The Effects of One-lung Ventilation on the Production of Endogenous Melatonin and NLRP3 Inflammasome-Related Inflammatory Cytokines in Patients Undergoing Laparoscopic Esophagectomy: A Prospective Randomized Double-Blind Controlled Study

Lixia Wang
First Affiliated Hospital of Anhui Medical University
Jun Li
First Affiliated Hospital of Anhui Medical University
Yuting Huang
Anhui Medical University
Yan Zhu
First Affiliated Hospital of Anhui Medical University
Qiying Shen
First Affiliated Hospital of Anhui Medical University
Hongyun Zou
First Affiliated Hospital of Anhui Medical University
Xue-sheng Liu (liuxuesheng@ahmu.edu.cn)
First Affiliated Hospital of Anhui Medical University https://orcid.org/0000-0003-4324-282X

Research article

Keywords: ventilator-induced lung injury, one-lung ventilation, NLRP3 inflammasome, endogenous melatonin, inflammation

Posted Date: March 3rd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-15882/v1

Abstract

Background: NLRP3 inflammasome has been confirmed to play a pivotal role in ventilator-induced lung injury (VILI), while exogenous melatonin can attenuate VILI by inhibiting NLRP3 inflammasome activation in mouse model. However, the relationship between endogenous melatonin and the NLRP3 inflammasome-related inflammatory cytokines in VILI induced by one-lung ventilation (OLV) remains unknown. In this study, we aimed to reveal the relationship between the NLRP3 inflammasome-related inflammatory cytokines: interleukin (IL)-1β, IL-18 and endogenous melatonin in OLV-induced VILI during esophageal cancer surgery.

Methods: Twenty-eight patients were randomized to receive “conventional” ventilation (Vt=8 mL/kg) or lung protective ventilation (Vt=5 mL/kg along with 5 cm H 2 O positive end-expiratory pressure (PEEP)). Respiratory variables were evaluated. IL-1β, IL-18 and melatonin in bronchoalveolar lavage fluid (BALF) and plasma were measured.

Results: we found that lung protective ventilation during OLV decreased peak airway pressure (Ppeak), plateau airway pressure (Pplat) and driving pressure (ΔP) compared with that in “conventional” ventilation group. Moreover, lung protective ventilation inhibited polymorphonuclear (PMN) cells invasion into BALF. Likewise, lung protective ventilation not only suppressed alveolar and plasma IL-1β secretion, but also reduced increased production of IL-18 in both BALF and plasma after OLV. Furthermore, we found that both alveolar and plasma endogenous melatonin levels in “conventional” ventilation group were lower than that in lung protection group.

Conclusion: Taken together, the present study suggested that lung protective ventilation during OLV prevented VILI via suppressing NLRP3 inflammasome-related inflammatory cytokines secretion and restoring the level of endogenous melatonin in patients.

Trial registration: the Chinese Clinical Trial Registry, ChiCTR1900026190. Registered 25 September 2019, http://www.chictr.org.cn/edit.aspx?pid=34677&htm=4

Background

One-lung ventilation (OLV) is required for esophageal cancer and can contribute to the surgical field [1]. However, inappropriate ventilation modes may cause or augment acute lung injury, which is known as ventilator-induced lung injury (VILI) [2]. Lung-protective ventilation [low tidal volume + positive end-expiratory pressure (PEEP)] in OLV was shown to achieve good clinical effects and protect against VILI [3, 4]. Furthermore, clinical studies have demonstrated that lung-protective ventilation induced an immune response with lower concentrations of inflammatory mediators than that of “conventional” ventilation [5]. Therefore, further study of the pulmonary immune response is essential for the prevention of VILI.

Increasing studies have shown that OLV may lead to proinflammatory cytokine release and inflammatory signaling pathway activation [5–8]. Overdistension in ventilated lungs followed by compression of

alveolar vessels initiates a robust release of proinflammatory cytokines, such as interleukin (IL)-6, IL-8 and tumor necrosis factor (TNF)-a, in bronchoalveolar lavage fluid (BALF) [5, 9]. These proinflammatory cytokines are important chemotactic factors for polymorphonuclear (PMN) cells [10]. Excessive PMN cell aggregation will amplify the inflammatory cascade. Furthermore, a recent study showed that in mouse alveolar macrophages, Nucleotide-binding domain and leucine-rich repeat protein 3 (NLRP3) inflammasome activation contributes to the development of VILI [11]. However, whether OLV activates the NLRP3 inflammasome during esophageal cancer surgery remains unknown.

Melatonin (N-acetyl-5-methoxytryptamine, MT), which is mainly secreted in the pineal gland, has well-documented anti-inflammatory and immunomodulatory functions [12, 13]. Early preliminary studies have shown that exogenous MT ameliorates VILI by increasing the anti-inflammatory response [14]. Recently, Zhang et al. demonstrated that exogenous MT inhibited NLRP3 inflammasome activation in mice with acute lung injury [15]. However, the crosstalk between endogenous MT and the NLRP3 inflammasome in VILI induced by OLV remains unknown.

