Review Article

Inhalational versus intravenous anesthetics during one lung ventilation in elective thoracic surgeries: A narrative review

ABSTRACT

The anesthesia regimen used during one lung ventilation (OLV) carry the potential to affect intra-operative course and post-operative outcomes, by its effects on pulmonary vasculature and alveolar inflammation. This narrative review aims to understand the pathophysiology of acute lung injury during one lung ventilation, and to study the effects of inhalational versus intravenous anaesthetics on intraoperative and post-operative outcomes, following thoracic surgery. For this purpose, we independently searched 'PubMed', 'Google Scholar' and 'Cochrane Central' databases to find out randomized controlled trials (RCTs), in English language, which compared the effects of intravenous versus inhalational anaesthetics on intraoperative and post-operative outcomes, in elective thoracic surgeries, in human beings. In total, 38 RCTs were included in this review. Salient results of the review are- Propofol reduced intraoperative shunt and maintained better intraoperative oxygenation than inhalational agents. However, use of modern inhalational anaesthetics during OLV reduced alveolar inflammation significantly, as compared to propofol. Regarding post-operative complications, the evidence is not conclusive enough but slightly in favour of inhalational anaesthetics. Thus, we conclude that modern inhalational anaesthetics, by their virtue of better anti-inflammatory properties, exhibit lung protective effects and hence, seem to be safe for maintenance of anesthesia during OLV in elective thoracic surgeries. Further research is required to establish the safety of these agents with respect to long term post-operative outcomes like cancer recurrence.

Key words: Inhalational anaesthetics, intravenous anaesthetics, one lung ventilation, thoracic surgeries

Introduction

One lung ventilation (OLV) is considered as an established technique during thoracic surgeries, which helps in aiding the space for the surgery in the thoracic cavity and in minimizing the contamination of the other lung, without compromising the safety of the patient. General anesthesia with controlled mechanical ventilation is the preferred method during OLV. However, OLV, in itself, is an unphysiological entity. Various physiological and pathological alterations like increase in the shunt fraction, dead space ventilation, hypoxia, hypoxic pulmonary vasoconstriction (HPV), pulmonary hypertension, alveolar and systemic inflammation occur during OLV. In recent years, acute lung injury (ALI) following OLV has been identified as a prognostic factor for post-operative outcomes.[1] The incidence of ALI following

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thoracotomy ranges between 4 and 15%, depending on the degree of lung resection and contributes significantly to post-operative mortality.[1] In addition to the mechanical injury to the pulmonary parenchyma and vasculature due to surgery, ventilation induced lung injury, oxidative stress, and reperfusion injury have been identified as the proposed mechanisms for ALI during thoracic surgeries. Ventilation parameters like use of inappropriate tidal volumes, raised airway pressures, lack of adequate positive end-expiratory pressure (PEEP) and high fraction of oxygen in inspired air (FiO2) induce mechanical, hypoxic and oxidative stress that lead to ALI.[2] Injury occurs primarily at alveolar- capillary membrane and in particular, endothelial glycocalyx on the luminal surface of the vascular endothelium plays an important role in development of ALI.[3] It leads to the generation of inflammatory cytokines like interleukins (IL-6, IL-8, IL-1β etc.) and tumor necrosis factor-α (TNF-α). Inflammatory cytokines then activate the macrophages and recruit neutrophils into the lung. The pathophysiological process of ALI during OLV is schematically represented in Figure 1. Studies have shown that the levels of inflammatory cytokines in the lungs are closely related to the development of ALI.[4] Hence, the current focus in the field of thoracic anesthesia is to develop strategy to minimize the occurrence of ALI during thoracic surgery. One aspect of this strategy is to follow the principles of 'protective one lung ventilation', which include minimal use of OLV, low tidal volumes with application of adequate PEEP to the ventilated lung, use of continuous positive airway pressure (CPAP) to the collapsed lung, use of lowest possible FiO2, and allowance of mild hypercapnia.[2] Other aspect to prevent ALI during thoracic surgery is to modify the anesthesia regimen used during OLV.

Volatile anesthetics are known to have immunomodulating effects. Few animal studies have shown that use of inhalational agents like sevoflurane and isoflurane could attenuate the inflammatory markers and thus could have a protective role against ALI. Preconditioning with isoflurane has shown to reduce the polymorphonuclear leucocytes recruitment and microvascular protein leakage in the lung in animal models.[5] Volatile anesthetics also have a protective role on endothelial glycocalyx.[6] Intravenous anesthetics like propofol as well, have been identified to reduce the pulmonary inflammation.[7] Propofol has been shown to reduce the intrapulmonary shunt and thus, minimize the occurrence of hypoxemia during OLV. Thus, both intravenous and volatile agents carry potential to affect the alveolar inflammation, oxidative stress and the tone of pulmonary vasculature. In this regard, a number of studies have been done in last decade, which compare the effects of anesthetic agents on alveolar inflammation, immunomodulation and the subsequent post-operative pulmonary complications. However, these studies carry limitations like small sample sizes, heterogenous nature of studies, and lack of multicentric trials. Hence, there is not yet a consensus regarding which anesthetic regimen is better during OLV.

In this narrative review, we attempted to compile the available evidence regarding the effects of intravenous versus inhalational anesthetic agents during one lung ventilation in elective thoracic surgeries.

