Sevoflurane downregulates interleukin-6 and interleukin-8 levels in patients after cardiopulmonary bypass surgery: a meta-analysis

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ABSTRACT. This study aimed to investigate the effect of sevoflurane on serum levels of interleukin (IL)-6 and IL-8 in patients who underwent cardiopulmonary bypass (CPB). The strength of the association between sevoflurane treatment and serum level of IL-6 and IL-8 was determined in patients who underwent CPB by summary standard mean differences (SMDs); 95% confidence interval (CI) was used. In total, seven case-control studies showed decreased IL-6 and IL-8 levels in sevoflurane-treated patients than in controls (IL-6: SMD = 1.56, 95%CI: 0.95-2.17, P < 0.001; IL-8: SMD = 2.17, 95%CI: 1.40-2.95, P < 0.001, respectively). Further, IL-6 and IL-8 levels were significantly higher in sevoflurane-treated patients than in sevoflurane-pretreated patients (IL-6 post *vs* pre: SMD = 2.17, 95%CI: 1.40-2.95, P < 0.001; IL-8 post *vs* pre: SMD = 4.01, 95%CI: 2.80-5.21, P < 0.001, respectively). CPB-stratified analysis showed significant decrease in IL-6 and IL-8 levels in sevoflurane-treated patients than in controls, irrespective of the time after CPB surgery (P < 0.05).

Moreover, sevoflurane-pretreated patients under the <12-h subgroup showed decreased IL-6 levels (P = 0.698), while all other subgroups showed decreased IL-8 levels (P < 0.05). Further, subgroup analysis by different dose of sevoflurane showed decreased IL-6 and IL-8 levels in subgroups administered with a dose of <2 and ≥2% sevoflurane under the case *vs* control and pre- *vs* post-treatment of sevoflurane models. Serum IL-6 and IL-8 levels were significantly lower in sevoflurane-treated patients who underwent CPB, suggesting sevoflurane pretreatment to be more beneficial than post-treatment.

Key words: Interleukin-6; Interleukin-8; Sevoflurane; Meta-analysis; Cardiopulmonary bypass

INTRODUCTION

Sevoflurane is a new anesthetic agent that is used for inducing and maintaining general anesthesia (Ogurlu et al., 2014). Although anesthetics are important in alleviating surgical pain in patients, they also contribute to postoperative conditions such as agitation, excitement, nausea, and vomiting, which are also seen in sevoflurane inhalation (Yin et al., 2014). Sevoflurane has several beneficial effects that are actively pursued for their clinical application. For example, sevoflurane treatment in breast cancer patients may increase IL-10 levels to inhibit the production of various pro-inflammatory cytokines such as interleukin (IL)-1/-6/-8, tumor necrosis factor (TNF)-α, and matrix metalloproteinases (MMPs), suggesting the clinical application of sevoflurane in immunomodulation (Deegan et al., 2010). Cardiopulmonary bypass (CPB) is associated with myocardial ischemia-reperfusion injury that results in high production of proinflammatory cytokines such as IL-6 and IL-8. Here we analyze the sevoflurane-mediated effects on proinflammatory mediators in CBP settings, as it is suggested that sevoflurane might suppress inflammation (Cho et al., 2009).

IL-6 is a cytokine that is produced by T cells and macrophages exhibiting either pro- or anti-inflammatory properties (Zhang et al., 2014). Pro-inflammatory role of IL-6 mediates immune responses after infection and trauma, possibly resulting in massive tissue injuries (Lenski and Scherer, 2014). IL-8 is a chemokine mainly secreted by epithelial, endothelial, and smooth muscle cells and macrophages, and plays an important role in the innate immune system (Zarogoulidis et al., 2014). IL-8 is also known as neutrophil chemotactic factor that induces chemotaxis of target cells by causing neutrophils and granulocytes to migrate toward the site of infection (Sunaga et al., 2014). IL-6 and IL-8 levels in patients during coronary artery bypass grafting (CABG) sharply increase from normal at the time of surgery, to its highest levels by the end of surgery. Elevated levels of IL-6 and IL-8 may have fatal influence on pulmonary function resulting from endocrine stress response and inflammatory activation (Winterhalter et al., 2008). Hence, sevoflurane involvement modulates IL-6 and IL-8 expression, which may have a potential role in CPB patients. Sevoflurane is administered as a premedication during CPB and can inhibit the expression and release of tumor necrosis factor (TNF), thus contributing to the suppression of IL-6 and IL-8 production, regulating the activation of inflammation, and eventually may result in the protection of myocardial function (Schmid et al., 2012). Hence, sevoflurane treatment is closely associated with the serum levels of IL-6 and IL-8 in patients with CPB (Nader et al., 2006; Wang et al., 2013); however, results from previous studies are inconsistent with this hypothesis (Zhang et al., 2007; Ma et al., 2009). Therefore, we conducted a comprehensive meta-analysis to investigate sevoflurane effect on IL-6 and IL-8 levels in patients with CPB.