Our study aimed to investigate the effects of different ventilation strategies on NLRP3 inflammasome-related inflammatory cytokines secretion and reveal the relationship between NLRP3 inflammasome-related inflammatory cytokines and endogenous MT in OLV-induced VILI during esophageal cancer surgery. In addition, the impact of different ventilation strategies during OLV on postoperative complications was investigated.

Material And Methods

Study Design

Patients scheduled for elective laparoscopic esophagectomy at the First Affiliated Hospital of Anhui Medical University (Anhui, China) were included in the study. The study protocol had received prior approval from the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (No. 20190385), and this trial was registered in the Chinese Clinical Trial Registry (No. ChiCTR1900026190). Before participation in the study, all patients provided informed consent.

Study Population

Patients with esophageal cancer in our hospital were considered for enrollment. The inclusion criteria were as follows: American Society of Anesthesiologists' (ASA) physical status I or II, requirement for OLV during operation, and 49–77 years old. Exclusion criteria were preexisting hypoxemia, diagnosed major obstructive or restrictive pulmonary disease [preoperative forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) <70% of the predicted value], pulmonary infection before surgery, body mass index (BMI) of less than 20 or more than 35, and use of immune modulators.

Randomization and Blinding

The randomized numbers were generated by a research coordinator using block sizes on a 1 : 1 ratio. This ensured that each group had an equal number of subjects. Then, the research coordinator sealed the numbers in opaque envelopes. During OLV, the anesthesia assistant opened the envelopes, set the breathing parameters and covered the breathing parameters using opaque paper. The anesthesia assistant did not participate in the next study. One anesthesiologist collected the specimens, and another anesthesiologist recorded the breathing parameters. Both physicians were blinded to the allocation.

Study Protocol

Standard monitoring devices were applied after admission to the operating room. Before induction of anesthesia, an artery catheter was inserted into the left radial artery. Anesthesia induction was performed with 2.0 mg/kg propofol, 0.05 mg/kg midazolam, 4 μg/kg sufentanil and 0.9 mg/kg rocuronium. A double-lumen endotracheal tube (Broncho-Cath® 35 F or 37 F; Covidien, Ireland) was inserted into the left main bronchus. Anesthesia was maintained with 6–8 mg/kg propofol, 0.1–0.3 μg/kg remifentanil per minute, and 5.0–10.0 μg/kg rocuronium per minute. A forced-air warming system (3M Company, Shanghai, China) was used to keep the patients warm.

After intubation, conventional two-lung ventilation (TLV) with a tidal volume of 8 mL/kg of ideal body weight (IBW) was performed for 15 minutes. Then, all patients were turned to the left lateral position, and OLV was initiated. During OLV, the patients were randomly divided into 2 groups. In the control group (group A), OLV with a routine tidal volume (V_t=8 mL/kg IBW) and volume-controlled ventilation mode was used. In the lung-protective ventilation group (group B), OLV with a low tidal volume (V_t=5 mL/kg IBW) and 5 cm H_2O PEEP was chosen. With both TLV and OLV, mechanical ventilation was performed with an inspiratory to expiratory ratio of 1:2, 100% oxygen, and an I respiratory rate to maintain an end-tidal CO_2 ($ETCO_2$) of 35–40 mmHg.

Observational Indexes

Peak airway pressure (Ppeak), plateau airway pressure (Pplat) and blood gas analyses were evaluated at three stages: during TLV before surgery, 30 minutes after OLV and during TLV at the end of surgery. Furthermore, the driving pressure (ΔP) was recorded. ΔP was defined and calculated as follows: ΔP=Pplat−PEEP [16].

Bronchoalveolar lavage was performed after induction of general anesthesia and at the end of the surgical procedures. BALF was aspirated from the left lung after instillation of 10 mL of sterile isotonic saline. Then, the recovered BALF was centrifuged at 700 g for 10 minutes at 4°C, and the supernatant was stored at -80°C. The cell pellets were resuspended in ice-cold sterile isotonic saline for staining and counting.

Blood samples were obtained before induction of general anesthesia and at the end of the surgical procedures. Five milliliters of arterial blood samples was centrifuged at 800 g for 5 minutes. The upper plasma was separated and stored at -80°C.

MT, IL-18 and IL-1β concentrations in the plasma and BALF were determined by commercial ELISA kits (Cusabio, Wuhan, China). We performed the assays according to the manufacturer's instructions. The limitations for MT, IL-18 and IL-1β were 0.1 pg/mL, 2.2 pg/mL and 7.8 pg/mL, respectively.

The primary outcomes were pulmonary complications, including pulmonary infection, acute lung injury or acute respiratory distress syndrome and reintubation or invasive mechanical ventilation. In addition, secondary outcomes, including anastomotic fistula, incision infection, ICU stay and death before hospital discharge, were recorded.