Materials and Methods

Data retrieval

Three authors independently searched PubMed, Cochrane Central Register of Controlled Trials and Google Scholar

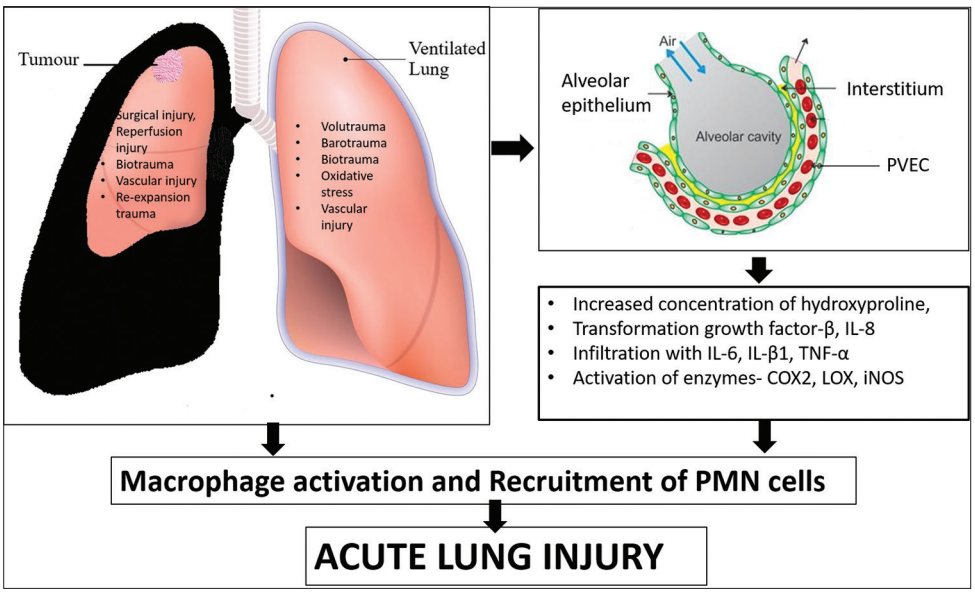

Figure 1: Pathophysiology of Acute Lung Injury in one lung ventilation

databases, for trials published from inception to 28th October 2020. The criteria for inclusion of a trial in this review were -the prospective randomized controlled trials (RCTs) comparing intravenous anesthetics (e.g. propofol) versus inhalational anesthetics (e.g. sevoflurane) during OLV in elective thoracic surgeries for lung or esophageal cancers in human beings. Full text articles published in English language were reviewed in this narrative review. Date of publication and sample size of the trials had no bar. Exclusion criteria for the trials were- non availability of full text, non-English language, animal studies, non-thoracic or cardiac surgeries, emergency surgeries, retrospective studies, and non-randomized trials. Accordingly, search terms included- ''propofol'', ''ketamine'', ''intravenous anesthetic'', ''total intravenous anesthesia (TIVA)'', ''inhalational anesthetic'', ''sevoflurane'', ''isoflurane'', ''desflurane'', ''enflurane'', ''halothane'', ''one lung ventilation (OLV)'', ''lung resection surgery'', ''esophagectomy'', elective thoracic surgery'' and ''thoracotomy''. In addition, the reference lists of published articles were screened to find other potential eligible trials. The search was performed at regular intervals to find the recently published trials. In case of multiple publications on the same data, the latest publication or the one with largest sample size was selected. The authors agreed uniformly over the selection of the studies considered for this review.

Assessment of the quality of the studies

The quality of the studies considered for the review was evaluated using the 'Revised Cochrane risk of bias tool for randomized trials (RoB2 tool)'.[8] The domains assessed were randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and the selection of the reported result. Each domain was categorized as yes or no or unclear. The overall summary of the assessment of the risk of bias for each study was categorized as low risk of bias, some concerns of bias and high risk of bias.

Outcomes assessed

We identified five outcomes that were commonly addressed by the most of the RCTs in this review. These included intraoperative outcomes like effect on intraoperative shunt and oxygenation, effect on alveolar and systemic inflammation, effect on oxidative stress, effect on hemodynamic and parameters and effect on post-operative outcomes like pulmonary complications, intensive care unit stay, hospital stay and mortality.

Results

Flow chart for screening and identification of eligible clinical trials is shown in Figure 2.

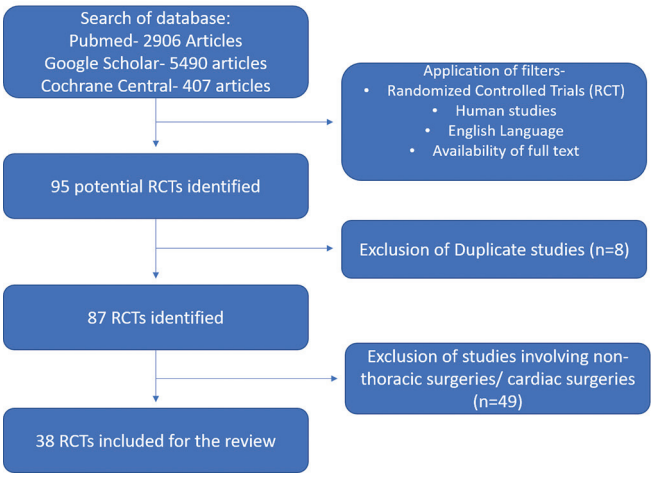

Figure 2: Flowchart for screening and inclusion of the RCTs for the review

Characteristics of the trials included for the review:

Table 1 describes the characteristics of 38 randomized controlled trials that were included in this review. These studies were published between 1995 and 2020. All these studies compared an intravenous anesthetic agent versus inhalational agent during OLV in elective thoracic surgeries for treatment of lung or esophageal cancer. The intravenous agent used in all the studies was propofol except one study which used combination of ketamine and propofol. Twenty-four studies used sevoflurane, 10 studies used isoflurane, 4 studies used desflurane and one study used halothane as inhalational agent during OLV.

Quality of the studies:

Quality of the studies, in terms of risk of bias, was assessed using RoB2 tool. Table 2 describes the assessed risk of bias in five domains. Twenty-three studies had some concerns with regards to presence of bias, fourteen studies were having low risk of bias and one study was identified to have high risk of bias.

