medline with computers. Manual retrieval and literature review were used as a complementary. English search terms included total intravenous anesthesia, sevoflurane, cardiac surgery and cardio-protection.

Literature Inclusive Criteria

(1) The research objects were patients in cardiac surgery. (2) The experiment was designed as randomized controlled trial, non-randomized controlled trial and animal experiment. (3) Anesthesia: the experiment group received sevoflurane volatile anesthesia in the whole course or at intervals; the control group received total intravenous anesthesia; and the two groups didn't receive epidural anesthesia or analgesia during the surgery. (4) Data of literature were integral, including the number of specific cases, controls and people completed the experiment. (5) The study endpoint had at least one index in the following: postoperative cardiac index (CI), cardiac output (CO), postoperative myocardial Troponin I (cTnI), postoperative assisted respiratory time, ICU (Intensive Care Unit) stay, hospitalization stay, and the usage of vasoactive drugs, incidence of atrial fibrillation, recurrence rate of angina pectoris and mortality of patients postoperatively in the hospitalization period.

Literature Quality Evaluation

Jadad scale[6] was used to evaluate the quality of literature. The research design, patients, interventions and observations were evaluated according to literature inclusive criteria mentioned above. Two evaluators chose experiments independently and collected data. A disaccord was settled by discussion or another researcher. The research with Jadad ≥3 was considered as high quality.

Data Collection

A form was designed to collect all data in the research. The two researchers collected data together, including cases, dosage of total intravenous anesthesia, dosage and method of administration of sevoflurane, and endpoint data.

RevMan (Review Manager) was used to conduct meta-analysis.

Statistical Analysis

Inclusive clinical heterogeneity and methodological heterogeneity were analyzed through chi-square test. If $p > 0.05$, fixed-effect model would be used to analyze. If $p \leq 0.05$, random-ef-

fect model would be performed. Mean difference (MD) was used to explain effect size for the results of continuous variables while odds ratio (OR) for the results of noncontiguous variables. A 95% confidence interval was used in interval estimation (95% CI).

Results

Literature retrieval

In this research, there were totally [7-23] articles in accordance with the inclusive criteria and all of them were in English with the study sites being abroad. Each article was more than 3 points in Jadad scale. General information is shown in Table I.

Results evaluation

Of the 17 inclusive articles, 7 articles study cardiac function in the surgery, 6 of them have recorded postoperative 12h cardiac index (CI) and 3 of them have recorded postoperative 12h cardiac output (CO). Among the 17 inclusive articles, 7 of them have introduced change of myocardial Troponin I after operation, 5 have recorded postoperative assisted respiratory time, 6 have recorded hospitalization stay, 10 have recorded postoperative usage of vasoactive drugs, 6 have recorded postoperative recurrence rate of angina pectoris, 4 have recorded postoperative occurrence of atrial fibrillation and 9 have recorded mortality of patients in hospitalization period. The result of meta-analysis is as follows.

Effect of sevoflurane anesthesia on cardiac indexes after operation

Data about postoperative 12h cardiac index (CI) are provided in 6 studies. Fixed-effect model is used because heterogeneity doesn't exist among studies ($p = 0.67$). The result (Figure 1) suggests that postoperative 12h CI in sevoflurane anesthesia group is higher than that in total intravenous anesthesia group with statistical significance (WMD: weighted mean difference = 0.17, 95% CI0.05-0.29; $p = 0.006$). Data about postoperative 12h cardiac output (CO) are provided in 3 studies. Random-effect model is used because heterogeneity exists among studies ($p = 0.01$). The result (Figure 2) suggests that postoperative 12h CO in sevoflurane anesthesia group is higher than that in total intravenous anesthesia group with statistical significance (WMD = 0.58, 95% CI0.19-0.97; $p = 0.004$).

Table I. General Information of Final Inclusive Literature.