Statistical Aanalysis

According to previous studies, the cell numbers in the BALF increased more than 30% after OLV [5].We assumed that the cell numbers in the BALF increased at least 25% with a power of 80% and an α of 5%, and thus, 12–14 patients in each group were needed. Data are presented as the mean ± SD or number of patients. One-way ANOVA with a post hoc Bonferroni test was used to analyze normally distributed data. Non-normally distributed data were analyzed by chi-square tests. All statistical analyses were performed with SPSS 19, and a P value of <0.05 was considered significant.

Results

Baseline Parameters of Patients

In total, 34 patients were included and assessed. 4 patients did not meet the criteria, and 30 were included in this study. However, 2 patients withdrew for technical reasons, and at last 28 completed the study (Fig. 1). The patient characteristics and preoperative details showed no significant differences between the groups (Table 1).

Changes in the Respiratory Parameters

The respiratory and gas exchange variables are presented in Table 2. During OLV, an increase in Ppeak and Pplat was observed in all patients. ΔP in the control group increased substantially compared with that at baseline. Furthermore, our readings for Ppeak, Pplat and ΔP during OLV in the control group were higher than those in the lung-protective ventilation group. Additionally, in both groups, the oxygenation index decreased during OLV compared with that at baseline; however, there was no difference between the two groups.

Changes in the Number of Cells in the BALF

The cells in the BALF were counted after Wright-Giemsa staining. The number of total cells and PMN cells in the BALF was substantially increased during mechanical ventilation (Fig. 2). However, in the lung-protective strategy group, the total cells and PMN cells in the BALF were significantly reduced compared to those in the control group (Fig. 2).

Changes in IL-1β and IL-18 in the BALF and Plasma

Recently, researchers demonstrated that NLRP3 inflammasome activation is important for exacerbating VILI [17, 18]. The activation of the NLRP3 inflammasome produces IL-1β and IL-18 [19]. Therefore, commercial ELISA kits were used to detect the production of both IL-1β and IL-18 in the BALF and plasma. As expected, the IL-1β and IL-18 levels in the BALF showed an increased trend after OLV, but the increase in IL-1β was not significant in the lung-protective strategy group (Fig. 3A, B). In addition, a significant reduction in the IL-1β and IL-18 levels in the BALF was observed in the lung-protective strategy group compared with the control group (Fig. 3A, B).

In all patients, the plasma IL-1β and IL-18 concentrations were significantly increased after OLV (Fig. 3D, E). However, lung-protective ventilation resulted in a significant decrease in the plasma IL-1β and IL-18 concentrations after OLV compared to those in the control group (Fig. 3D, E).

Changes in MT in the BALF and Plasma

Endogenous MT levels in both the BALF and plasma were also detected. In contrast to the IL-18 and IL-1β levels, the plasma MT levels in both groups were significantly decreased after OLV, as was the BALF MT level in the control group (Fig. 3C, F). Additionally, both the BALF and plasma MT concentrations in the control group were lower than those in the lung protection group (Fig. 3C, F).

The Incidence of Complications

As shown in Table 3, there was no difference in the incidence rates of complications between the two groups.

Discussion

Our study indicated that the lung-protective ventilation improved respiratory variables, including Ppeak, Pplat and ΔP. The lung-protective ventilation not only inhibited PMN cell invasion but also suppressed IL-1β and IL-18 secretion. In addition, we found that lung-protective ventilation resulted in decreased inhibition of endogenous MT production compared to “conventional” ventilation.

OLV is an established procedure during laparoscopic esophagectomy. However, clinical studies have shown that the extended use of OLV is an independent risk factor for postoperative pulmonary dysfunction [20]. Excessive stretching or repeated opening of lung tissues is an important cause of VILI during OLV [21]. A lung-protective strategy using low Vt along with PEEP during OLV was confirmed to improve postoperative pulmonary dysfunction [6]. In our study, we found that the lung-protective strategy notably decreased Ppeak and Pplat, indicating that the shear force was reduced via a lung-protective strategy. Meanwhile, we also observed a substantial decrease in ΔP with the lung-protective strategy during OLV, which suggested that the lung-protective strategy was associated with a reduced incidence of postoperative pulmonary complications [16]. However, our research failed to find a difference in the incidence of complications between the two groups, which may be related to the small sample size.