METHODS

Data sources and keywords

This meta-analysis was conducted and reported according to the PRISMA guidelines (as shown in Annex I). Studies published before 30 June 2014 were selected based on the correlation between sevoflurane treatment and serum level of IL-6 and IL-8 in patients who underwent CABG with CPB. Computerized literature databases such as Embase, Web of Science, Google Scholar, PubMed, China BioMedicine (CBM) and China National Knowledge Infrastructure (CNKI) were searched by combining medical subject headings (Mesh) and keywords for sevoflurane ("sevoflurane" or "sevoflurane" or "sevorane" or "Ultane") and ILs ("Interleukins" or "IL"). No restriction was set for the published languages or dataset. A manual search using cross-references also retrieved additional articles. When data were not clear in the original article, authors were contacted for clarifications.

Study selection

Studies selected in this meta-analysis conformed to the following inclusion criteria: 1) case-control trials within a human population to explore the association of sevoflurane treatment with the serum levels of IL-6 and IL-8 in patients underwent CPB were incorporated; 2) only those participants who underwent CPB were included; 3) study subjects were divided into two groups: control, who received fentanyl and propofol instead of sevoflurane, and cases, who received fentanyl and sevoflurane; 4) data from the included articles must be original; 5) this meta-analysis evaluates the alternations in IL-6 and IL-8 levels, so sufficient information must be provided regarding the serum levels of IL-6 and IL-8. The exclusion criteria were: 1) those that did not satisfy the inclusion criteria; 2) abstracts, case report, letters, proceedings, or meta-analysis; 3) duplicated papers or studies with overlapping data.

Data extraction

For the purpose of reducing bias and enhancing confidence, two investigators (HM L and LL L) independently selected and evaluated the studies based on the selection criteria. Discussion and reexamination was used as a format to resolve disagreements (SY W). In addition to the measurement of outcomes, the following relevant data were extracted: 1) surname of first author and time of publication; 2) country and ethnicity of publication; 3) number of samples, age, and sex of subjects; 4) detection method for serum IL-6 and IL-8 levels; 5) follow-up time; 6) preoperative and postoperative serum levels of IL-6 and IL-8. Ratings were completed by two independent reviewers (HM L and LL L), with a third independent reviewer (SY W) resolving disagreements.

Quality Assessment

Two authors independently used a set of predefined criteria based on the Newcastle-Ottawa scale (NOS) criteria to decide whether the study in question is of high quality (Stang, 2010). The following three grades were set: 1) subject selection: 0-4; 2) comparability of subject: 0-2; 3) clinical outcome: 0-3. Total NOS scores ranged from 0-9 (lowest to highest), and there were two levels: low quality (0-6), high quality (7-9), respectively. Each item was assessed and finally judged as low or high.

Statistical analysis

Meta-analysis of effect sizes was performed using the STATA software, version 12.0 (Stata Corp, College Station, TX, USA). All results with P < 0.05 were regarded statistically significant. The strength of the association between sevoflurane treatment and serum level of IL-6 and IL-8 was determined in patients who underwent CPB by summary standard mean differences (SMDs); 95% confidence interval (CI) was used to gauge the precision of the summary SMD. The significance of the summary SMD was determined using Z-test. Quantitative analysis was performed with 95% CI using a random-effects model (DerSimonian and Laird method) or a fixed-effects model (Mantel-Haenszel method) to minimize the variance of the summary SMDs. Random-effects model was applied when significant heterogeneity existed among studies, or we chose the fixed-effects model. Cochran's *Q*-statistic was used to evaluate the heterogeneity across the studies. Because the Cochran's *Q*-statistic has low statistical power, I^2 test (0%, no heterogeneity; 100%, maximal heterogeneity) was also used (Peters et al., 2006; Jackson et al., 2012). For evaluating the extent of heterogeneity, stratified subgroup analyses by time point after CPB was conducted to explore potential effect modification. Funnel plot was constructed to investigate whether publication bias affects the validity of the overall estimation (Zintzaras and Ioannidis, 2005). A symmetric figure may indicate no possible existence of publication bias. Egger's linear regression test measured the symmetry of the funnel plot (Egger et al., 1997) using the *t*-test, and P < 0.05 showed statistical significance of publication bias.