Studies	Types of surgery	Cases of sevoflurane anesthesia group (n)	Cases of total intravenous anesthesia group (n)	Major research indexes
De Hert 2002	Coronary artery bypass grafting	10	10	Postoperative usage of vasoactive drugs and postoperative recurrence rate of angina pectoris
Julier K 2002	Coronary artery bypass grafting	37	35	Postoperative usage of vasoactive drugs, postoperative recurrence rate of angina pectoris and postoperative appearance of atrial fibrillation
Pouzet B 2002	Coronary artery bypass grafting	10	10	Postoperative usage of vasoactive drugs
De Hert 2003	Coronary artery bypass grafting	15	15	Cardiac index (CI) in 12h after operation and mortality of patients in hospitalization period
EI A 2003	Coronary artery bypass grafting	10	10	Postoperative usage of vasoactive drugs, postoperative recurrence rate of angina pectoris, ICU stay and mortality of patients in hospitalization period
De Hert 2004a	Coronary artery bypass grafting	150	50	Cardiac output (CO) in 12h after operation, myocardial Troponin I (cTnI) in 24h after operation, postoperative usage of vasoactive drugs, postoperative recurrence rate of angina pectoris, postoperative appearance of atrial fibrillation and mortality of patients in hospitalization period
De Hert 2004b	Coronary artery bypass grafting	80	160	Cardiac index (CI) in 12h after operation, postoperative assisted respiratory time, postoperative usage of vasoactive drugs, postoperative recurrence rate of angina pectoris, postoperative appearance of atrial fibrillation and mortality of patients in hospitalization period
Malagon I 2005	Cardiac operation for congenital heart disease	30	60	Mortality of patients in hospitalization period
Cromheecke S 2006	Aortic regurgitation	15	15	Cardiac index (CI) in 12h after operation, myocardial Troponin I (cTnI) in 24h after operation, ICU stay and hospitalization stay
Lorsomradee S 2006	Coronary artery bypass grafting	160	160	Cardiac output (CO) in 12h after operation, ICU stay, hospitalization stay, postoperative usage of vasoactive drugs, postoperative recurrence rate of angina pectoris and mortality of patients in hospitalization period
Piriou V 2007	Coronary artery bypass grafting	36	36	Cardiac index (CI) in 12h after operation, myocardial Troponin I (cTnI) in 24h after operation, postoperative usage of vasoactive drugs and mortality of patients in hospitalization period
Bein B 2008	Coronary artery bypass grafting	24	14	Postoperative assisted respiratory time, ICU stay and hospitalization stay
Jan F 2009	Coronary artery bypass grafting	10	10	Cardiac index (CI) in 12h after operation and myocardial Troponin I (cTnI) in 24h after operation
Vedat Y 2009	Coronary artery bypass grafting	20	20	Cardiac index (CI) in 12h after operation, cardiac output (CO) in 12h after operation, myocardial Troponin I (cTnI) in 24h after operation and mortality of patients in hospitalization period

Table continued

Table I. General Information of Final Inclusive Literature (*Continued*).

Studies	Types of surgery	Cases of sevoflurane anesthesia group (n)	Cases of total intravenous anesthesia group (n)	Major research indexes
E B 2012	Coronary artery bypass grafting	50	50	Myocardial Troponin I (cTnI) in 24h after operation, postoperative assisted respiratory time, ICU stay, hospitalization stay, postoperative usage of vasoactive drugs and postoperative appearance of atrial fibrillation
Jan H 2012	Coronary artery bypass grafting	49	50	Postoperative assisted respiratory time, ICU stay and hospitalization stay
Miomir M 2012	Aortic valve replacement	11	11	Myocardial Troponin I (cTnI) in 24h after operation, postoperative assisted respiratory time, ICU stay, hospitalization stay and mortality of patients in hospitalization period

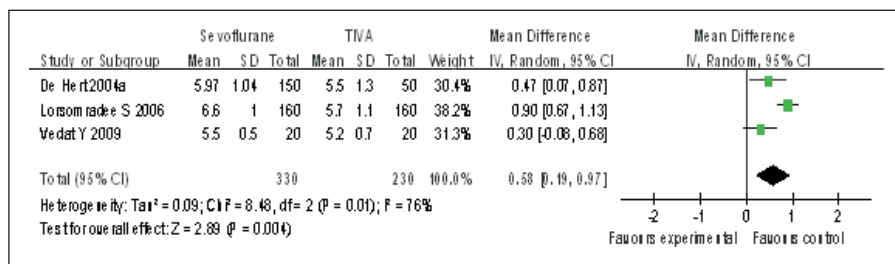### Effect of sevoflurane anesthesia on postoperative 24h cTnI

cTnI is an effective index that reflects early postoperative myocardial damage. Data about postoperative 24h cTnI are provided in 7 studies. Fixed-effect model is used because heterogeneity doesn't exist among studies ($p = 0.24$). The result (Figure 3) suggests that postoperative 24h cTnI in sevoflurane anesthesia group is higher than in total intravenous anesthesia group with statistical significance (WMD = -1.18, 95% CI-1.64-0.71; $p < 0.00001$). It shows that postoperative myocardial damage in sevoflurane anesthesia group is milder than that in total intravenous anesthesia group.