Increased mechanical strain further activating the inflammatory response is a key event during the development of VILI [5]. The results from previous and recent studies have shown that IL-1β is a special proinflammatory cytokine that promotes VILI in animal models and patients [22–25]. Regulation and inhibition of IL-1β can finally achieve organ protection because blockade of the IL-1 receptor has been demonstrated to inhibit neutrophil sequestration and edema formation in VILI [26]. In our study, we clearly showed that OLV increased the concentration of IL-1β in the plasma as well as the alveolar PMN cell counts in the BALF. However, lung-protective ventilation blocked the elevated IL-1β level and PMN cell recruitment. Most interestingly, we observed a dramatic increase in both the alveolar and plasma concentrations of IL-18 after OLV, while lung-protective ventilation resulted in a profound reduction in IL-18. IL-1β and IL-18 were confirmed to be products of NLRP3 inflammasome activation [19]. Furthermore, current studies have demonstrated that NLRP3 inflammasome activation plays a key role in the pathogenesis of VILI in a mouse model [17, 18]. Therefore, lung-protective ventilation may inhibit inflammatory responses by inhibiting activation of the NLRP3 inflammasome during OLV. For the first time, our results provide evidence that NLRP3 inflammasome activation may be involved in the initiation and development of VILI during OLV.

As discussed above, the precise mechanism of how OLV activated the NLRP3 inflammasome during laparoscopic esophagectomy was unclear. In recent years, the anti-inflammatory effects of both exogenous and endogenous MT have been observed in many conditions [27, 28]. Paula et al. demonstrated that the exogenous addition of MT protected against VILI through decreasing the levels of inflammatory cytokines in a mouse model [14]. Further research confirmed that exogenous replenishment of MT alleviated lipopolysaccharide (LPS)-induced acute lung injury by inhibiting NLRP3 inflammasome activation [15]. Therefore, we hypothesized that endogenous MT may mediate VILI through inhibiting NLRP3 inflammasome activation. As expected, we found that OLV substantially reduced the production of endogenous MT in patient plasma and the BALF level of MT in the control group. Surprisingly, pulmonary protective ventilation significantly inhibited the reduction of endogenous MT. Accordingly, our results suggested that NLRP3 inflammasome activation regulated by endogenous MT may be involved in the pathogenesis of VILI.

Conclusion

In conclusion, our study suggested that pulmonary protective ventilation during OLV improved lung function and suppressed NLRP3 inflammasome-related inflammatory cytokines secretion in patients undergoing laparoscopic esophagectomy. These effects may be attributable to pulmonary protective ventilation-mediated restoration of the reduction of endogenous MT.

Abbreviations

OLV
one-lung ventilation
VILI

ventilator-induced lung injury
PEEP
positive end-expiratory pressure
IL
interleukin
TNF
tumor necrosis factor
BALF
bronchoalveolar lavage fluid
PMN
polymorphonuclear
NLRP3
Nucleotide-binding domain and leucine-rich repeat protein 3
MT
melatonin
FEV
forced expiratory volume
FVC
forced vital capacity
BMI
body mass index
TLV
two-lung ventilation
IBW
ideal body weight
ETCO2
end-tidal pressure of carbon dioxide
Ppeak
peak airway pressure
Pplat
plateau airway pressure
ΔP
driving pressure

Declarations

Ethics approval and consent to participate

The study protocol had received prior approval by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (No. 20190385). In the study, all patients signed written informed consent.

Consent for publication

All authors have consented to publication of the manuscript. **Availability of data and materials**

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interests.

Funding

This work was supported by grants from the National Nature Science Foundation of China (No. 81902003), Youth Research Foundation of the Anhui Medical University First Affiliated Hospital (Nos. 2018kj28 and 2019kj11), Doctoral Research Foundation of the First Affiliated Hospital of Anhui Medical University (No. 1326). These funds provided financial help to this study, but had no role in the design of the study, the collection, analysis, interpretation of data or in writing the manuscript.

Authors' Contributions

LXW, JL and YTH collected the data, and drafted the manuscript, they contributed equally as co-first authors; YZ performed the statistical analysis; QYS and HYZ revised the manuscript critically for important intellectual content. All authors were responsible for the conception and design of the trial, and approved the final manuscript.

Acknowledgments

We acknowledge the support by Dr. Zhilai Yang. We are also thankful to the patients and their families who consented to participate in our trial.

References

1. Blank RS, Colquhoun DA, Durieux ME, et al. Management of One-lung Ventilation: Impact of Tidal Volume on Complications after Thoracic Surgery. Anesthesiology. 2016;124(6):1286-1295.
2. Choi YS, Shim JK, Na S, et al. Pressure-controlled versus volume-controlled ventilation during one-lung ventilation in the prone position for robot-assisted esophagectomy. Surgical endoscopy. 2009;23(10):2286-2291.
3. Hemmes SN, Serpa Neto A, Schultz MJ Intraoperative ventilatory strategies to prevent postoperative pulmonary complications: a meta-analysis. Current opinion in anaesthesiology. 2013;26(2):126-133.
4. Fernandez-Perez ER, Keegan MT, Brown DR, et al. Intraoperative tidal volume as a risk factor for respiratory failure after pneumonectomy. Anesthesiology. 2006;105(1):14-18.