RESULTS

Included studies

A total of seven papers, published between 2004 and 2013, out of 288 relevant articles identified by computerized databases and manual searching methods, met our inclusion criteria by providing information on the association of sevoflurane treatment with the serum level of IL-6 and IL-8 in patients who underwent CPB (Nader et al., 2004, 2006; Zhang et al., 2007; Ma et al., 2009; Gao et al., 2012; Mao et al., 2012; Wang et al., 2013). Methodological quality of the extracted studies is presented in Table 1. A total of five studies were performed in Asians and two in Caucasians involving 192 subjects, in China and USA. The range of dose distributions of sevoflurane was 1~3%. Enzyme linked immunosorbent assay (ELISA) was used to detect serum levels of IL-6 and IL-8 pre- and post-treatment of sevoflurane. The steps for screening and the study selection procedure are given in Figure 1.

Association of sevoflurane with serum IL-6 and IL-8 levels in CPB patients

The pooled SMDs for serum IL-6 and IL-8 levels revealed that their serum levels were significantly lower in the case groups as compared to normal controls (IL-6: SMD = 1.56, 95% CI: 0.95-2.17, P < 0.001; IL-8: SMD = 2.17, 95% CI: 1.40-2.95, P < 0.001; respectively), as given in Figure 2. Patients with CPB who received post-treatment of sevoflurane showed higher serum IL-6 and IL-8 levels than those who received pretreatment of sevoflurane (IL-6: SMD = 1.63, 95%CI: 0.30-2.96, P = 0.016; IL-8: SMD = 4.01, 95%CI: 2.80-5.21, P < 0.001; respectively).

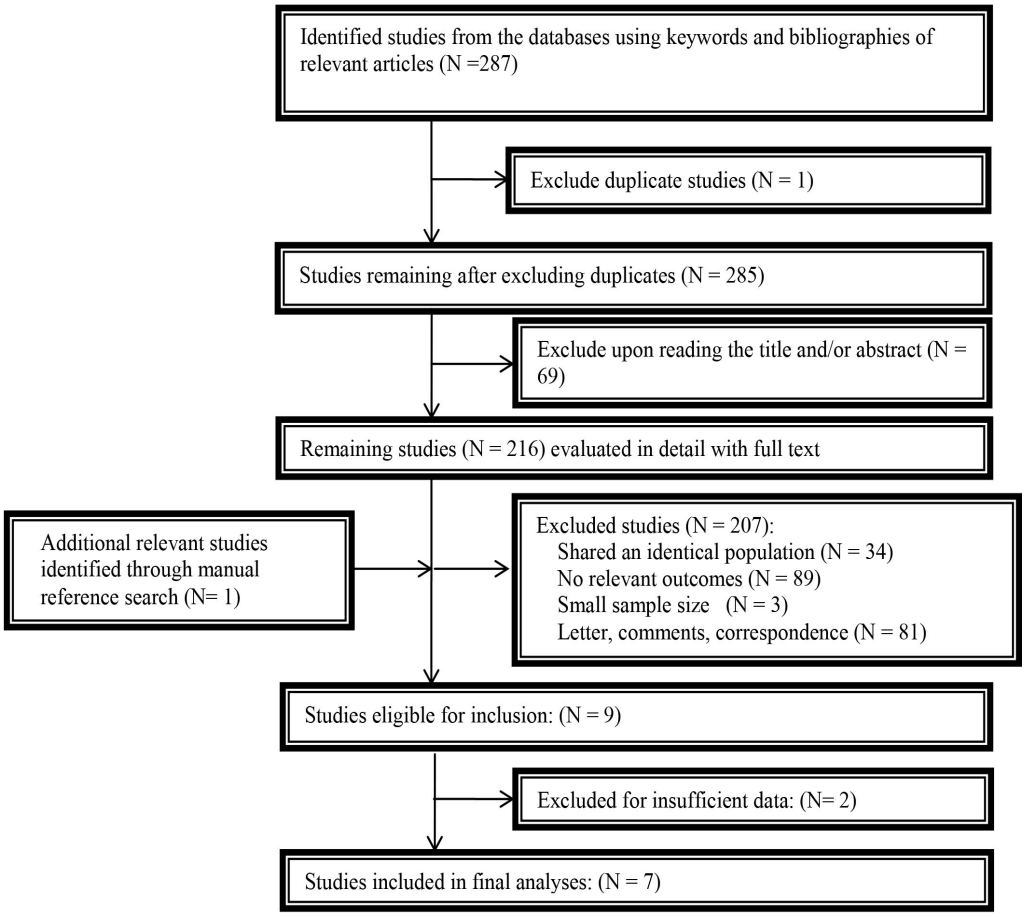

Figure 1. Flow chart showing study selection procedure. This meta-analysis involved seven studies.