Assessment of the outcomes:

A. Effect of alveolar and systemic inflammation:

Thirteen RCTs assessed the effect of intravenous and inhalational anesthetics on the generation of inflammatory mediators in bronchoalveolar lavage or in plasma.[7,9-20] Intravenous anesthetic agent in all the studies was propofol. Sevoflurane was used as inhalational agent in 10 studies, desflurane was used in 2 studies, and isoflurane was used in one study. The primary pro-inflammatory markers assessed in these studies were interleukins (IL)-6, IL-8, IL-1β, and tumor necrosis factor (TNF)- α whereas anti-inflammatory marker assessed was IL-10. Some studies (n = 8) assessed the levels

Table 1: Characteristics of all the studies included in the review

Name of the investigator, year	Surgery	Intravenous Arm (sample size)	Inhalational Arm (sample size)	Primary Outcome	Secondary Outcome
Kellow *et al*. 1995	Thoracic surgery	Propofol (*n*=12)	Isoflura*ne* (*n*=11)	Qs/Qt	PaO_2, SaO_2, MAP, HR
Reid *et al*. 1996	Thoracic surgery	Propofol (*n*=15)	Isoflura*ne* (*n*=15)	Arterial blood gases	MAP, HR
Gasowska *et al*. 1999	Thoracic surgery	Propofol (*n*=13)	Isoflura*ne* (*n*=14), Halotha*ne* (*n*=20)	PaO_2, Qs/Qt	
Dossow V *et al*. 2000	Lung surgery	Propofol (*n*=25)	Isoflura*ne* (*n*=25)	Qs/Qt, PaO_2	
Beck *et al*. 2001	Thoracic surgery	Propofol (*n*=19)	Sevoflurane (*n*=19)	Qs/Qt	HR, MAP
Abd El-Hakeem *et al*. 2003	Lung resection	Propofol (*n*=15)	Sevoflurane (*n*=15)	PaO_2, PvO_2, Qs/Qt	HR, MAP, SVRI
Pruszkowski *et al*. 2007	Lung surgery	Propofol (*n*=32)	Sevoflurane (*n*=33)	PaO_2	HR, MAP
Schilling *et al*. 2007	Lung surgery	Propofol (*n*=15)	Desflurane (*n*=15)	BAL concentration of IL-8, TNFα, ICAM-1	HR, MAP, CVP, PAOP, Qs/Qt
Ozcan *et al*. 2007	Lung surgery	Propofol (*n*=50)	Isoflurane (*n*=50)	PaO_2, PvO_2	Qs/Qt
Iwata *et al*. 2008	Lung surgery	Propofol (*n*=26)	Sevoflurane (*n*=26)	Jugular venous oxygen saturation	
Huang *et al*. 2008	Thoracic surgery	Propofol (*n*=15)	Sevoflurane (*n*=15)	Reactive oxygen species production	Oxygentation and HR, MAP
De Conno 2009	Lung resection	Propofol (*n*=27)	Sevoflurane (*n*=27)	BAL TNF α, IL-6, IL-8, IL-1β) and cells in lavage fluid	CRP & WBC counts on post-operative days, POC
Schwarzkopf *et al*. 2009	Thoracic surgery	Propofol (*n*=26)	Sevoflurane (*n*=28)	Oxygenation during OLV	HR, MAP
Fukuoka *et al*. 2009	Thoracic surgery	Propofol (*n*=16)	Sevoflurane (*n*=16)	PaO_2 values	
Schilling *et al*. 2011	Open Lung surgery	Propofol (*n*=21)	Sevoflurane (*n*=21), Desflurane (*n*=21)	BAL TNFα, IL-1β, IL-6, IL-8, IL-10, IL-12p70	HR, MAP, PaO_2, post-operative ICU stay, Hospital stay
Sugasawa *et al*. 2011	Lung surgery	Propofol (*n*=20)	Sevoflurane (*n*=20)	BAL IL-1β, IL-6, IL-8, IL-10, IL-12p70, TNF-α	
Mahmoud 2011	Lung resection	Propofol (*n*=25)	Isoflurane (*n*=25)	Plasma and alveolar IL-8, TNFα)	MDA, SOD, POC, ICU stay, Hospital stay
Abdelrahman *et al*. 2012	Lung resection	Propofol (*n*=30)	Isoflurane (n=30)	PaO_2, PvO_2, SaO_2, Qs/Qt	HR, MAP
Lee *et al*. 2012	Esophagectomy	Propofol (*n*=24)	Sevoflurane (*n*=24)	Plasma IL-6, MDA	POC, ICU stay, Hospital Stay
Hammouda *et al*. 2013	Lung surgery	Propofol (*n*=20)	Sevoflurane (*n*=20)	BAL and Plasma IL-6 and TNFα	CRP and WBC count post operatively
Yanwu *et al*. 2013	Lung surgery	Propofol (*n*=20)	Sevoflurane (*n*=20)	Plasma IL-6, IL-10, TNFα	Qs/Qt, dynamic compliance
Attar *et al*. 2014	Thoracic surgery	Propofol (*n*=30)	Isoflurane (*n*=30)	Oxygenation parameters	HR, MAP
Potocnik *et al*. 2014	Lung resection	Propofol (*n*=19)	Sevoflurane (*n*=17)	Plasma IL-6, IL-8, IL-10	Postoperative clinical outcomes
Xu WY *et al*. 2014	Esophagectomy	Propofol (*n*=20)	Sevoflurane (*n*=20)	Right Ventricular function	Qs/Qt, CI, MAP, HR, PAWP
Wakabayashi *et al*. 2014	Esophagectomy	Propofol (*n*=10)	Sevoflurane (*n*=10)	BAL IL-1β, IL-6, IL-8, IL-10, $IL\text{-}1_2p70$	POPC
Erturk *et al*. 2014	Thoracic surgery	Propofol-ramifentanil (*n*=22)	Sevoflurane (*n*=22)	PaO_2, HR, MAP	Plasma MDA & IMA levels
Feng H *et al*. 2015	Lung surgery	Propofol (*n*=15)	Sevoflurane (*n*=15)	Plasma MDA levels	Oxygenation index
Beck-Schimmer *et al*. 2016	Lung resection	Propofol (*n*=230)	Desflurane (*n*=230)	Time for occurrence of first major complication	Time for occurrence of major complication in 6 months follow up, ICU stay, Hospital stay
Cho YJ *et al*. 2016	Lung surgery	Propofol (*n*=52)	Desflurane (*n*=52)	PaO_2	Haemodynamic, ICU stay, Hospital stay.
de La Gala 2017	Lung resection	Propofol (*n*=88)	Sevoflurane (*n*=86)	PaO_2, $PaCO_2$, MAP, HR,	PPC, 1 month mortality, 1 year mortality,
Tian HT *et al*. 2017	Lung surgery	Propofol (*n*=31)	Sevoflurane (*n*=31)	Plasma IL-6, MMP-9	RI, Qs/Qt, A-aDO_2, MMSE
Tsuchiya *et al*. 2018	Esophagectomy	Propofol (*n*=92)	Sevoflurane (*n*=94)	Days for normalization of WBC counts, and CRP	Post operative plasma ferric reducing ability, length of hospital stay and post operative complications
Sheybani *et al*. 2018	Right thoracotomy	Propofol (*n*=61)	Isoflurane (*n*=61)	Gas exchange parameters	
Kim HJ *et al*. 2018	Lung surgeries	Propofol (*n*=40)	Sevoflurane (*n*=38)	EGL injury markers, VCAM-1 levels	
Zheng Xia *et al*. 2018	Thoracic surgery	Propofol (*n*=40)	Isoflurane (*n*=40)	Qs/Qt, PaO_2	HR, MAP
Mohamed Sherin *et al*. 2018	Thoracic surgery	Propofol (*n*=14)	Sevoflurane (*n*=14)	PaO_2	HR, MAP
Zhiguo *et al*. 2019	Thoracic surgery	Propofol (*n*=49)	Sevoflurane (*n*=49)	A-aDo_2, Respiratory index	Qs/Qt, MMP-9, MDA

