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ORIGINAL ARTICLE

Effects of volatile vs. propofol-based intravenous anesthetics on the alveolar inflammatory responses to one-lung ventilation: a meta-analysis of randomized controlled trials

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Abstract
Objective The aim of this meta-analysis is to compare the potential effects of inhalation anesthetics with total intravenous anesthetics on alveolar cytokine expression and lung-related clinical outcomes in patients undergoing one-lung ventilation (OLV) for thoracic surgery.
Methods We retrieved the PubMed, EMBASE, and the Cochrane Library respectively to identify randomized controlled trials comparing different anesthetics (volatile anesthetics vs. intravenous anesthetics) on the pulmonary inflammatory response to OLV. The primary outcomes were the levels of alveolar concentrations of inflammatory cytokines.
Results Eight randomized controlled trials that included 365 patients were screened. Overall, there were significant differences in the concentration of alveolar inflammatory mediators between volatile group and intravenous group, in which volatile group had lower levels of TNF-α (SMD −1.51; 95 % CI −2.15 to −0.87; $p < 0.001$), IL-6 (SMD −0.70; 95 % CI −0.99 to −0.41; $p < 0.001$) and IL-8 (SMD −1.32; 95 % CI −2.20 to −0.45; $p = 0.003$). The overall number of pulmonary complications in the volatile group was smaller (RR 0.42; 95 % CI 0.23–0.77; $p = 0.005$) and patients in that group had significantly abridged hospitalization stay (WMD −3.59 days; 95 % CI −5.70 to −1.48 days; $p = 0.001$).
Conclusions Inhalation anesthetics might be preferable in patients undergoing OLV for thoracic surgery and their protective effects might work via attenuating inflammatory responses.

Keywords Meta-analysis · One-lung ventilation · Inhalation anesthetics · Intravenous anesthetics · Pulmonary inflammation

Introduction

One-lung ventilation (OLV), an established procedure in thoracic surgery, enhances the field of thoracic surgery and reduces the contamination of the contralateral lung, with the efficacy of the surgery and the safety of the patients ensured [1]. However, OLV may also be injurious in terms of increased mechanical stress characterized by alveolar cell stretch, over distension, increased cyclic recruitment of alveolar units, compression of alveolar vessels and increased pulmonary alveolar resistance [2]. Consequently, a variety of inflammatory cytokines [3] could be released, triggering local or systemic inflammatory responses, and increased mortality has been reported in patients with elevated concentrations of interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α in bronchoalveolar lavage during their clinical course, precluding resolution of the pulmonary inflammatory processes [4, 5].

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It is well acknowledged that general anesthesia during mechanical ventilation can mediate several immune effects which may affect postoperative outcomes. In addition, pro-inflammatory reactions during OLV were indicated to be subject to anesthesia approaches. However, it is still controversial as to whether inhalation anesthesia or propofol-based intravenous anesthesia is more preferred for anti-inflammatory responses to OLV. Propofol has been known to attenuate lung inflammations and has a protective effect on pulmonary functionality [6, 7]. Moreover, studies suggested that volatile anesthetics may serve as immunomodulator in the patients undergoing OLV with significant reduction of inflammatory cytokines and a significantly superior clinical outcome to those under anesthesia with intravenous administration of propofol [1, 8].

Given the fact that risks of morbidity or mortality might be elevated particularly after OLV, any intervention to reduce such risks should be emphasized. Unfortunately, there is no consensus on the efficacy of anesthetic agents on inflammatory response and clinical outcomes in patients with OLV. The aim of this meta-analysis is to compare the effects of potential modulation of the expressions of alveolar inflammatory cytokines by inhalation anesthesia with those by propofol-based intravenous anesthesia in thoracic surgery in patients undergoing OLV.

Materials and methods

Retrieval strategy

Two authors (B. S. & J. F. W) retrieved the PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for relevant publications until September 20th, 2014. Retrieval items included "anesthetics, intravenous" "intravenous anesthesia", "intravenous anesthetics," "intravenous anesthetic agent", "propofol*", "diisopropylphenol", "diprivan*", "disoprivan", "disoprofol", "pofol", "anesthetics, inhalation", "Inhalation anesthesia", "inhalation anesthetics", "Inhalation "nesthetic agent", "sevofluran*", "sevorane", "ultane", "desfluran*", "s"prane", "isofluran*", and "one-lung ventilation". There was no language restriction for the retrieval. The search was limited to human subjects and randomized controlled trials (RCTs). In addition, the reference lists of identified studies were checked manually to include other potentially eligible trials. This process was performed iteratively until no more articles could be available.