Table 1. Methodologic quality of studies included in the final analysis based on the Newcastle-Ottawa scale for assessing the quality of case-control studies.

	Selection (score)				Comparability (score)	Exposure (score)			
Study	Adequate definition of patient case	Representativeness of patient cases	Selection of controls	Definition of controls additional factor	Control for important factor or	Ascertainment of of exposure (blinding)	Same method ascertainment for participants	Nonresponse rate*	Total score**
ang YW	1	1	1	1	1	0	1	0	6
Mao QQ	1	0	1	1	0	1	1	0	5
Gao CJ	1	1	1	1	0	1	1	1	7
Ma J	1	0	1	1	1	0	1	1	6
Zhang XL	1	1	1	1	1	0	1	0	6
Nader ND	1	1	1	1	0	1	1	1	7
Nader ND	1	1	1	1	1	0	1	1	7

*When there was no significant difference in the response rate between both groups by using X^2 test ($P > 0.05$), one point was awarded. **Total score could range from 0 to 9 points.

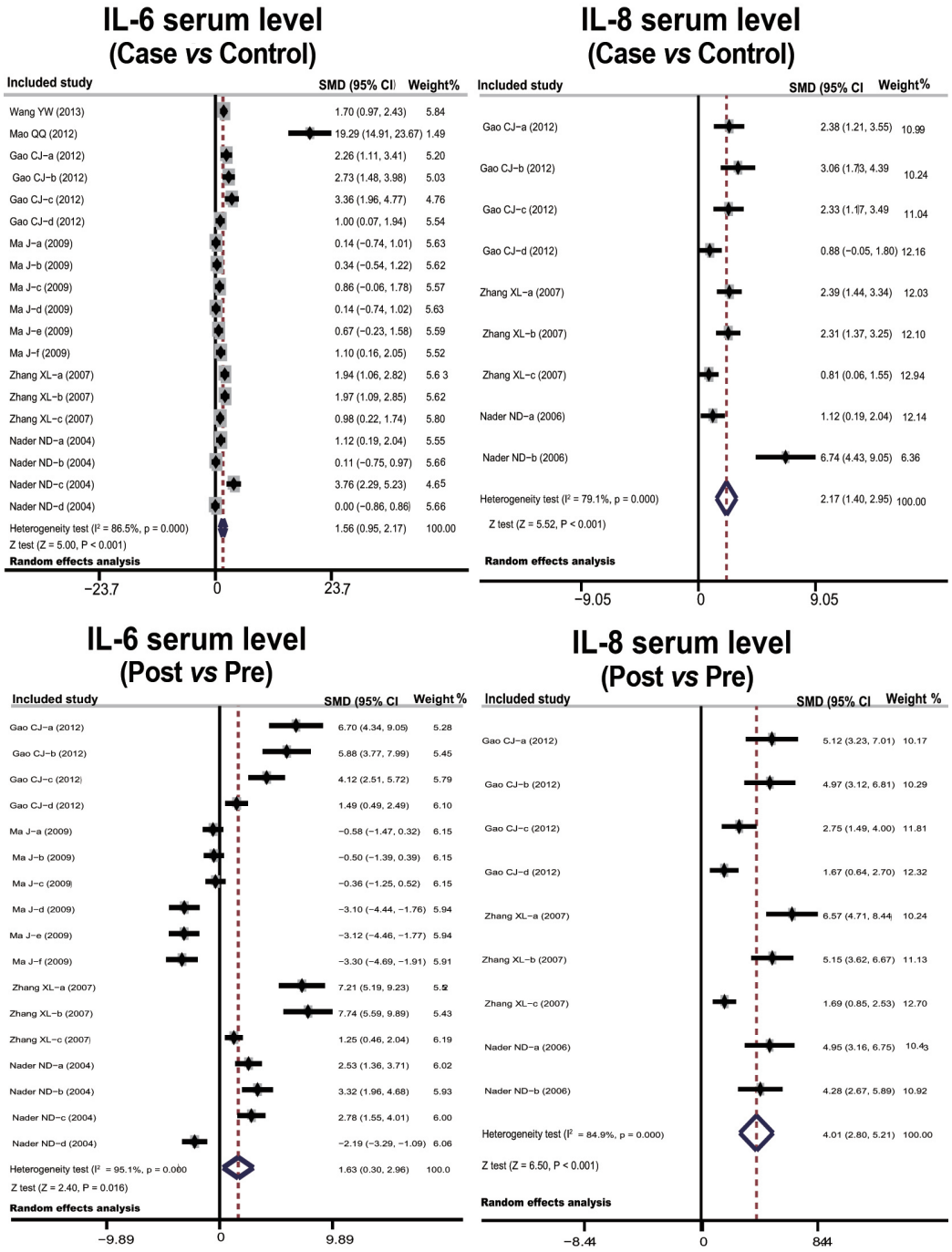

Figure 2. Forest plots showing the difference of serum IL-6 and IL-8 levels between healthy subjects and sevoflurane-treated patients after cardiopulmonary bypass surgery via pre- and post-treatment of sevoflurane.

Subgroup analysis