Effect of sevoflurane anesthesia on assisted respiratory time after operation

Information about assisted respiratory time after operation is provided in 5 studies. Fixed-effect model is used because there is no statistical significance in heterogeneity test ($p = 0.27$). The result (Figure 4) suggests that compared with total intravenous anesthesia, sevoflurane anesthesia can significantly reduce assisted respiratory time after operation (WMD = -0.55, 95% CI-0.98- -0.13; $p = 0.01$).
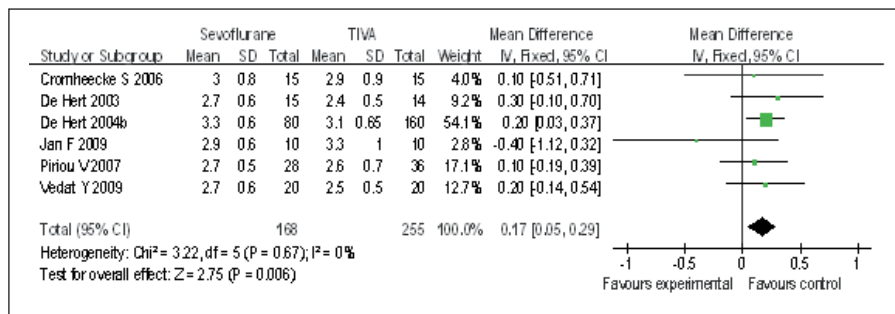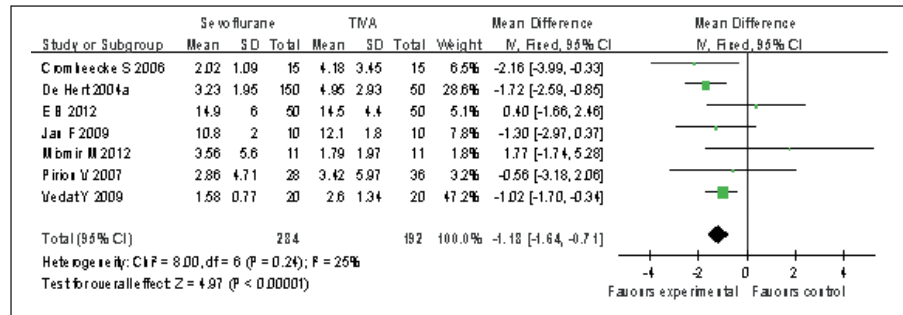

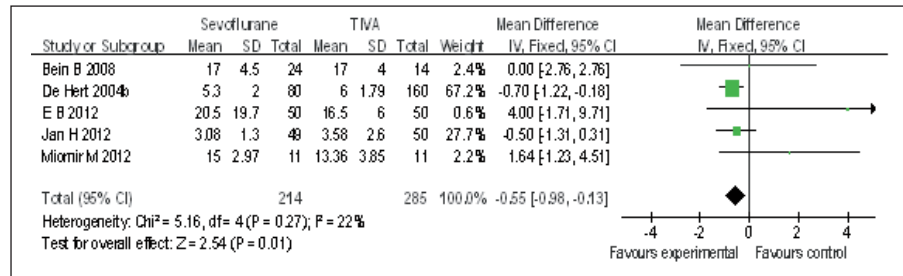**Figure 1.** Forest plot of effect of sevoflurane anesthesia on postoperative 12h CI.

Figure 2. Forest plot of effect of sevoflurane anesthesia on postoperative 12h CO.