Study screening

Human studies, regardless of sample size, were included providing they met the following criteria: RCTs of intravenous (e.g., propofol) versus inhalation (e.g., isoflurane, sevoflurane, or desflurane) anesthesia for OLV in thoracic surgery. In the case of multiple publications on the same topic or data overlapping, we designated the most recent reports or those with the largest population. The number of participants in groups as well as the mean and standard deviation (SD) of concentrations should be provided, or can be converted from median and range or extracted or calculated from figures. For the studies without adequate data, we contacted the authors for the unpublished data; if the author cannot provide the data as required, these studies were also excluded. Last but not the least, we excluded the studies of participants who had only one lung. Agreement between reviewers regarding trial inclusion was assessed using the Cohen K statistics [9].

Quality assessment

The quality of trials was evaluated with the methods recommended by the Cochrane Collaboration for assessing risk of bias. The criteria used for quality assessment were sequence generation of allocation, allocation concealment, blinding, selective outcome reporting, and other sources of bias. Each criterion was categorized as 'yes', 'no', or 'unclear', and the summary assessments of the risk of bias for each important outcome within and across studies was categorized as 'low risk of bias', 'unclear risk of bias', and 'high risk of bias'.

Data extraction

With standard data extraction forms, two authors (B. S. and J. F. W) independently performed data extraction: publication information (first author's name, publication year), characteristics of participants (sample size, age, gender, type of case/control, type of surgery) and outcome information. Extracted data were entered into the standardized Excel (Microsoft Corp) file and were checked by another author (L. L. B). In the case of studies without indication of exact time points for outcomes, we designated the time point closest to pool. Any disagreements were resolved by discussion and consensus.

The primary outcomes were the levels of alveolar concentrations of inflammatory mediators (i.e., IL-1β, IL-6, IL-8, and TNF-α). Secondary outcomes included duration of ICU stay, incidence of atelectasis, pneumonia, total number of pulmonary complications (such as, atelectasis, pneumonia, edema, ARDS, ALI, and reintubation) and length of hospital stay.

If the study provided medians and ranges instead of means and SDs, we calculated the means and SDs using the method developed by Hozo et al. [10]. For those reports that only provided figures and no exact data were available

despite contact with the authors, we extracted exact means and SDs from figures using the program Engauge Digitizer 5.1 (M. Mitchell, Engauge Digitizer, http://digitizer.sourceforge.net), which can read exact values by digitizing data points from an image file after manually setting coordinate axis. In studies with subdivision of volatile groups, the subgroups were combined for pooled analyses.

Statistical analysis

Differences were expressed as relative risks (RRs) with 95 % confidence intervals (CIs) for dichotomous outcomes, and standardized mean differences (SMDs) or weighted mean differences (WMDs) with 95 % CIs for continuous outcomes. SMD is the difference in mean outcome between groups divided by standard deviation of outcome among participants. Due to the variety of methods and units involved in assessment of concentration levels among different studies, we adopted SMD to standardize the study results to a uniform scale before combination. Heterogeneity across studies was tested using the I^2, which is a quantitative measure of inconsistency across studies. Studies with an I^2 statistics of 25–50 % were considered to be low heterogeneous, those with an I^2 statistic of 50–75 % were considered to have moderate heterogeneity, and those with an I^2 statistic of >75 % were considered to have high heterogeneity [11]. Random effects model was only applicable for specified heterogeneity (p value of χ^2 test less than 0.10 and I^2 greater than 50 %). Because of the inconsistency in patient characteristics, surgical approaches, OLV duration and other confounding factors among studies, we further conducted sensitivity analyses to explore possible heterogeneity explanations and the influence of various exclusion criteria on the overall pooled estimates. We also investigated the impact of a single study on the overall pooled estimates by omitting one study in each turn. Publication bias was evaluated by funnel plots and Begg's tests [12]. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using STATA, ver. 12.0 (Stata Corp.).

Results

Study identification and screening

A total of 108 RCTs were identified by the initial database retrieval. Nineteen RCTs were excluded due to study duplicates, and 63 RCTs were excluded based on the titles and abstracts. The remaining 26 full-text articles were reviewed for more detailed evaluation, of which 18 were excluded because of lack of endpoints as required, and one was excluded due to questionable authentication. An additional RCT was identified by reference check, and eight RCTs meeting our inclusion criteria were included in the present meta-analysis [1, 8, 13–18]. The Cohen K statistics for agreement on study inclusion was 0.93. The selection process for RCTs included in the meta-analysis is shown in Fig. 1.