Subgroup analysis based on time point after CPB showed that serum IL-6 levels in sevoflurane-treated patients decreased significantly compared to that of control group within both the <12 h after CPB (SMD = 1.86, 95%CI: 0.99-2.72, P < 0.001) and >12 h after CPB groups (SMD = 1.09, 95%CI: 0.42-1.76, P = 0.001). Similar results were also found in the comparison of serum IL-8 levels between the cases and controls (all P < 0.05) (Figure 3). However, serum IL-6 level was found to increase only in the <12 h subgroup post-treated with sevoflurane (SMD = 2.80, 95%CI: 1.07-4.53, P = 0.001), but not in the subgroup of >12 h after CPB (SMD = -0.44, 95%CI: -2.66-1.78, P = 0.698). In addition, positive correlation was seen between the serum IL-8 levels of sevoflurane-treated <12 h and >12 h subgroups (all P < 0.05). Subgroup analysis with different dose of sevoflurane showed decreased IL-6 and IL-8 levels in sevoflurane-treated patients than in control group with <2 and ≥2% doses (all P < 0.05). Moreover, pre- and post-treatment levels of IL-6 and IL-8 decreased in both subgroups of different sevoflurane dose (all P < 0.05) (Figure 4).

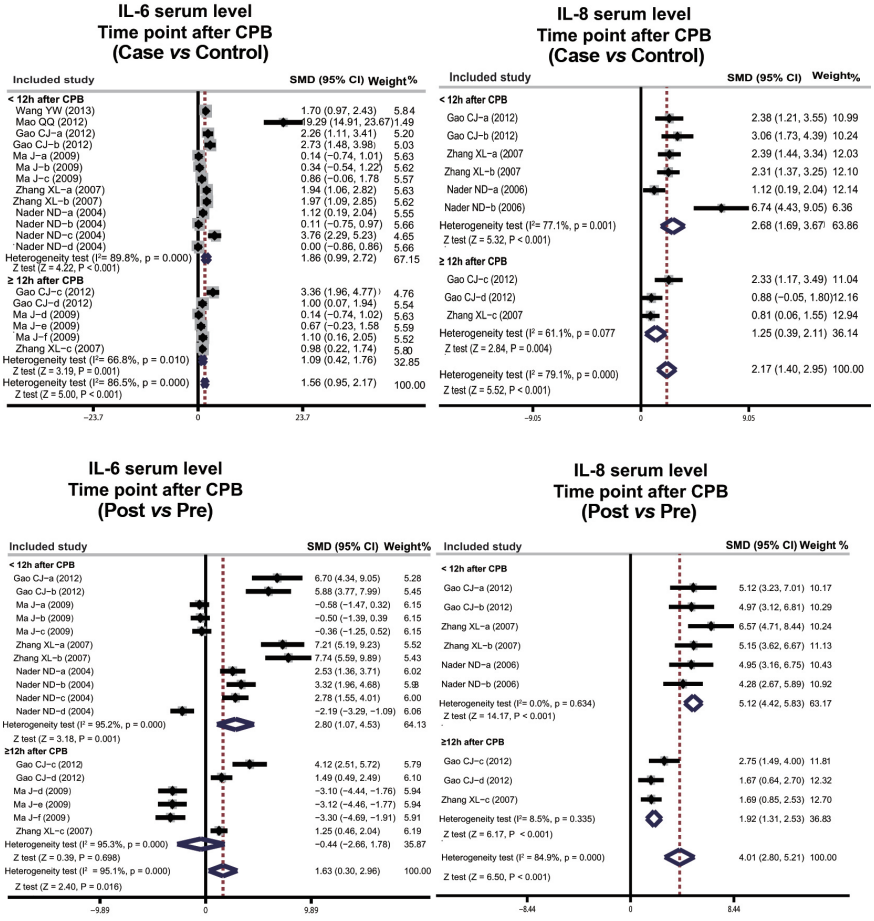

Figure 3. Subgroup analyses by time point on the difference of serum IL-6 and IL-8 levels between healthy subjects and sevoflurane-treated patients after cardiopulmonary bypass surgery via pre- and post-treatment of sevoflurane.