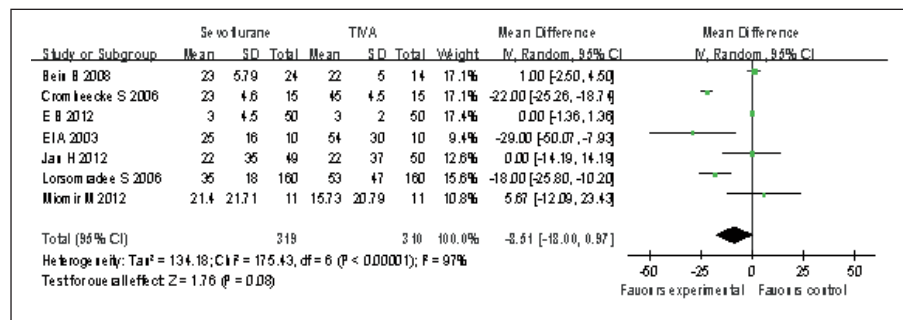**Figure 3.** Forest plot of effect of sevoflurane anesthesia on cTnI after operation.

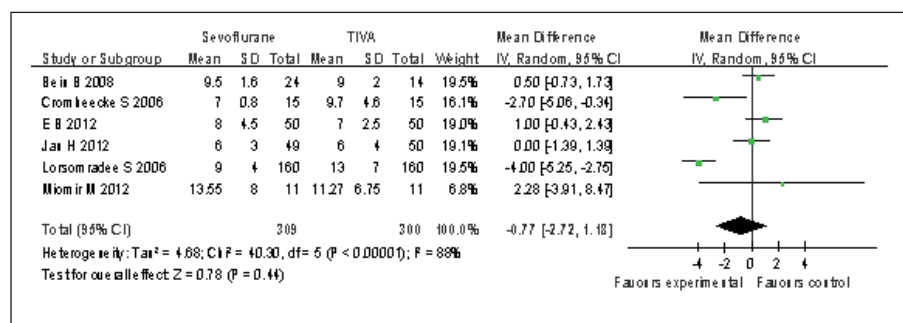**Figure 4.** Forest plot of effect of sevoflurane anesthesia on assisted respiratory time after operation.

Effect of sevoflurane anesthesia on ICU stay after operation

Information about ICU stay after operation is provided in 7 studies. Random-effect model is used because there is statistical significance in heterogeneity test ($p < 0.00001$). The result (Figure 5) suggests that there is no statistical significance in ICU stay between sevoflurane anesthesia group and total intravenous anesthesia group (WMD = –8.51, 95% CI-18.00-0.97; $p = 0.08$).

Effect of sevoflurane anesthesia on hospitalization stay after operation

Information about hospitalization stay after operation is provided in 6 studies. Random-effect model is used because there is statistical significance in heterogeneity test ($p < 0.00001$). The result (Figure 6) suggests that there is no statistical significance in hospitalization stay after operation between sevoflurane anesthesia group and total intravenous anesthesia group (WMD = –0.77, 95% CI-2.72-1.18; $p = 0.44$).

Figure 5. Forest plot of effect of sevoflurane anesthesia on ICU stay after operation.

Figure 6. Forest plot of effect of sevoflurane anesthesia on hospitalization stay after operation.
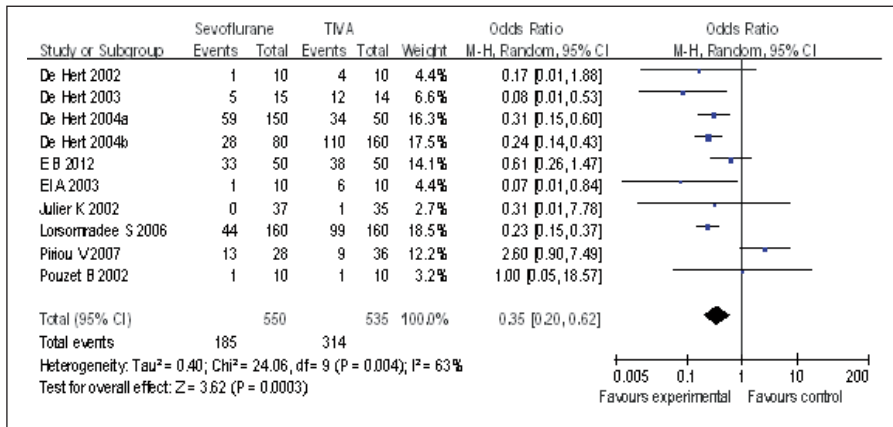
Figure 7. Forest plot of effect of sevoflurane anesthesia on postoperative usage of vasoactive drugs.