5. Schilling T, Kozian A, Huth C, et al. The pulmonary immune effects of mechanical ventilation in patients undergoing thoracic surgery. Anesthesia and analgesia. 2005;101(4):957-965, table of contents.
6. Senturk M, Slinger P, Cohen E Intraoperative mechanical ventilation strategies for one-lung ventilation. Best practice & research Clinical anaesthesiology. 2015;29(3):357-369.
7. Kotani N, Lin CY, Wang JS, et al. Loss of alveolar macrophages during anesthesia and operation in humans. Anesthesia and analgesia. 1995;81(6):1255-1262.
8. Kotani N, Hashimoto H, Sessler DI, et al. Intraoperative modulation of alveolar macrophage function during isoflurane and propofol anesthesia. Anesthesiology. 1998;89(5):1125-1132.
9. Lohser J, Slinger P Lung Injury After One-Lung Ventilation: A Review of the Pathophysiologic Mechanisms Affecting the Ventilated and the Collapsed Lung. Anesthesia and analgesia. 2015;121(2):302-318.
10. Dreyfuss D, Ricard JD, Saumon G On the physiologic and clinical relevance of lung-borne cytokines during ventilator-induced lung injury. American journal of respiratory and critical care medicine. 2003;167(11):1467-1471.
11. Wu J, Yan Z, Schwartz DE, et al. Activation of NLRP3 inflammasome in alveolar macrophages contributes to mechanical stretch-induced lung inflammation and injury. Journal of immunology (Baltimore, Md : 1950). 2013;190(7):3590-3599.
12. Liu YJ, Meng FT, Wang LL, et al. Apolipoprotein E influences melatonin biosynthesis by regulating NAT and MAOA expression in C6 cells. Journal of pineal research. 2012;52(4):397-402.
13. Calvo JR, Gonzalez-Yanes C, Maldonado MD The role of melatonin in the cells of the innate immunity: a review. Journal of pineal research. 2013;55(2):103-120.
14. Pedreira PR, Garcia-Prieto E, Parra D, et al. Effects of melatonin in an experimental model of ventilator-induced lung injury. American journal of physiology Lung cellular and molecular physiology. 2008;295(5):L820-827.
15. Zhang Y, Li X, Grailer JJ, et al. Melatonin alleviates acute lung injury through inhibiting the NLRP3 inflammasome. Journal of pineal research. 2016;60(4):405-414.
16. Neto AS, Hemmes SN, Barbas CS, et al. Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: a meta-analysis of individual patient data. The Lancet Respiratory medicine. 2016;4(4):272-280.
17. Liu H, Gu C, Liu M, et al. Ventilator-induced lung injury is alleviated by inhibiting NLRP3 inflammasome activation. Molecular immunology. 2019;111:1-10.
18. An X, Sun X, Yang X, et al. Oxidative stress promotes ventilator-induced lung injury through activating NLRP3 inflammasome and TRPM2 channel. Artificial cells, nanomedicine, and biotechnology. 2019;47(1):3448-3455.
19. Bryant C, Fitzgerald KA Molecular mechanisms involved in inflammasome activation. Trends in cell biology. 2009;19(9):455-464.

20. Della Rocca G, Coccia C Acute lung injury in thoracic surgery. Current opinion in anaesthesiology. 2013;26(1):40-46.
21. Kim KN, Kim DW, Jeong MA, et al. Comparison of pressure-controlled ventilation with volume-controlled ventilation during one-lung ventilation: a systematic review and meta-analysis. BMC anesthesiology. 2016;16(1):72.
22. Belperio JA, Keane MP, Lynch JP, 3rd, et al. The role of cytokines during the pathogenesis of ventilator-associated and ventilator-induced lung injury. Seminars in respiratory and critical care medicine. 2006;27(4):350-364.
23. Lionetti V, Recchia FA, Ranieri VM Overview of ventilator-induced lung injury mechanisms. Current opinion in critical care. 2005;11(1):82-86.
24. Wagner J, Strosing KM, Spassov SG, et al. Sevoflurane posttreatment prevents oxidative and inflammatory injury in ventilator-induced lung injury. PloS one. 2018;13(2):e0192896.
25. Conway Morris A, Kefala K, Wilkinson TS, et al. Diagnostic importance of pulmonary interleukin-1beta and interleukin-8 in ventilator-associated pneumonia. Thorax. 2010;65(3):201-207.
26. Frank JA, Pittet JF, Wray C, et al. Protection from experimental ventilator-induced acute lung injury by IL-1 receptor blockade. Thorax. 2008;63(2):147-153.
27. Mauriz JL, Collado PS, Veneroso C, et al. A review of the molecular aspects of melatonin's anti-inflammatory actions: recent insights and new perspectives. Journal of pineal research. 2013;54(1):1-14.
28. Wu HM, Shen QY, Fang L, et al. JNK-TLR9 signal pathway mediates allergic airway inflammation through suppressing melatonin biosynthesis. Journal of pineal research. 2016;60(4):415-423.