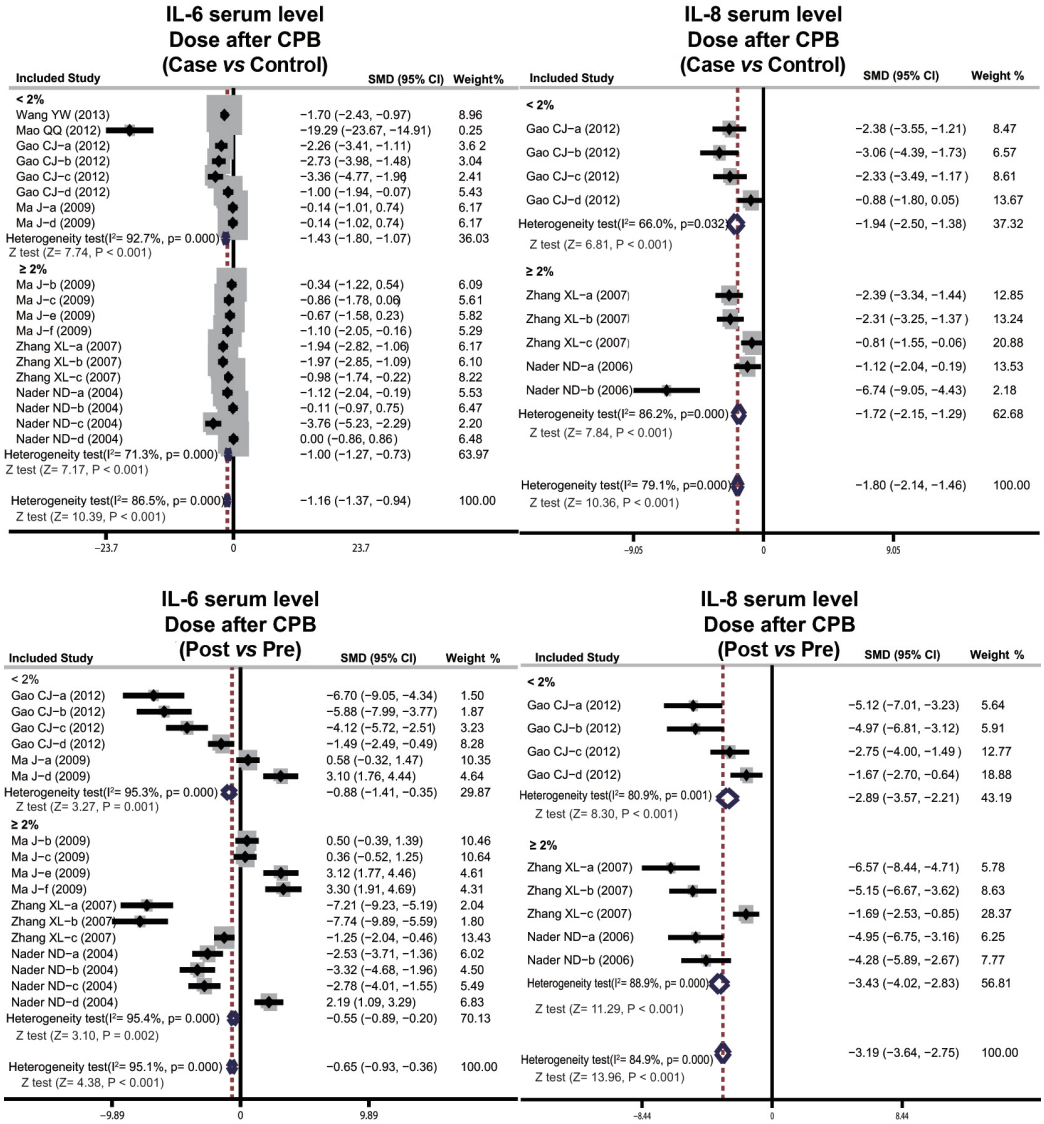

Figure 4. Subgroup analyses by different dose of sevoflurane on the difference of serum IL-6 and IL-8 levels between healthy subjects and sevoflurane-treated patients after cardiopulmonary bypass surgery via pre- and post-treatment of sevoflurane.