Contd...

Table 1: Contd...

Name of the investigator, year	Surgery	Intravenous Arm (sample size)	Inhalational Arm (sample size)	Primary Outcome	Secondary Outcome
Hahm *et al*. 2020	Lung surgery	Propofol (n=60)	Sevoflurane (n=60)	Systemic oxygen delivery Do_2	Correlation between SaO_2 and DO_2

Qs/Qt - Pulmonary shunt, HR- Heart rate, MAP - Mean Arterial Pressure, PaO2 - Partial pressure of oxygen in arterial blood, SaO2 - Oxygen saturation of arterial blood, PvO2 - Partial pressure of oxygen in venous blood, DO2 - Delivery of oxygen, (A-a) O2 - Difference in alveolar-arterial oxygen pressures, MDA - Serum Malondialdehyde levels, MMP-9- Matrix Metalloproteinase-9, CRP - C-Reactive protein, OI - Oxygenation index, CI - cardiac index, EGL- Endothelial Glycocalyx layer, VCAM - Vascular cell adhesion molecule, POPC - Post-operative pulmonary complication, POC- Post-operative complication, ICU - Intensive care unit, SOD - Superoxide dismutase, BAL - Bronchoalveolar Lavage, MMSE - Mini-mental state examination, IMA - Ischemia modified albumin

of these markers in bronchoalveolar fluid whereas some studies (n = 8) used blood samples to find plasma levels of inflammatory markers.

Schilling *et al*. (2007) found that the fraction of alveolar granulocytes, TNF-α and S-ICAM increased significantly in propofol group as compared to desflurane group, in 30 patients undergoing elective lung surgery.[9] De Conno *et al*. (2009) found that rise in all pro-inflammatory mediators (i.e. TNF-α, IL-6, IL-8, MCP-1), except IL-1β, in BAL was significantly more in propofol group, as compared to sevoflurane group, in 54 adults undergoing lung resection surgery.[10] Similar findings were also reported from three RCTs [Sugasawa *et al*. (n = 40), Mahmoud *et al*. (n = 50), Schilling *et al*. (n = 63)] published in 2011.[11-13] These findings were further supported by results of RCTs by Hammouda *et al*. (2013), Potocnik *et al*. (2014) and de la Gala F *et al*. (2017), in 250 patients undergoing elective lung surgery.[14-16] In these studies, pro-inflammatory mediators (IL-6, IL-8, and TNF-α) increased significantly in propofol group, whereas anti-inflammatory mediators (IL-10) were significantly low in propofol group, as compared with sevoflurane group. Lee *et al*. (2012) assessed the inflammatory markers in 48 patients undergoing esophagectomy surgery and found that plasma IL-6 was significantly higher in propofol group as compared to sevoflurane group.[17]

On the contrary, the studies by Yanwu *et al*. (2013) and Tian H *et al*. (2017), plasma levels of pro-inflammatory mediators were found significantly high in sevoflurane group, as compared with propofol group, in 102 patients undergoing elective lung surgeries.[7,18] Wakabayashi *et al*. (2014) found similar results in 20 patients undergoing elective esophagectomy surgery.[19] Kim HJ *et al*. (2018) found that the markers of endothelial glycocalyx injury were not different between propofol and sevoflurane in 78 patients undergoing lung surgery.[20]

A meta-analysis by Sun B *et al.* assessed 8 RCTs (n = 365) and found that levels of IL-6 (Standardized mean difference- SMD : -0.70, 95% CI: -0.99 to -0.41, $P < 0.001$), IL-8 (SMD: -1.32, 95% CI: -2.2 to -0.45; $P = 0.003$) and TNF-α (SMD: -1.51, 95% CI: -2.15 to -0.87, $P < 0.001$) were significantly low in inhalational group as compared to the intravenous group. The RCTs were relatively homogenous with I^2 value being more than 75%.[21]

Thus, inhalational anesthetics may be better than intravenous anesthetics in terms of controlling the alveolar and systemic inflammation induced by OLV in elective thoracic surgeries.