Study characteristics and quality

The main characteristics of the eight RCTs included in this meta-analysis are presented in Table 1. These studies were published between 2007 and 2014. The sample size of the RCTs ranged from 30 to 63 (total 365). Among the eight studies herein included, five reported the levels of TNF-α [1, 8, 13, 14, 16] and IL-8 [1, 8, 13–15], four reported the levels of IL-6 [1, 14–16] and length of ICU stay [1, 8, 17, 18], three reported the levels of IL-1β [1, 14, 15], the incidence of atelectasis [1, 8, 17], pneumonia [1, 8, 18] and length of hospital stay [8, 17, 18]. The quality of the studies retrieved was assessed with the methods recommended by the Cochrane Collaboration for assessing risk of bias. One trial [8] was determined as low risk of bias (plausible bias unlikely to seriously alter the results), and seven trials [1, 13–18] were at unclear risk of bias (plausible bias that rises up to uncertainty about the results). An overview of the quality appraisal was shown in Table 2.

The primary outcomes: inflammatory mediators

Figure 2 shows the pooled results from the random effects model combining the SMDs for TNF-α and IL-1β. The amount of studies investigating alveolar concentrations of TNF-α is five [1, 8, 13, 14, 16], among which the concentrations of alveolar TNF-α were lower in volatile group than those in propofol group (SMD −1.51; 95 % CI −2.15 to −0.87; $p < 0.001$). Further exclusion of any single study did not substantially alter the overall combined SMD in a range from −1.75 (95 % CI −2.31 to −1.19; $p < 0.001$) to −1.26 (95 % CI −1.80 to −0.72; $p < 0.001$). The amount of studies investigating alveolar concentrations of IL-1β is three [1, 14, 15], and the pooled results of IL-1β (SMD −0.76; 95 % CI −1.72 to 0.21; $p = 0.123$) indicated a declining, but statistically insignificant, trend of IL-1β levels in Volatile Group.

Data for alveolar IL-6 concentration were extracted from four trials [1, 14–16]. As Fig. 3 shows, propofol group had significantly higher levels of alveolar IL-6 than volatile group (SMD –0.70; 95 % CI −0.99 to −0.41; $p < 0.001$), with no heterogeneity among the studies ($I^2 = 0$, $p = 0.994$). Further exclusion of any single study did not materially alter the overall combined SMD, in a range from −0.72 (95 % CI −1.05 to −0.39; $p < 0.001$) to −0.69 (95 % CI −1.02 to −0.36; $p < 0.001$).