Publication bias

Graphical funnel plots for serum IL-6 and IL-8 levels presented to be asymmetrical. Egger's test suggested a possible existence of publication bias in both the case *vs* control models (IL-6: t = 5.82, P < 0.001; IL-8: t = 5.34, P = 0.001; respectively) and pretreatment *vs* post-treatment models (IL-6: t = 2.33, P = 0.034; IL-8: t = 8.10, P < 0.001; respectively) (Figure 5).

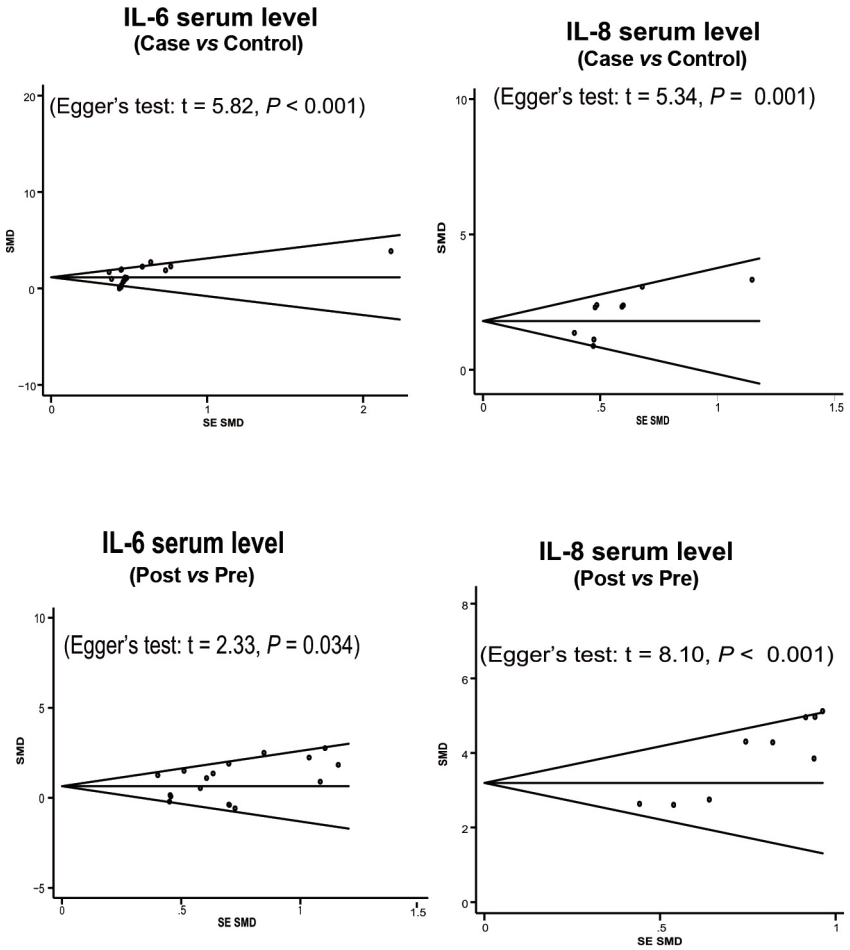

Figure 5. Funnel plot of publication biases showing the difference of serum IL-6 and IL-8 levels between healthy subjects and sevoflurane-treated patients after cardiopulmonary bypass surgery via pre- and post-treatment of sevoflurane.

DISCUSSION

Inhaled anesthetics (including sevoflurane) reduce myocardial injury and the need for inotropic support in cardiac patients (Zhao et al., 2013). Our meta-analysis explored the role of inflammatory cytokines, IL-6 and IL-8, in groups pretreated and post-treated with sevoflurane. The results of this meta-analysis indicated that both IL-6 and IL-8 levels were decreased after CPB in sevoflurane-treated patients, confirming that inflammatory cytokines play important roles in myocardial ischemia reperfusion injury. One possible explanation might be that during CPB procedures, direct contact of blood with pipeline, ischemia/reperfusion, and other anesthesia and surgical factors might induce systemic inflammatory response at the surface-blood interface or during ischemic reperfusion, and lead to the production of inflammatory mediators (Xu et al., 2011; Kortekaas et al., 2014). The accumulation and activation of inflammatory mediators and neutrophils, in turn,

play leading roles in increasing the pulmonary endothelial permeability; hence, damage to lung tissue structure is a critical event for initiating an pulmonary edema, atelectasis, or hypoxemia postoperatively (Grommes and Soehnlein, 2011; Muller-Redetzky et al., 2014). Sevoflurane could successfully decrease the production of inflammatory mediators, which is largely attributed to the mechanism of sevoflurane in blocking the activation of the complement system and downregulating the generation of inflammatory mediators, and thereby help to reduce inflammatory response caused by CPB (Schmid et al., 2012; Watanabe et al., 2013; Aguado et al., 2014). Hence, control of inflammatory cytokine levels may help to reduce myocardial and pulmonary injury (Seki et al., 2010; Lee and Yang, 2012).