Tables

Table 1 Baseline parameters of patients

Group Parameter	Group A (n=14)	Group B (n=14)	P
Male/Female (n)	12/2	12/2	1.0
Age, y	64.8±8.5	64.5±7.9	0.928
BMI, kg/m^2	23.7±3.5	23.1±2.8	0.660
Oxygenation index (PaO_2/FiO_2, mm Hg)	395.6±45.7	408.0±39.8	0.449
$PaCO_2$, mm Hg	40.8±3.7	40.1±3.9	0.626
SpO_2 (%)	96.9±1.7	97.8±1.8	0.152
FEV1%	86.2±7.8	84.4±5.5	0.499
FVC%	92.4±12.9	86.6±6.9	0.153
Operative time, min	285.4±53.2	289.9±66.4	0.845
OLV time, min	118.2±37.5	132.2±35.1	0.317

Data are presented as the mean ± SD.

BMI: body mass index; PaO_2: arterial oxygen tension; FiO_2: fraction of inspired oxygen; $PaCO_2$: arterial carbon dioxide tension; FEV: forced expiratory volume; FVC: forced vital capacity; OLV: one-lung ventilation; SpO_2, oxygen saturation.

Table 2 Respiratory variables and Oxygenation Index During TLV Before Surgery (TLV, Preoperatively), During OLV (After 30 Min) and at TLV Postoperatively

	TLV, Preoperatively		OLV		TLV, Postoperatively	
	Group A (n=14)	Group B (n=14)	Group A (n=14)	Group B (n=14)	Group A (n=14)	Group B (n=14)
Peak pressure (cm H_2O)	12.4±2.2	11.9±1.7	25.6±2.5†	21.6±2.6†*	14.4±1.0	14.0±2.2
Plateau pressure (cm H_2O)	8.64±2.1	9.3±2.3	21.5±2.7†	18.2±2.7†*	11.6±1.2†	11.3±2.5
Driving pressure (cm H_2O)	12.4±2.2	11.9±1.7	16.5±2.7†	13.2±2.7*	14.4±1.0	14.0±2.2
Oxygenation index (PaO2/FiO2, mmHg)	395.6±45.7	408.0±39.8	323.9±33.4†	336.7±41.9†	397.1±34.1	404.9±30.3

Data are presented as the mean and SD.

* P < 0.05 between groups, †P <0.05 within groups.

PaO2: arterial oxygen tension; FiO2: fraction of inspired oxygen; OLV: one-lung ventilation; TLV: two-lung ventilation.

Table 3 The incidence of complications [n (%)] among 2 groups

	Group A (n=14)	Group B (n=14)
Pulmonary infection (n)	1	2
ALI/ARDS (n)	0	1
Reintubation (n)	1	0
Anastomotic fistula (n)	3	2
Incision infection (n)	1	1
ICU stay (n)	1	0
Hospital death (n)	0	0
Incidence of Complications (%)	50	42.9
P		0.705

ALI: acute lung injury; ARDS: acute respiratory distress syndrome.