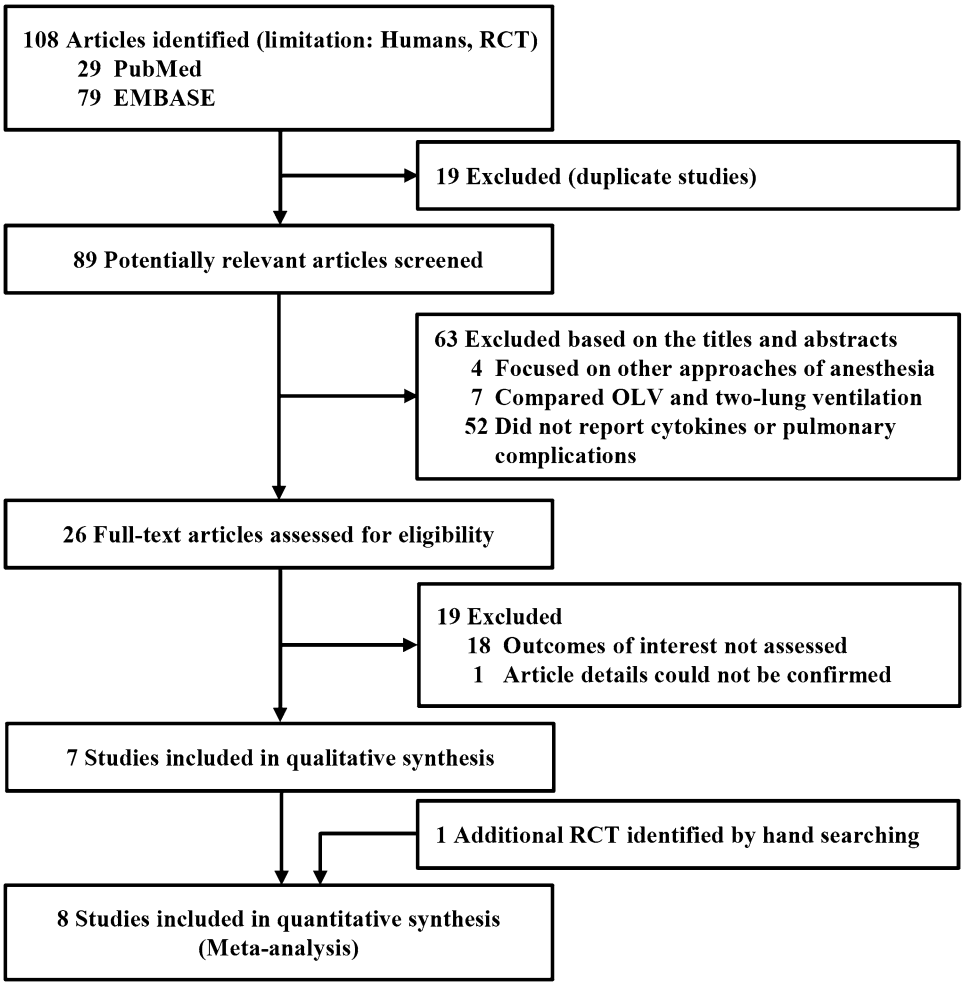

Fig. 1 Flowchart of study selection. *RCT* randomized controlled trial, *OLV* one-lung ventilation

Table 1 Main characteristics of randomized controlled trials included

References	No. (M/F)	Age (years): I/V	Type of surgery	Study design	Volatile group	Intravenous group
[1]	54 (32/22)	58 ± 12/55 ± 15	Lung resection	P, RCT	Sevoflurane (n = 27)	Propofol ($n = 27$)
[8]	50 (35/15)	50.3 ± 13/48.8 ± 14	Lung resection	P, DB, RCT	Isoflurane ($n = 25$)	Propofol ($n = 25$)
[13]	30 (21/9)	59.3 ± 11.1/58.8 ± 9.4	Lung resection	P, SB, RCT	Desflurane ($n = 15$)	Propofol ($n = 15$)
[14]	63 (41/22)	56.4 ± 17.0/57.3 ± 15.8	Lung resection	P, SB, RCT	Sevoflurane ($n = 21$) Desflurane ($n = 21$)	Propofol ($n = 21$)
[15]	40 (31/9)	61.7 ± 13.5/62.9 ± 13.8	Lung resection	P, RCT	Sevoflurane ($n = 20$)	Propofol ($n = 20$)
[16]	40 (25/15)	52.9 ± 9.8/54.5 ± 12.4	Lung resection	P, RCT	Sevoflurane ($n = 20$)	Propofol ($n = 20$)
[17]	48 (48/0)	63.2 ± 7.5/60.4 ± 7.5	Esophagectomy	P, SB, RCT	Sevoflurane ($n = 24$)	Propofol ($n = 24$)
[18]	40 (29/11)	59.0 ± 7.8/60.6 ± 6.6	Esophagectomy	P, RCT	Sevoflurane ($n = 20$)	Propofol ($n = 20$)

M/F male/female, *I/V* intravenous group/volatile group, *P* prospective, *RCT* randomized controlled trial, *DB* double-blind, *SB* single-blind

Figure 2 also shows the pooled results from the random effects model combining the SMDs for alveolar IL-8. Overall, five studies [1, 8, 13–15] were included in this analysis and compared with propofol group, the alveolar IL-8 concentrations was lower in volatile group (SMD −1.32; 95 % CI −2.20 to −0.45; $p = 0.003$). Further exclusion of any single study did not materially alter the overall combined SMD, in a range from −1.59 (95 % CI −2.58 to −0.60; $p = 0.002$) to −0.86 (95 % CI −1.16 to −0.55; $p < 0.001$). Table 3 shows the results of sensitivity analyses based on various exclusion criteria for TNF-α, IL-6, and IL-8.

Table 2 Assessment of bias risks

References	Sequence generation	Allocation concealment	Blinding	Incomplete outcome date addressed	Selective outcome reporting	Free of other bias	Summary risk of bias
[1]	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear
[8]	Yes	Yes	Yes	Yes	Yes	Yes	Low
[13]	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear
[14]	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear
[15]	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear
[16]	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear
[17]	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
[18]	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear

