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 anesthetics 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 anesthetics 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 anesthetics 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 anesthetics. Thus, we conclude that modern inhalational anesthetics, 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...
thoracotomy ranges between 4 and 15%, depending on the degree of lung resection and contributes significantly to post-operative mortality. 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. 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. 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. 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. 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. Volatile anesthetics also have a protective role on endothelial glycocalyx. Intravenous anesthetics like propofol as well, have been identified to reduce the pulmonary inflammation. 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, heterogeneous 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.
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.
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)              | Isoflurane (n=11)             | Qs/Qt          | PaO$_2$, SaO$_2$, MAP, HR |
| Reid et al. 1996               | Thoracic surgery | Propofol (n=15)              | Isoflurane (n=15)             | Arterial blood gases | MAP, HR |
| Gasowska et al. 1999           | Thoracic surgery | Propofol (n=13)              | Isoflurane (n=14)             | PaO$_2$, Qs/Qt  |                   |
| Dossow V et al. 2000           | Lung surgery     | Propofol (n=25)              | Isoflurane (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$_2$, Qs/Qt, 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, TNF-$\alpha$, ICAM-1 | HR, MAP, CVP, PAOP, Qs/Qt |
| Ozcan et al. 2007              | Lung surgery     | Propofol (n=50)              | Isoflurane (n=50)             | PaO$_2$, Qs/Qt, Qs/Qt |                   |
| Ivata et al. 2008              | Lung surgery     | Propofol (n=26)              | Sevoflurane (n=26)            | Qs/Qt          |                   |
| Huang et al. 2008              | Thoracic surgery | Propofol (n=15)              | Sevoflurane (n=15)            | Reactive oxygen species production | Oxygenation and HR, MAP |
| De Conno 2009                  | Lung resection   | Propofol (n=27)              | Sevoflurane (n=27)            | BAL TNF-$\alpha$, IL-8, IL-10, IL-1$\beta$ | 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)            | BAL TNF-$\alpha$, IL-1$\beta$, 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-1$\beta$, IL-6, IL-8, IL-10, IL-12p70, TNF-$\alpha$ |                   |
| Mahmoud 2011                   | Lung resection   | Propofol (n=25)              | Isoflurane (n=25)             | Plasma and alveolar IL-8, TNF-$\alpha$ | MDA, SOD, POC, ICU stay, Hospital stay |
| Abdelrahman et al. 2012        | Lung resection   | Propofol (n=30)              | Sevoflurane (n=30)            | PaO$_2$, Qs/Qt, PaO$_2$, SaO$_2$ | HR, MAP |
| Lee et al. 2012                | Esophagectomy    | Propofol (n=24)              | Sevoflurane (n=24)            | Plasma IL-6, MDA | POC, ICU stay, Hospital Stay |
| Harmmouda et al. 2013          | Lung surgery     | Propofol (n=20)              | Sevoflurane (n=20)            | BAL and Plasma IL-6 and TNF-$\alpha$ | CRP and WBC count post operatively |
| Yanwu et al. 2013              | Lung surgery     | Propofol (n=20)              | Sevoflurane (n=20)            | Plasma IL-6, IL-10, TNF-$\alpha$ | Qs/Qt, dynamic compliance |
| Attar et al. 2014              | Thoracic surgery | Propofol (n=30)              | Sevoflurane (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-1$\beta$, IL-6, IL-8, IL-10, IL-10, IL-12p70 | 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 | Time for occurrence of major complications in 6 months follow up, ICU stay, Hospital stay |
| Beck-Schimmer et al. 2016      | Lung resection   | Propofol (n=230)             | Desflurane (n=230)            | Time for occurrence of first major complication | Haemodynamic, ICU stay, Hospital stay |
| Cho YJ et al. 2016             | Lung surgery     | Propofol (n=52)              | Desflurane (n=52)             | PaO$_2$        | PPC, 1 month mortality, 1 year mortality, |
| de La Gala 2017                | Lung resection   | Propofol (n=88)              | Sevoflurane (n=86)            | PaO$_2$, PaCO$_2$, MAP, HR, | RI, Qs/Qt, A-aDo$_2$, MMSE |
| Tian HT et al. 2017            | Lung surgery     | Propofol (n=31)              | Sevoflurane (n=31)            | Plasma IL-6, MMP-9 | Post operative plasma ferric reducing ability, length of hospital stay and post operative complications |
| Tsuchiya et al. 2018           | Esophagectomy    | Propofol (n=92)              | Sevoflurane (n=94)            | Days for normalization of WBC counts, and CRP |                   |
| Sheybani et al. 2018           | Right thoracotomy | Propofol (n=61)              | Isoflurane (n=61)             | Gas exchange parameters | EGL injury markers, VCAM-1 levels |
| 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 |
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.68 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.109 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 2011.111-13 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.17,18 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 I² value being more than 75%.21