B. Effects on oxidative stress:

Oxidative stress during thoracic surgeries was assessed by levels of by-products like malondialdehyde (MDA). Four RCTs assessed the effects of volatile agents versus intravenous propofol on oxidative injury during OLV. Huang *et al* (2008) found that propofol infusion attenuated the ROS production, as compared to isoflurane.[22] Mahmoud *et al*. (2011) found that alveolar and plasma levels of MDA were significantly lower in the propofol group as compared to isoflurane. Also, levels of superoxide dismutase (SOD), which is an anti-oxidant enzyme that helps in scavenging free radicals, were found in significantly higher proportion in propofol group.[12] Erturk *et al*. (2014), in 44 patients undergoing OLV for thoracic surgery, found that the levels of MDA are comparable in propofol and sevoflurane groups. But, the levels of ischemia modified albumin (IMA) were significantly less in sevoflurane group.[23] Feng *et al*. (2015) showed that MDA levels were significantly low in sevoflurane group as compared to propofol group. Also, expression of HO-1 protein, which reduces oxidative stress, was found higher in sevoflurane group.[24]

C. Effect on Pulmonary complications:

Data on post-operative pulmonary complications came from ten RCTs (total number of patients-1131). Propofol was used as an intravenous agent by all the studies. Eight studies used sevoflurane as inhalational agent, whereas two studies used desflurane and one study used isoflurane. De Conno *et al*. (2009) compared propofol versus sevoflurane in 54 adult patients undergoing elective thoracic surgeries.[10] The overall number of adverse events in the propofol group was significantly higher than in the sevoflurane group. Also, ICU stay for patients in propofol group was significantly

Table 2: Risk of bias assessment for the included studies

Study	Risk of bias					Overall Risk of bias
	Due to randomization process	Due to deviations from intended interventions	Due to missing outcome data	In measurement of the outcome	In selection of the reported result	
Attar *et al*.	LR	SC	SC	SC	LR	SC
De la Gala *et al*.	LR	LR	LR	LR	LR	LR
Erturk *et al*.	LR	LR	LR	LR	LR	LR
Feng *et al*.	SC	SC	LR	LR	LR	SC
Hammouda *et al*.	SC	SC	LR	LR	LR	SC
Kim HJ *et al*.	LR	LR	LR	LR	LR	LR
Lee *et al*.	LR	LR	LR	LR	LR	LR
Mahmoud *et al*.	LR	LR	LR	LR	LR	LR
Potocnik *et al*.	LR	LR	LR	LR	LR	LR
Schilling T *et al*. (2007)	LR	LR	LR	SC	LR	SC
Schilling T *et al*. (2011)	LR	LR	LR	LR	LR	LR
Sugasawa *et al*.	LR	SC	LR	LR	LR	SC
Tian HT *et al*.	SC	SC	LR	LR	LR	SC
Wakabayashi *et al*.	LR	SC	LR	LR	LR	SC
Yanwu J *et al*.	LR	LR	LR	LR	LR	LR
Beck-Schimmer *et al*.	LR	LR	LR	LR	LR	LR
Tsuchiya *et al*.	LR	LR	LR	LR	LR	LR
Xu WY *et al*.	LR	SC	LR	LR	LR	SC
Abdelrahman *et al*.	SC	SC	LR	LR	SC	SC
Cho YJ *et al*.	LR	SC	LR	SC	SC	SC
Hahm *et al*.	LR	LR	SC	LR	LR	SC
Sherin *et al*.	LR	SC	SC	SC	LR	SC
Sheybani *et al*.	LR	LR	LR	LR	LR	LR
Ozcan *et al*.	LR	LR	LR	LR	LR	LR
Zheng Xia *et al*.	LR	LR	LR	LR	LR	LR
Zhiguo *et al*.	SC	SC	LR	LR	LR	SC
Beck *et al*.	SC	SC	LR	LR	LR	SC
De Conno *et al*.	SC	LR	LR	LR	LR	SC
Abd El-Hakeem *et al*.	SC	SC	LR	SC	SC	SC
Fukuoka *et al*.	SC	LR	LR	LR	LR	SC
Gasowaska *et al*.	SC	SC	SC	SC	LR	SC
Huang *et al*.	LR	LR	LR	LR	LR	LR
Iwata *et al*.	LR	SC	SC	SC	LR	SC
Kellow *et al*.	SC	LR	SC	SC	LR	SC
Pruszkowski *et al*.	HR	SC	SC	SC	SC	HR
Reid *et al*.	LR	SC	SC	SC	LR	SC
Dossow V *et al*.	SC	LR	LR	LR	SC	SC
Schwarzkopf *et al*.	LR	SC	SC	SC	SC	SC

LR - Low risk, SC - Some concerns, HR - High risk

longer than that in sevoflurane group. (1.52 ± 2.33 *vs.* 0.87 ± 0.43 days; $P < 0.05$). However, CRP and WBC counts were comparable in both the groups during post-operative period. Another RCT by Mahmoud *et al* (2011), in which propofol was compared with isoflurane as a maintenance agent during OLV in 50 adult patients undergoing lung surgery, found that total number of post-operative complications (10 vs 3, $P = 0.02$), ICU stay (37 ± 7 hours vs 26 ± 8 hours, $P = 0.02$) and hospital stay (11 ± 5 days vs 7 ± 4 days, $P = 0.03$) were significantly less in isoflurane group.[12] In same year, Schilling *et al*. found that post-operative outcomes were not different in intravenous or inhalational groups in 63 patients undergoing lung surgeries.[13] Lee *et al.* (2012), however found no significant difference between propofol and sevoflurane in terms of post-operative pulmonary complications, ICU stay and hospital stay, in 48 patients undergoing esophagectomy.[17] In 2014, another RCT by Xu *et al*. in 40 patients undergoing esophagectomy showed that post-operative ICU stay was significantly less in sevoflurane group as compared to propofol group.[25] However, the study did not find any significant difference in the incidence of post-operative complications and hospital stay. Another study by Wakabayashi *et al*. (2014) found no difference in the post-operative pulmonary complications between propofol