Effect of sevoflurane anesthesia on postoperative usage of vasoactive drugs

Information about postoperative usage of vasoactive drugs is provided in 10 studies. Random-effect model is used because there is statistical significance in heterogeneity test ($p = 0.002$). The result suggests (Figure 7) that compared with total intravenous anesthesia group, usage of vasoactive drugs in sevoflurane anesthesia group has been significantly reduced with statistical significance (RR = 0.37, 95% CI 0.21-0.62; $p = 0.0002$).

Effect of sevoflurane anesthesia on postoperative recurrence rate of angina pectoris

Information about postoperative recurrence rate of angina pectoris is provided in 6 studies.

Fixed-effect model is used because there is no statistical significance in heterogeneity test ($p = 0.93$). The result (Figure 8) suggests that there is no statistical significance in postoperative recurrence rate of angina pectoris between sevoflurane anesthesia group and total intravenous anesthesia group (RR = 0.59, 95% CI 0.26-1.33; $p = 0.21$).

Effect of sevoflurane anesthesia on postoperative appearance of atrial fibrillation

Information about postoperative appearance of atrial fibrillation is provided in 4 studies. Fixed-effect model is used because there is no statistical significance in heterogeneity test ($p = 0.17$). The result (Figure 9) suggests that there is no statistical significance in postoperative appearance
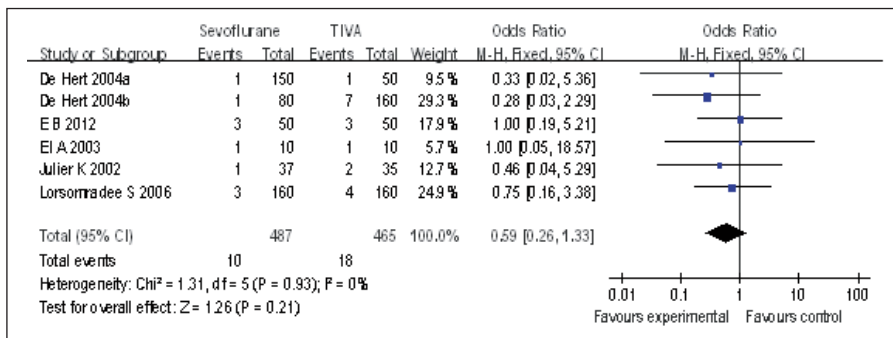

Figure 8. Forest plot of effect of sevoflurane anesthesia on postoperative recurrence rate.
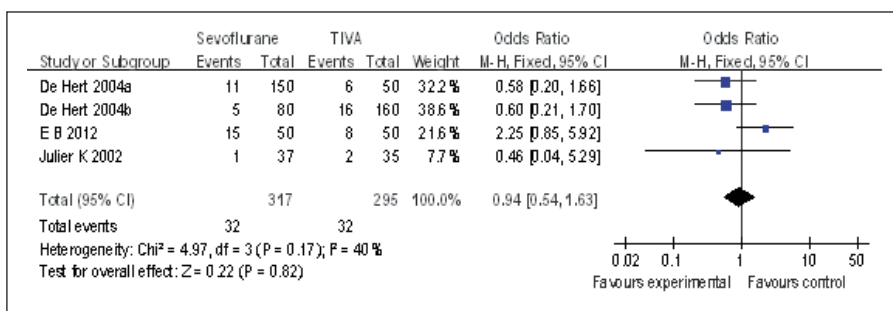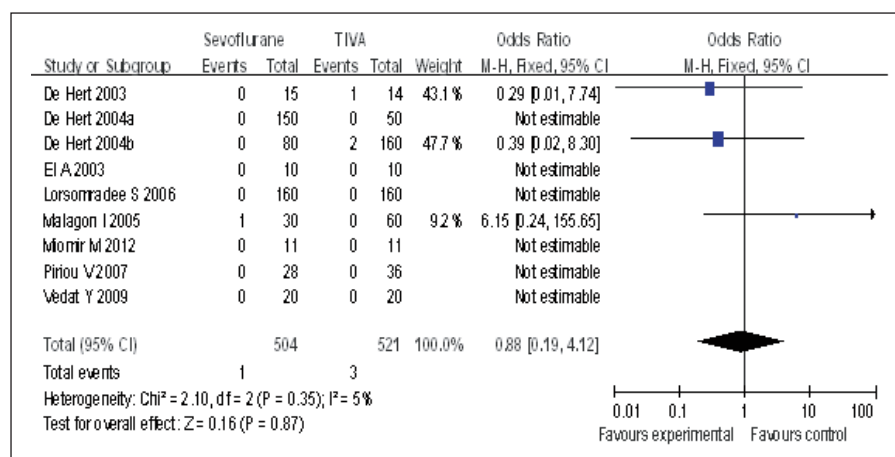