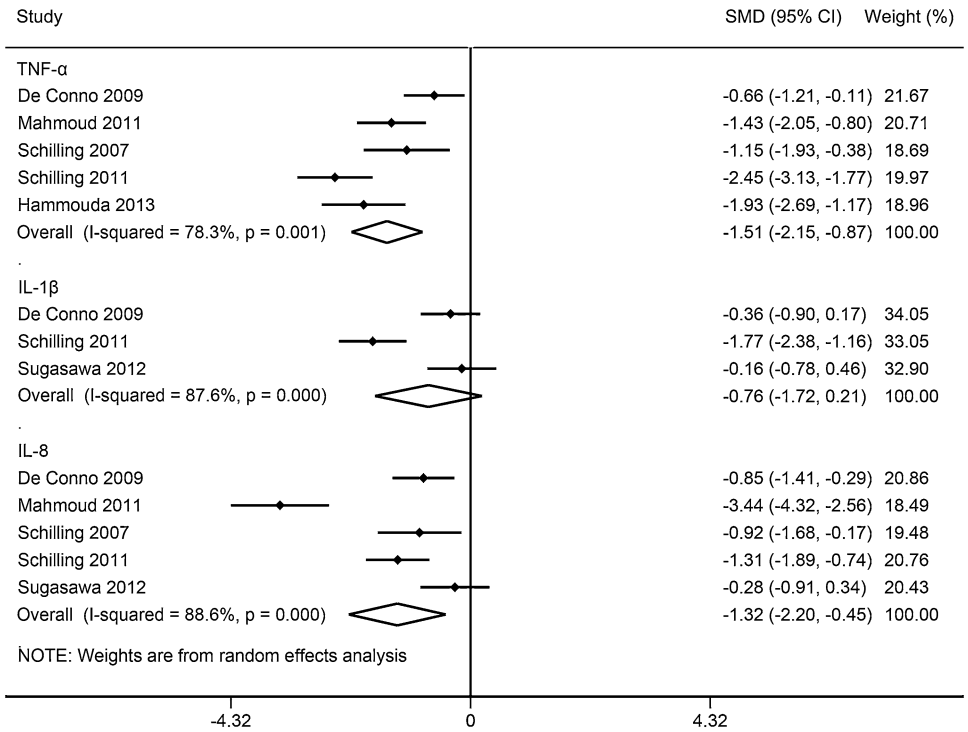

Fig. 2 Meta-analysis of RCTs evaluating alveolar levels of TNF-α, IL-1β, IL-8 after OLV between volatile group and intravenous group. *SMD* standardized mean difference

The secondary outcomes

Tables 4 and 5 outline the secondary outcomes. The types of anesthetics were not associated with significant differences in atelectasis (RR 0.57; 95 % CI 0.25–1.29; $p = 0.176$), pneumonia (RR 0.37; 95 % CI 0.11–1.20; $p = 0.098$) or length of ICU stay (WMD −12.84 h; 95 % CI −27.17 to 1.49 h; $p = 0.079$) between volatile and intravenous groups. While the overall number of pulmonary complications was smaller in the volatile group (RR 0.42; 95 % CI 0.23–0.77; $p = 0.005$) (Fig. 4). In addition, patients in the volatile group spent significantly less time in hospital (WMD −3.59 days; 95 % CI −5.70 to −1.48 days; $p = 0.001$) compared with patients in the intravenous group.

Publication bias

Publication bias was assessed, but the low power with only five studies restrained the interpretability of the findings.

Discussion

This is a systematic review and meta-analysis of eight RCTs aimed to evaluate the effects of different anesthetics (volatile anesthetics versus propofol-based intravenous anesthetics) on the pulmonary inflammatory responses to OLV and clinical outcome in patients undergoing thoracic surgery. Compared with propofol-based