and sevoflurane in 20 patients undergoing esophagectomy surgery.[19] In same year, Potocnik *et al*. found that patients who received propofol had higher numbers of post-operative complications as compared to those who received sevoflurane during lung resection surgeries.[15] However, both the studies were limited by small sample size. A more robust evidence followed in 2016, when a multicentred RCT by Beck-Schimmer *et al.* compared propofol versus desflurane as maintenance agent during OLV in 460 patients undergoing elective lung resection surgery across 5 centers.[26] Incidence of major complications during hospitalization was 16.5% in the propofol and 13.0% in the desflurane groups (hazard ratio- 0.75; 95% CI, 0.46 to 1.22; $P = 0.24$). Incidence of major complications within 6 months from surgery was 40.4% in the propofol and 39.6% in the desflurane groups (hazard ratio- 0.95; 95% CI, 0.71 to 1.28; $P = 0.71$). Thus, the study did not find any significant difference in terms of post-operative complications, ICU and hospital stay. In 2017, de la Gala *et al*. compared propofol and sevoflurane in 174 patients undergoing elective lung resection surgery and found that patients in the propofol group had significantly more incidence of postoperative pulmonary complications (28.4% vs 14%, OR 2.44 [95% CI, 1.14–5.26]).[16] Also, first-year mortality was significantly higher in the propofol group (12.5% vs 2.3%, OR 5.37 [95% CI, 1.23–23.54]). Similar large study was conducted by Tsuchiya *et al.* (2018) in 186 patients undergoing radical esophagectomy.[27] The study found that patients who received propofol had the lower incidence of severe postoperative complications (7 of 92 versus 18 of 94, $P = 0.030$, odds ratio = 0.35), and faster uneventful recovery time (WBC normalization days 7.1 ± 5.2 versus 13.6 ± 10.2, $P < 0.001$) as compared to those who received sevoflurane.

A meta-analysis by Pang *et al*. found a moderate quality evidence in favor of inhalational anesthesia as compared to intravenous anesthesia in elective thoracic surgeries, when pulmonary complications were analyzed in 9 RCTs.[28] For the outcome of pulmonary complications, the included studies had less heterogeneity ($I^2 = 4\%$). However, the study by Tsuchiya *et al*. was not included in the meta-analysis.

Thus, the available evidence is not sufficient enough to suggest that inhalational anesthetics are safer than intravenous anesthetics for maintenance of anesthesia during OLV in elective thoracic surgeries.

D. Effect on the intraoperative oxygenation and shunt:

Twenty-seven studies evaluated the effect of inhalational agents versus intravenous agents on intraoperative oxygenation and pulmonary shunt during one lung ventilation in elective thoracic surgeries. Except one study by Sherin *et al*., where the investigators used combination of intravenous propofol and ketamine, rest all studies used propofol as the intravenous agent during OLV. Fifteen studies used sevoflurane as the inhalational agent during OLV whereas ten studies used isoflurane and two studies used desflurane and one study used halothan.

Intraoperative obligatory pulmonary shunt is the major cause of hypoxemia during one lung ventilation. Maintenance anesthetic agents, by virtue of their vasodilator ability can cause pulmonary vasodilation and increase the shunt. Eight studies assessed the effects of intravenous versus inhalational anesthetic during OLV on the intraoperative pulmonary shunt. All these studies had calculated pulmonary shunt by measuring arterial partial pressure of oxygen (PaO2), partial pressure of oxygen in mixed venous blood (PvO2) and arterial partial pressure of carbon dioxide (PaCO2). The equation used was-

$Qs/Qt = (CcO2 \_ CaO2)/(CcO2 \_ CvO2)$ where

$CaO2 = (PaO2 \times 0{:}0031) + (Hb \times 1{:}36 \times SaO2)$,

$CvO2 = (PvO2 \times 0{:}0031) + (Hb \times 1{:}36 \times SvO2)$ &

$CcO2 = ([FiO2 \times (PB - PH\ 2O) - PaCO2/RQ]) \times 0{:}0031 + (Hb \times 1.36)$

Kellow *et al*. (1995) found that the shunt increased significantly in isoflurane group as compared to propofol.[29] Gasowska *et al*. (1999) found that shunt fraction was significantly high in propofol group as compared with halothane, however the study found no difference in the intraoperative shunt between propofol and isoflurane groups.[30] In 2001, two RCTs by Dossow *et al*. and Beck *et al.* (2001) found no difference in the intraoperative shunt between propofol and inhalational groups.[31,32] However, Abd El-Hakeem *et al*. (2003), Ozcan *et al*. (2007), Abdelrahman *et al*. (2012), Xu WY *et al*. (2013), Yanwu *et al*. (2013), Zheng *et al*. (2018) and Zhiguo *et al*. (2019) found that the intraoperative shunt increased significantly in inhalational group as compared to propofol group.[7,25,33-37]

Intraoperative oxygenation parameters (e.g. oxygenation index, respiratory index, partial pressure of oxygen in arterial blood, tissue oxygen delivery, jugular venous oxygenation etc.) were assessed by 21 RCTs. Sixteen studies (Reid *et al*. 1996,[38] Gasowksa *et al.* 1999,[30] Beck *et al*. 2001,[32] Pruszkowski *et al*. 2007,[39] Huang *et al*. 2008,[22] Iwata *et al*. 2008,[40] Fukuoka *et al*. 2009,[41] Schwarzkopf *et al*. 2009,[42] Schilling *et al*. 2011,[13] Mahmoud *et al*. 2011,[12] Hammouda *et al*. 2013,[14] Attar *et al*. 2014,[43] de la Gala *et al*. 2017,[16] Sheybani *et al*.

2018,[44] Zheng *et al*. 2018[36] and Hahm *et al*. 2019[45]) found no difference in the oxygenation parameters between intravenous and inhalational anesthetic groups during OLV in elective thoracic surgeries.

Studies by Abd El-Hakeem *et al*. (2003),[33] Abdelrahman *et al*. (2012),[35] Xu WY *et al*. (2013),[25] Yanwu J *et al*. (2013),[7] Erturk *et al*. (2014),[23] Cho *et al*. (2017),[46] Sherin *et al*. (2018)[47] and Zhiguo *et al*. (2019)[37] showed that oxygenation parameters were significantly better in propofol group as compared to inhalational group.