Further, both pre- and post-treatment of sevoflurane have protective myocardial effects (Anzai et al., 2013).There are significant differences between pretreatment and post-treatment of sevoflurane because of its *in vivo* mechanisms. With the opening of the ATP-sensitive potassium channel, pretreatment of sevoflurane may contribute to an increased mitochondrial matrix volume and maintenance of the integrity of mitochondria, and eventually exerting its effects on myocardial protection (Bouwman et al., 2007; Onishi et al., 2012). Myocardial ischemia reperfusion injury contributes to the opening of the mitochondrial permeability transition pore (mPTP). This causes damage to the inner mitochondrial membrane, the barrier that separates the intramitochondrial solutes from the extra-mitochondrial environment, which leads to the release of cytochrome C that is related to apoptosis (Kristen et al., 2013; Ong et al., 2015). In addition, post-treatment of sevoflurane may suppress myocardial injury by inhibiting mPTP opening (Li et al., 2013). Generally, sevoflurane pretreatment occurs before ischemia to improve ischemic tolerance; while post-treatment with sevoflurane is focused on the intraoperative or postoperative lung injury during CPB to reduce ischemic injury in the acute phase (Orriach et al., 2013; Zhou et al., 2013). By the suppression of advanced glycation end products synthesis and activation, sevoflurane post-treatment was suggested to eventually contribute to the downregulation of inflammatory mediators (Dong et al., 2014). In this meta-analysis, serum IL-6 and IL-8 levels in patients who received post-treatment of sevoflurane were much higher than in those who received pretreatment of sevoflurane, indicating that pretreatment of sevoflurane might be beneficial to patients after CPB through suppressing the release or expression of inflammatory cytokines and thereby reducing the degree of inflammation after CPB.

Further subgroup analysis by time point after CPB implicated that the serum IL-6 and IL-8 levels in sevoflurane-pretreated patients decreased more significantly than those in the control group within the <12 h after CPB and >12 h after CPB groups. However, post-treatment of sevoflurane the serum IL-6 levels only decreased in the <12 h after CPB group, but not in the subgroup of >12 h after CPB. This result suggests that sevoflurane may have short-term effect in improving cardiac function after weaning from CPB, but showed no long-term effect. This hypothesis, however, needs further investigation in more patients. Additionally, subgroup analysis by different doses of sevoflurane showed that both IL-6 and IL-8 levels decreased in sevoflurane-treated patients than that of control group in the dose <2 and ≥2% subgroups, and there were no difference of the serum levels of IL-6 and IL-8 under the model of pre- and post-treatment of sevoflurane. These results suggest that different doses of sevoflurane may have no significant influence in the efficacy of sevoflurane.

We understand the limitations of the current meta-analysis. First, there were only seven articles enrolled and most were conducted in Asians. Moreover, the number of patients involved in the study was also too small to predict valid conclusion in the meta-analysis, which might cause selection bias. Furthermore, cytokines might be readily released during or after heart surgery, suggesting the need of a much larger and homogeneous population for valid conclusions. Second, subgroup analysis (time point after CPB) was relatively small and further excluded potential

heterogeneity sources that affect our results. Other factors (e.g., ethnicity, country, sample size, or dosage) should also be further explored. Third, there was no further dose effect of sevoflurane investigation on the levels of IL-6 and IL-8 in patients with CPB, which clearly restricted the wider applicability of our results. Finally, although we wanted to study the effects of sevoflurane on ischemia-reperfusion injury, there were only two cytokines (IL-6/IL-8) studied, which was not enough to answer the question we posed. Several other parameters should be included in the meta-analysis to provide a more comprehensive assessment.

In conclusion, serum IL-6 and IL-8 levels were significantly lower after sevoflurane treatment in patients who underwent CPB, and pretreatment with sevoflurane might be more beneficial than post-treatment of sevoflurane. Future investigation is needed to interpret the association between sevoflurane treatment and the enrollment of more parameters during intra-cardiac surgery with CPB.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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