Figures

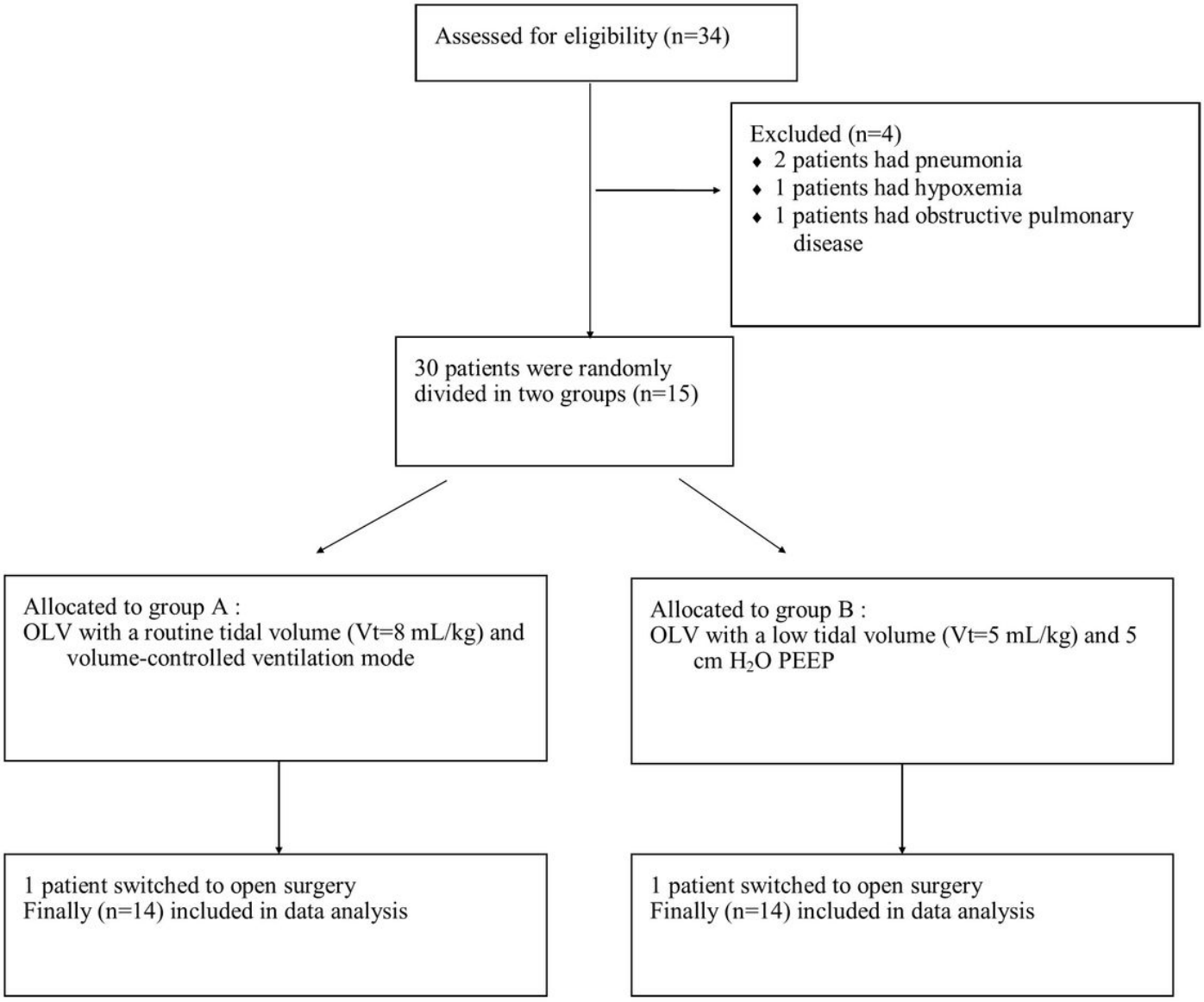

Figure 1

Consort flow chart that outline patients assignment and treatment protocols. Group A: One lung ventilation with a routine tidal volume (Vt=8 mL/kg) and volume-controlled ventilation mode was used; Group B: One lung ventilation with a low tidal volume (Vt=5 mL/kg IBW) and 5 cm H2O PEEP was chosen.