In a meta-analysis of 18 RCTs (n = 1132) by Pang *et al*. oxygenation index within 30 minutes of OLV was found significantly higher in intravenous anesthesia group as compared to inhalational group (P = 0.001), however, there was no significant difference between two groups after 30 minutes of OLV (p = 0.38).[28]

Thus, the evidence available so far indicates that propofol decreases intraoperative shunt and maintains better oxygenation during OLV in elective thoracic surgeries, as compared to inhalational anesthetics.

E. Effect on hemodynamic parameters and cardiovascular complications:

Data on hemodynamic parameters during OLV came from twelve RCTs. Propofol was used as an intravenous agent by all the studies. Seven RCTs used sevoflurane as inhalational agent, whereas 2 RCTs used desflurane and 3 RCTs used isoflurane during maintenance of anesthesia.

Kellow *et al*. (1995) found that cardiac index (CI) and right ventricular ejection fraction (RVEF) dropped significantly in propofol group as compared to isoflurane group in patients undergoing thoracic surgery.[29] On other hand, Dosswo *et al*. (2001) found that cardiac index increased significantly in propofol group, as compared to isoflurane group.[31] Abd El-hakeem *et al*. (2003) found significant drop in systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) in propofol group as compared to sevoflurane.[33]

In another RCT by Xu *et al*. (2014) in 40 adult patients undergoing esophagectomy, hemodynamic parameters during OLV [viz. MAP, SVI, mean pulmonary artery pressure, central venous pressure and pulmonary artery wedge pressure (PAWP)] did not significant differ between propofol and sevoflurane groups.[25] However, cardiac index (CI) was significantly lesser in propofol group than in sevoflurane group throughout the surgery ($P = 0.007$). systemic vascular resistance index (SVRI) was significantly greater in propofol group than in sevoflurane group ($P = 0.022$). Right ventricular ejection fraxtion (RVEF), right ventricular end diastolic volume index (RVEDVI) and right ventricular stroke volume index (RVSWI) were significantly smaller in propofol group than in sevoflurane group throughout the surgery. Thus, anesthesia with sevoflurane preserved right ventricular function better than propofol in patients undergoing esophagectomy.

Lee *et al*. (2012), in the randomized controlled trial of 48 patients undergoing esophagectomy, found no significant difference in the incidence of post-operative cardiac complications (that included postoperative elevation of cardiac enzymes and or newly developed arrythmias requiring treatment) between sevoflurane and propofol groups.[17]

RCTs by Reid *et al*. (1996),[38] Beck *et al*. (2001),[32] Pruszkowski *et al*. (2007),[39] Schilling *et al*. (2007),[9] Huang *et al*. (2008),[22] Cho *et al*. (2017)[46] and de la Gala *et al*. (2017)[16] found no difference in hemodynamic parameters between propofol and inhalational agents.

A meta-analysis by Pang *et al*. showed that CI was higher in inhalational group (mean difference 0.19, 95% CI- 0.10 to 0.28, $P < 0.001$) as compared to propofol in 355 patients undergoing thoracic surgery.[28]

Thus, as compared with propofol, inhalational agents like sevoflurane and isoflurane maintain stable hemodynamic parameters and higher cardiac index during OLV.

Discussion

The results of our review showed that, when used for maintenance of anesthesia during one lung ventilation, newer inhalational anesthetics (i.e. sevoflurane, isoflurane, desflurane), increased intraoperative pulmonary shunt and reduced oxygenation, as compared to propofol. However, they exhibit better anti-inflammatory properties than propofol. Although there is a trend towards lesser post-operative complications in inhalational group, the data is insufficient to say whether inhalational anesthetics are better than propofol. Hence, at present, based on current evidence, modern inhalational anesthetics are safe for maintenance of anesthesia during one lung ventilation in elective thoracic surgeries.

Reason why inhalational anesthetics reduce intraoperative oxygenation could be due to the effect of inhalational anesthetics on hypoxic pulmonary vasoconstriction (HPV). HPV is a protective reflex phenomenon in which reduced tissue

oxygenation (i.e. reduced mixed venous oxygen saturation, in case of one lung ventilation) in region of pulmonary arterioles is sensed by pulmonary artery smooth muscle cells (PASMC) and it brings about vasoconstriction of the distal pulmonary arteries to reduce the effective blood flow in the hypoxic region.[48] Thus, blood flow is diverted away from hypoxic region of the lung to other areas which are non-hypoxic. In case one lung ventilation, the pulmonary blood flow is diverted away from collapsed lung to ventilated lung. It reduces the intrapulmonary shunt and helps in maintaining the arterial oxygenation during one lung ventilation.

Anesthetic drugs used to maintain anesthesia during one lung ventilation have varying effects on HPV. All inhalational anesthetic agents inhibit HPV in dose dependent manner, older agents more than the modern ones. Halothane inhibits HPV potently even at concentration of 0.5 MAC, as proven in an animal study, whereas isoflurane was found to be less potent inhibitor of HPV than halothane.[49] Human studies by Wang *et al*. and Pagel *et al*. proved that modern inhalational anesthetic agents i.e., sevoflurane, isoflurane and desflurane are comparable in their ability to inhibit HPV in patients undergoing one lung ventilation.[50,51] On the other hand, total intravenous anesthesia with propofol does not inhibit HPV.[52] The review mentions eight RCTs which compared propofol versus modern inhalational anesthetic agents (sevoflurane and isoflurane) for their effects on intrapulmonary shunt during OLV. All the studies measured partial pressures of oxygen in arterial and mixed venous blood and calculated Qs/Qt. All the studies had common finding that the intrapulmonary shunt increases as soon as OLV begins. However, more importantly, the shunt was found to be significantly less in propofol group as compared to inhalational group. Propofol causes systemic vasodilation however, its effects on HPV are minimal. Consequently, oxygenation index was well maintained in propofol group as compared to inhalational group in most of the RCTs.