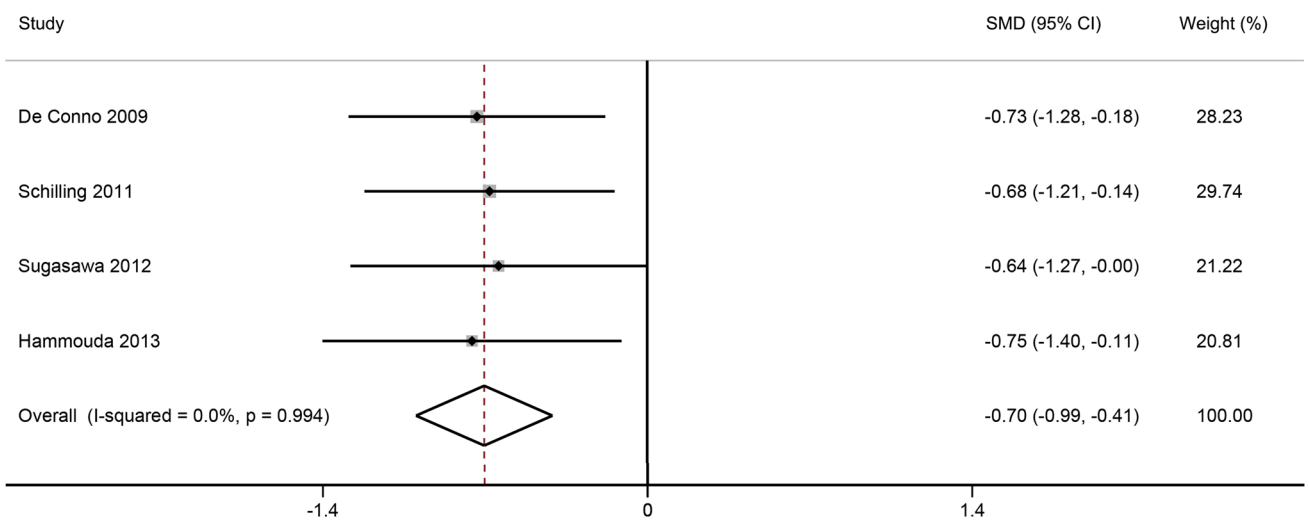

Fig. 3 Meta-analysis of RCTs evaluating alveolar levels of IL-6 after OLV between volatile and intravenous groups. *SMD* standardized mean difference

Table 3 Sensitivity analyses based on various exclusion criteria

Outcome	No. of patients	No. of trials	SMD (95 % CI)	*p* value	I^2 %	*p* value for heterogeneity
Alveolar TNF-α						
Studies provided dates [1, 8, 16]	144	3	−1.30 (−2.03 to −0.57)	<0.001	74.3	0.020
Dates obtained from Figs. [13, 14]	93	2	−1.81 (−3.08 to −0.54)	0.005	83.5	0.014
BALF obtained from DL [8, 13, 14]	143	3	−1.69 (−2.45 to −0.92)	<0.001	72.5	0.026
Alveolar IL-6						
Studies provided dates [1, 16]	94	2	−0.74 (−1.16 to −0.32)	0.001	0.0	0.961
Dates obtained from Figs. [14, 15]	103	2	−0.66 (−1.07 to −0.25)[a]	0.002	0.0	0.927
BALF obtained from DL [14, 15]	103	2	–0.71 (–1.12 to −0.29)[b]	0.001	0.0	0.875
Alveolar IL-8						
Studies provided dates [1, 8]	104	2	−2.12 (−4.66 to 0.42)	0.101	95.8	<0.001
Dates obtained from Figs. [13, 15]	133	3	−0.84 (−1.48 to −0.21)[a]	0.009	65.2	0.057
BALF obtained from DL [8, 13, 15]	183	4	−1.45 (−2.62 to −0.28)[b]	0.015	91.3	<0.001

SMD standardized mean difference, *BALF* bronchoalveolar lavage fluid, *DL* dependent lung, *NDL* nondependent lung

[a] One study [15] combined DL group data and NDL group data as final data, [b] One study [15] used DL group data as final data

Table 4 The secondary outcomes: dichotomous data

Outcome	No. of patients	No. of trials	Volatile group	Intravenous group	RR (95 % CI)	*p* value	I^2 (%)	*p* value for heterogeneity
Atelectasis [1, 8, 17]	152	3	8 of 76	14 of 76	0.57 (0.25–1.29)	0.176	29.9	0.240
Pneumonia [1, 8, 18]	144	3	3 of 72	9 of 72	0.37 (0.11–1.20)	0.098	0.0	0.686
Total number of complications [1, 8, 17, 18]	192	4	12 of 96	29 of 96	0.42 (0.23–0.77)	0.005	7.0	0.358

RR relative risk

intravenous anesthetic, volatile anesthetics inhibited the expression of alveolar inflammatory cytokines after OLV.

There is a meta-analysis published in Cochrane Library demonstrating that very little evidence obtained from RCTs suggests differences in participant outcome with anesthesia

Table 5 The secondary outcomes: continuous data

Outcome	No. of patients	No. of trials	WMD (95 % CI)	*p* value	I^2 (%)	*p* value for heterogeneity
Length of ICU stay [1, 8, 17, 18]	192	4	−12.84 (−27.17 to 1.49)	0.079	62.0	0.048
Length of hospital stay [8, 17, 18]	138	3	−3.59 (−5.70 to −1.48)	0.001	25.2	0.263