Thus, inhalational anesthetics may be better than intravenous anesthetics in terms of controlling the alveolar and systemic inflammatory 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.22 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                      | 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 | Overall Risk of bias |
|----------------------------|------------------------------|-----------------------------------------------|-----------------------------|------------------------------|------------------------------------|----------------------|
| Attar et al.               | LR                           | SC                                            | LR                          | SC                           | SC                                 | LR                   |
| De la Gala et al.          | LR                           | SC                                            | LR                          | SC                           | LR                                 | SC                   |
| Erturk et al.              | LR                           | SC                                            | LR                          | SC                           | LR                                 | LR                   |
| Feng et al.                | SC                           | SC                                            | LR                          | SC                           | LR                                 | SC                   |
| Hammouda et al.            | SC                           | SC                                            | LR                          | LR                           | LR                                 | SC                   |
| Kim HJ et al.              | LR                           | LR                                            | LR                          | LR                           | LR                                 | SC                   |
| Lee et al.                 | LR                           | LR                                            | LR                          | LR                           | LR                                 | SC                   |
| Mahmoud et al.             | LR                           | LR                                            | LR                          | LR                           | LR                                 | SC                   |
| Potocnik et al.            | LR                           | LR                                            | LR                          | LR                           | LR                                 | SC                   |
| Schilling T et al. (2007)  | LR                           | LR                                            | SC                          | LR                           | SC                                 | SC                   |
| Schilling T et al. (2011)  | LR                           | LR                                            | LR                          | SC                           | LR                                 | SC                   |
| Sugasawara et al.          | SC                           | 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                                 | SC                   |
| Beck-Schimmer et al.       | LR                           | LR                                            | LR                          | LR                           | LR                                 | SC                   |
| Tsuchiya et al.            | LR                           | LR                                            | LR                          | LR                           | LR                                 | SC                   |
| Xu WY et al.               | LR                           | SC                                            | LR                          | LR                           | LR                                 | SC                   |
| Abdelrahman et al.         | SC                           | SC                                            | LR                          | LR                           | LR                                 | SC                   |
| Cho YJ et al.              | LR                           | SC                                            | LR                          | SC                           | SC                                 | SC                   |
| Hamh et al.                | LR                           | LR                                            | SC                          | LR                           | SC                                 | SC                   |
| Sherin et al.              | LR                           | SC                                            | SC                          | LR                           | SC                                 | 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                   |
| Zhi guo 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                           | SC                                            | LR                          | SC                           | LR                                 | SC                   |
| Gasovaska et al.           | SC                           | SC                                            | LR                          | SC                           | SC                                 | SC                   |
| Huang et al.               | LR                           | LR                                            | LR                          | LR                           | LR                                 | SC                   |
| Ivata et al.               | LR                           | SC                                            | SC                          | LR                           | SC                                 | SC                   |
| Kellow et al.              | SC                           | SC                                            | SC                          | LR                           | LR                                 | SC                   |
| Pruszkowski et al.         | HR                           | SC                                            | SC                          | SC                           | SC                                 | HR                   |
| Reid et al.                | LR                           | SC                                            | SC                          | SC                           | SC                                 | SC                   |
| Dossow V et al.            | SC                           | LR                                            | SC                          | SC                           | SC                                 | SC                   |
| Schwarzkopf et al.         | LR                           | SC                                            | SC                          | SC                           | SC                                 | SC                   |