However, the drop in oxygenation occurs in early part of OLV and recovers in later part of OLV, probably due to HPV. A meta-analysis of eighteen RCTs by Pang *et al*. showed that difference in the oxygenation index during OLV was significant ($P = 0.001$) in first 30 minutes of OLV, whereas the difference became non-significant after 30 minutes of OLV, probably by virtue of HPV.[28] Also, it's worth a note that drop in oxygenation during early part of OLV is not severe and mean partial pressure of oxygen in arterial blood remained above 100 mm Hg in all the studies. Overall incidence of hypoxemia during OLV has dropped to less than 5% in last 2 decades, due to better understanding of pulmonary physiology, better one lung ventilation devices and availability of bronchoscopes.[2] Thus, fear of hypoxia should not deter the thoracic anesthesiologist from using modern inhalational agents during OLV, provided the concentration is maintained below 1 MAC.

Real advantage that the inhalational agents offer over intravenous agents is the reduction in the alveolar and systemic inflammation. One lung ventilation leads to serious lung injury both in ventilated and non-ventilated lung. Mechanisms of lung injury in ventilated lung are volutrauma (due to inappropriate high tidal volumes), barotrauma (due to raised peak airway pressure), biotrauma (due to free oxygen radicals and inflammatory cytokines), oxidative trauma (due to exposure to high FiO2) and capillary shear injury (due to stretching of peri-alveolar capillaries during alveolar ventilation).[2] On the other hand, non-ventilated lung suffers from surgical injury, re-expansion trauma (due to sudden re-expansion of collapsed lung at the end of OLV), re-perfusion injury (due to resumption of blood flow through pulmonary vasculature after OLV), and biotrauma (from inflammatory mediators released from tissues). Alveolar-capillary membrane and pulmonary vascular endothelial cells (PVEC) are the most common sites to suffer from injury and generate the series of pro-inflammatory cytokines like IL-6, IL-8, TNFα, IL-1β etc.[2] These inflammatory cytokines then activate macrophages and recruit the neutrophils in the lung tissues. These changes occur in both lungs, which is evident from acute rise of inflammatory markers in the broncho-alveolar lavage fluids during and after OLV. The inflammation is not only local but also spreads into systemic circulation. It leads to increased vascular permeability and parenchymal damage in the inflamed areas of the lung, which leads to increased interstitial lung water, thickening of alveolar-capillary membrane and subsequent hinderance to gas exchange. Although the root causes of this lung injury are mechanical and ventilation parameters, the anesthetic agent administered during OLV also affect the process of tissue damage.

Volatile anesthetics have been proved to offer myocardial protection from ischemia reperfusion injury by pre-conditioning and post-conditioning mechanisms.[53] Investigations have proven that volatile anesthetics also protect central nervous, renal and hepatic systems from inflammatory injury.[54] The mechanism of the tissue protection is the reduction in the inflammatory cytokines by the volatile anesthetics. *In vitro* and *in vivo* studies have confirmed that alveolar epithelial cells incubated with sevoflurane showed reduced mRNA expression of IL-6, IL-8 and MCP-1 through an inhibition of nuclear translocation of nuclear factor kappa beta (NFKB) and its effect on Toll Like Receptors (TLR).[55]

Sevoflurane also protects against vascular endothelial cell dysfunction via through activation of eNOS/NO pathway and inhibition of NFKB.[55] In the present review, the results of nine RCTs showed that BAL and serum levels of pro-inflammatory cytokines are significantly reduced in inhalational anesthetic group as compared to propofol. Thus, inhalational agents are far more protective to reduce lung inflammation as compared to intravenous propofol. However, whether this protection is offered by all the volatile anesthetic agents in similar proportion or not, is not known. Comparison between sevoflurane and desflurane in the RCT by Schilling *et al*. did not find a significant difference in the levels of inflammatory cytokines between two volatile agents.[13] It has been proved that desflurane has lesser anti-inflammatory and anti-oxidant action as compared to sevoflurane.[56-58] Also, whether this anti-inflammatory action is dose dependent or not, is not clearly known. The RCTs mentioned above used volatile agents in doses equivalent to 1 MAC i.e., 4.5-7% of Desflurane, 1-1.2% of isoflurane and 1.5-2% of sevoflurane. Whether higher doses would increment the anti-inflammatory and anti-oxidant effects of these agents is not known. However, if used in higher concentrations during OLV, these drugs would probably inhibit HPV. Hence it is prudent to use the volatile agents in doses equivalent to 1 MAC.

It is now known that the acute insult to the tissues during one lung ventilation results in post-operative pulmonary and systemic complications. The levels of IL-6 and IL-8 are positively associated with mortality following ventilator associated pneumonia.[59] Also, use of IL-8 antagonist prior to the tissue injury has been proven protective against development of lung injury.[60] Whether this anti-inflammatory action of volatile anesthetic agents is translated into better post-operative outcomes following thoracic surgery, was studied by nine RCTs, five out of which had significantly smaller number of complications in volatile agent group as compared to propofol. However, the first large multicentred trial by Beck-Schimmer *et al*. failed to show any difference between propofol and desflurane groups.[26] Till further strong evidence comes, it is safe to believe that volatile agents should be preferred during OLV over intravenous agents.

Limitations

We accept the limitations of this narrative review. Firstly, being not a meta-analysis, we could not conglomerate the available data and provide statistical difference between the two groups. Secondly, many studies included in the review were heterogenous and of small sample sizes. Also, many studies had concerns regarding various types of bias. Hence, it would reduce the quality of evidence arising out of this review. Thirdly, we did not include the articles available in non-English language. Also, the articles, whose full texts were not available, were not included in this review. Hence, we might have missed certain important data arising from such articles. Lastly, although we could retrieve the Embase based articles from Cochrane Central, a formal Embase search could not be performed.

Conclusion

The available evidence suggests that propofol reduces the intraoperative shunt during one lung ventilation as compared to volatile agents and maintains better oxygenation during OLV. However, volatile agents exhibit better anti-inflammatory properties and seem to be more lung protective than propofol. Further multicentric large randomized controlled trials are required to prove the safety of these agents in thoracic surgeries, especially in terms of long term post-operative outcomes like cancer recurrence or cancer survival rates. Also, comparative studies between different volatile agents and their dose dependent effects should be the scope for future research.

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Conflicts of interest

There are no conflicts of interest.

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