WMD weighted mean difference

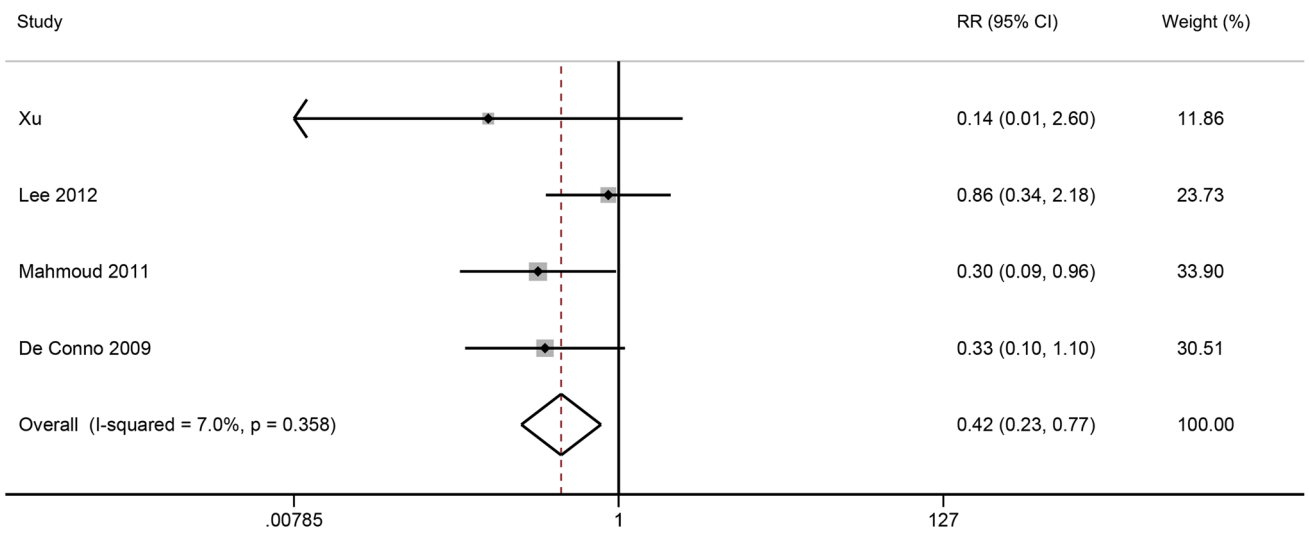

Fig. 4 Meta-analysis of RCTs evaluating the overall number of pulmonary complications between volatile and intravenous groups. *RR* relative risk

maintained by intravenous vs. inhalation anesthesia during OLV [19]. The review above was focused mainly on mortality, damages of vital organs as well as intraoperative awareness. Due to the lack of report of primary outcomes in the trials included, the meta-analysis could not be performed. However, our meta-analysis was aimed at inflammatory responses and lung-related clinical outcomes rather than those they focused on.

Inflammatory reactions could be attributable to multiple pulmonary factors, such as mechanical injury due to surgery, OLV-induced atelectasis and reexpansion [20, 21], alveolar hypoxia [22, 23], ischemia–reperfusion injury [24], damage due to oxygen inhalation at high concentrations [25] and airway pressure elevation from mechanical ventilation [26, 27]. Studies have shown that the increased levels of inflammatory cytokines subsequent to induction of systemic or local inflammatory reactions are closely related to the development of lung injury. IL-6 levels were correlated with the exacerbation and poor prognosis of the pulmonary infections [28]. IL-6 and IL-8 levels were positively associated with mortality rates in patients with ventilator-associated pneumonia [29] and administrations of IL-8 antagonists prior to the insult initiation have been shown to protect against the development of lung injury [30]. In addition, Bauer confirmed that increases in TNF-α and IL-1β levels reflect the severity of lung injury [31]. In the process of OLV, inflammatory cytokines may activate macrophages and recruit neutrophils in the lung. With the neutrophils activated, inflammatory cytokines IL-1β, IL-6, IL-8 and TNFα are released, resulting in tissue insults [32]. It is evidenced that pulmonary pathophysiology is closely correlated with the dysfunction of pulmonary vascular endothelial cells (PVEC). Moreover, PVECs are exposed to various inflammatory cytokines, the levels of which might contribute to the functional and morphological changes of PVECs [32].