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

Due to randomization process: LR - Low risk, SC - Some concerns, HR - High risk

Due to deviations from intended interventions: LR - Low risk, SC - Some concerns, HR - High risk

Due to missing outcome data: LR - Low risk, SC - Some concerns, HR - High risk

In measurement of the outcome: LR - Low risk, SC - Some concerns, HR - High risk

In selection of the reported result: LR - Low risk, SC - Some concerns, HR - High risk

Overall Risk of bias: 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, ICU stay and hospital stay, in 48 patients 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.
and sevoflurane in 20 patients undergoing esophagectomy surgery. 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. 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. 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]). 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. 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. For the outcome of pulmonary complications, the included studies had less heterogeneity (I² = 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:

\[
\text{Qs}/\text{Qt} = (\text{CcO}_2 - \text{CaO}_2)/(\text{CcO}_2 - \text{CvO}_2) \\
\text{CaO}_2 = (\text{PaO}_2 \times 0.0031) + (\text{Hb} \times 1.36 \times \text{SaO}_2), \\
\text{CvO}_2 = (\text{PvO}_2 \times 0.0031) + (\text{Hb} \times 1.36 \times \text{SvO}_2) \\
\text{CcO}_2 = (\text{FiO}_2 \times (\text{PB} - \text{PH}_2\text{O}) - \text{PaCO}_2/\text{RQ}) \times 0.0031 + (\text{Hb} \times 1.36)
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Kellow et al. (1995) found that the shunt increased significantly in isoflurane group as compared to propofol. 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. 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. However, Abd El-Hakeem 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.

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, Gasowksa et al. 1999, Beck et al. 2001, Pruszkowski et al. 2007, Huang et al. 2008, Iwata et al. 2008, Fukuoka et al. 2009, Schwarzkopf et al. 2009, Schilling et al. 2011, Mahmoud et al. 2011, Hammouda et al. 2013, Attar et al. 2014, de la Gala et al. 2017, Sheybani et al., et al.)
Zheng et al. 2018 and Hahm et al. 2019 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), Abdelrahman et al. (2012), Xu WY et al. (2013), Yanwu J et al. (2013), Erturk et al. (2014), Cho et al. (2017), Sherin et al. (2018) and Zhiguo et al. (2019) 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).

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. On the other hand, Dosswo et al. (2001) found that cardiac index increased significantly in propofol group, as compared to isoflurane group. 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.

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. 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 fraction (RVEF), right ventricular end diastolic volume index (RVEDVI) and right ventricular stroke volume index (RVSVI) 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.

Two RCTs by Reid et al. (1996), Beck et al. (2001), Pruszkowski et al. (2007), Schilling et al. (2007), Huang et al. (2008), Cho et al. (2017) and de la Gala et al. (2017) 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.

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. 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. 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. 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. 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. 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). 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 biontrauma (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. 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. Investigations have proven that volatile anesthetics also protect central nervous, renal and hepatic systems from inflammatory injury. 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 (NFκB) and its effect on Toll Like Receptors (TLR).
Sevoflurane also protects against vascular endothelial cell dysfunction via through activation of eNOS/NO pathway and inhibition of NFκB. 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. It has been proved that desflurane has lesser anti-inflammatory and anti-oxidant action as compared to sevoflurane. 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. Also, use of IL-8 antagonist prior to the tissue injury has been proven protective against development of lung injury. 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. 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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