Figure 9. Forest plot of effect of sevoflurane anesthesia on postoperative incidence of atrial fibrillation.

Figure 10. Forest plot of effect of sevoflurane anesthesia on mortality of patients after operation.

of atrial fibrillation between sevoflurane anesthesia group and total intravenous anesthesia group (RR = 0.94, 95% CI 0.54-1.63; *p* = 0.82).

Effect of sevoflurane anesthesia on mortality of patients after operation

Number of mortality of patients during hospitalization stay is provided in 9 studies, of which there are 3 cases in which patients died after operation. Fixed-effect model is used because there is no statistical significance in heterogeneity test (*p* = 0.35). The result indicates (Figure 10) that there is no statistical significance in mortality of patients after operation between sevoflurane anesthesia group and total intravenous anesthesia group (RR = 0.88, 95%CI 0.19-4.12; *p* = 0.87).

Discussion

To provide evidence for clinical anesthesia practice, this study evaluates the effect of sevoflurane anesthesia on myocardium in cardiac surgery from aspects of postoperative cardiac function, changes in myocardial enzyme, ICU stay, hospitalization stay and complications. The results of this study suggest that compared with total intravenous anesthesia group, patients' CO and CI after operation have been significantly improved in the sevoflurane anesthesia group; and concentration of postoperative 24 h cTnI in the sevoflurane anesthesia group has been reduced, as well as assisted respiratory time and ICU stay after operation. There is no significant difference in hospitalization stay between both groups; postoperative usage of vasoactive drugs in sevoflurane anesthesia group is less than in total intravenous anesthesia group. There is no significant difference in

postoperative occurrence of atrial fibrillation, recurrence rate of angina pectoris and mortality of patients after operation between both groups.

CO and CI are often used as indicator of cardiac function after operation. Analysis of the results in this study shows that compared with total intravenous anesthesia, sevoflurane anesthesia can significantly improve patients' CO and CI after operation, and can improve myocardial systolic function. Myocardial Troponin I (cTnI) is a specific diagnostic indicator for myocardial damage in the cardiac surgery perioperation. It is also a marker for myocardial protection, being used to evaluate the myocardial protection in perioperation and being used for prognosis. Due to myocardial damage that results from myocardial ischemia reperfusion injury, lengthy operation and cardiac pulmonary bypass, concentration of cTnI after operation increased to different degrees, which are in direct proportion to the damage [24, 25]. Analysis of the results suggests that the degree that patients' postoperative cTnI increased in sevoflurane anesthesia group is lower, which means the degree of myocardial ischemia in sevoflurane anesthesia group is lower than the control group, indicating that sevoflurane anesthesia can better protect myocardium after operation. Some studies suggest that volatile anesthetics can reduce the demand for postoperative usage of vasoactive drugs, probably because volatile anesthetics can better maintain the balance of myocardial energy metabolism during the period of ischemia and reperfusion[25]. Postoperative usage of vasoactive drugs in sevoflurane anesthesia group is less than in total intravenous anesthesia group, probably because myocardial damage after operation is milder in sevoflurane anesthesia group[26].

Although this study is more comprehensive than previous studies, there are shortcomings: as samples in some part of the study are small, bias can't be avoided; because of various clinical diagnosis and treatment in different institutions where researchers belong to, different definitions to the same index and different standards of treatment, validity of meta-analysis has been reduced; although all inclusive literature were strictly retrieved according to research strategy and the quality evaluations of all literature were obtained, the fact that there exists restrictions of language and update of databases and loss of some lately published non-English literature may have an impact on the results. To further prove the protection of sevoflurane to myocardium in cardiac surgery, a more reasonable, stricter and more polycentric randomized controlled trial with larger samples and enough follow-up time will be needed.

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