In the present meta–analysis, to obtain more authentic results, rigorous inclusion criteria were formulated. Entry of RCTs was restricted to those with clear enrollment of patients undergoing OLV and specified reference of the levels of inflammatory mediators. Our meta–analysis showed that the release of alveolar TNF–α (SMD −1.51; 95 % CI −2.15 to −0.87; $p < 0.001$), IL–6 (SMD −0.70; 95 % CI −0.99 to −0.41; $p < 0.001$) and IL–8 (SMD −1.32; 95 % CI −2.20 to −0.45; $p = 0.003$) were significantly decreased during volatile anesthetic administration compared with propofol–based intravenous anesthesia. The pooled results of IL–1β (SMD −0.76; 95 % CI −1.72 to 0.21; $p = 0.123$)

indicated a declining, but statistically insignificant, trend of IL–1β levels in Volatile Group. Moreover, exclusion of any single study and sensitivity analyses based on various exclusion criteria did not materially modify the pooled results, which adds robustness to our main findings. On the other hand, our analysis was in accordance with the results in animal models of acute lung injury (ALI). It has been reported that volatile anesthetics could attenuate pro–inflammatory process in the lung tissue with LPS–induced ALI [33, 34]. Xiong et al. [35] demonstrated that inhalation of sevoflurane during mechanical ventilation protects against lung injury by preventing pro-inflammatory responses, which is consistent with a previous reported by Faller et al. [36]. Volatile anesthetic also acts as protector in two-hit model of ALI by preventing pulmonary cytokine release [37].

Meanwhile, results from our present meta-analysis were in agreement with some in vitro studies. Several studies showed that exposure to volatile anesthetics could reduce secretion of inflammatory mediators in airway epithelial cells (AECs) [38–40]. Additionally, Watanabe et al. [41] confirmed that NF-κB-mediated production of pulmonary epithelial cell-derived inflammatory cytokines could be suppressed by sevoflurane. These results suggested that the application of volatile anesthetics might attenuate the pulmonary inflammatory response to OLV, which may account for their protective effect in thoracic surgery.

In our meta-analysis, duration of ICU stay, total number of pulmonary complications and length of hospital stay were also measured. In terms of the overall number of pulmonary complications (RR 0.42; 95 % CI 0.23–0.77; $p = 0.005$) and time spent in hospital (WMD −3.59 days; 95 % CI −5.70 to −1.48 days; $p = 0.001$), inhalation anesthetics were preferred. In addition, the observed differences of ICU stay ($p = 0.079$) and pneumonia morbidity ($p = 0.098$) between inhalation and propofol-based intravenous anesthetics were marginally significant and larger sample may increase the chance of finding a significant difference. Our finding suggested that volatile anesthetics might have potential advantages in patients undergoing OLV, which needs larger sample to strengthen. In parallel, propofol has been widely applied to anesthesia with a variety of advantages, particularly the risk reduction of postoperative nausea and vomiting (PONV), whereas its administration in total intravenous anesthesia (TIVA) is solely via the intravenous route, which requires involvements of other organs in contrast to inhalation anesthetics administered via the airway, which facilitates readily accessibility of anesthetics in the alveoli, exerting immediate impact on the functionality and morphology of the alveoli [42, 43]. Due to our focus on alveolar inflammatory cytokines and pulmonary complications, inhalation anesthesia is preferable for thoracic surgeries with OLV as compared with TIVA, whereas their impacts on other organs and systems are beyond our discussion.

There are several limitations in this study that should be considered when interpreting our results. First, the geographic regions covered in this meta-analysis included Europe (Germany and Switzerland), Asia (China, Japan and South Korea) and Africa (Egypt). Therefore, our results limited generalizability to other regions (for example, North America, Oceania, and Latin America). Second, taking the "effect size", for instance, despite the credibility of the method of "change from baseline", we took the final outcome as "effect size". It should be noted that in all documents, SDs were represented for the parameters at baseline and the final measurements rather than the mean difference of the pre- and post-OLV or intraoperative values, thus disabling the calculation of the SD of mean difference in the absence of raw data. However, if we designated the final outcome as the "effect size", a relatively wider confidence interval might result, especially for repeated measurements in the same patient, which would require more plausible interpretations of the outcomes. Finally, the relatively high heterogeneity was statistically significant across several outcomes, which requires more reasonable interpretations. Accordingly, we performed sensitivity analysis to track the potential source of heterogeneity and the duration of OLV may, at least in part, account for the heterogeneity. Other possible sources of heterogeneity may due to age, race, and determinations of inflammatory factors. Moreover, meta-analysis with multiple small studies might dilute the reliability of our results. The studies and amount of data concerning inflammatory mediator release with one-lung anesthesia is limited. This makes a meta-analysis of this subject of limited value.

In summary, this meta-analysis offers limited evidence, suggesting that compared with propofol-based intravenous anesthetics, inhalation anesthetics might be preferred in patients undergoing OLV for thoracic surgery and the protective effect might work via attenuating inflammatory responses.

Conflict of interest The authors have no conflict of interests regarding the work.

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