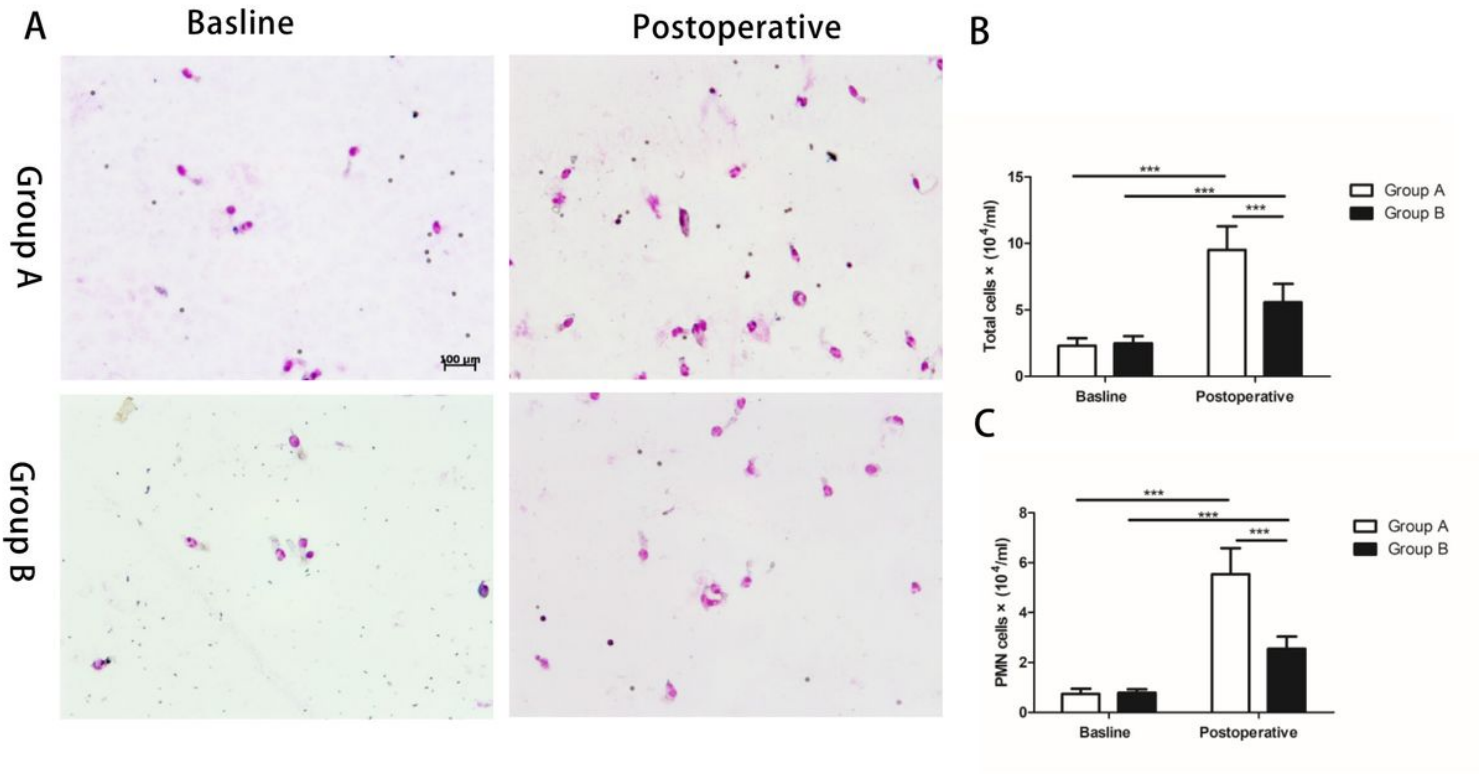

Figure 2

Effect of lung-protective ventilation on polymorphonuclear (PMN) cells in the BALF. (A) Representative Wright-Giemsa-stained smear of BALF from different groups (magnification ×20). The data shown represent changes in the total number of cells (B) and PMN cells (C) in the BALF. Data are expressed as the mean ± SD of 14 patients per group, ∗∗∗P < 0 001.

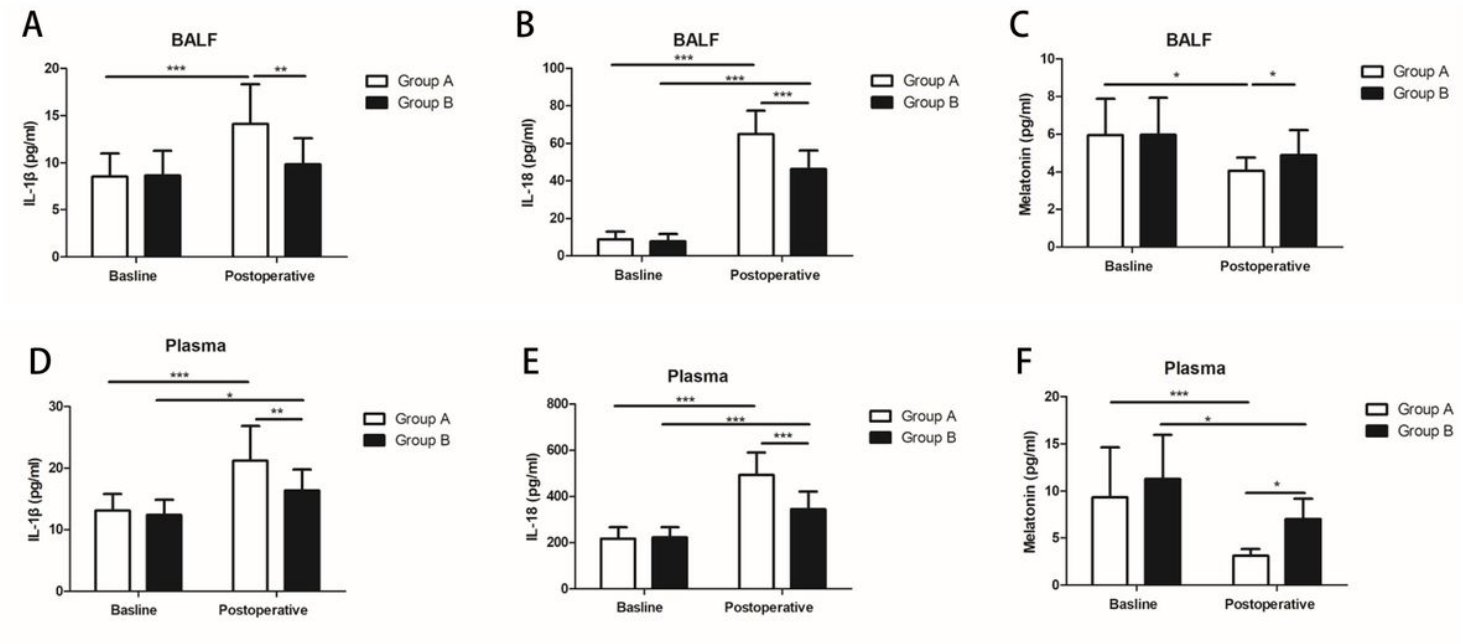

Figure 3

Effect of lung-protective ventilation on IL-1β, IL-18 and endogenous melatonin production in the BALF and plasma. (A-C) Production of IL-1β, IL-18 and endogenous melatonin in the BALF. (D-F) Production of IL-1β, IL-18 and endogenous melatonin in the plasma. Data are expressed as the mean ± SD of 14 patients per group, *P < 0.05, ** P < 0.01, *** P < 0.001.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010ChecklistMSWord.doc