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Original Research

CRITICAL CARE

Does a Protective Ventilation Strategy Reduce the Risk of Pulmonary Complications After Lung Cancer Surgery?

A Randomized Controlled Trial

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Background: **Protective ventilation strategy has been shown to reduce ventilator-induced lung injury in patients with ARDS. In this study, we questioned whether protective ventilatory settings would attenuate lung impairment during one-lung ventilation (OLV) compared with conventional ventilation in patients undergoing lung resection surgery.**

Methods: **One hundred patients with American Society of Anesthesiology physical status 1 to 2 who were scheduled for an elective lobectomy were enrolled in the study. During OLV, two different ventilation strategies were compared. The conventional strategy (CV group, n = 50) consisted of F_{IO_2} 1.0, tidal volume (V_T) 10 mL/kg, zero end-expiratory pressure, and volume-controlled ventilation, whereas the protective strategy (PV group, n = 50) consisted of F_{IO_2} 0.5, V_T 6 mL/kg, positive end-expiratory pressure 5 cm H_2O, and pressure-controlled ventilation. The composite primary end point included $P_{aO_2}/F_{IO_2} < 300$ mm Hg and/or the presence of newly developed lung lesions (lung infiltration and atelectasis) within 72 h of the operation. To monitor safety during OLV, oxygen saturation by pulse oximeter (S_{pO_2}), P_{aCO_2}, and peak inspiratory pressure (PIP) were repeatedly measured.**

Results: **During OLV, although 58% of the PV group needed elevated F_{IO_2} to maintain an $S_{pO_2} > 95\%$, PIP was significantly lower than in the CV group, whereas the mean P_{aCO_2} values remained at 35 to 40 mm Hg in both groups. Importantly, in the PV group, the incidence of the primary end point of pulmonary dysfunction was significantly lower than in the CV group (incidence of $P_{aO_2}/F_{IO_2} < 300$ mm Hg, lung infiltration, or atelectasis: 4% vs 22%, $P < .05$).**

Conclusion: **Compared with the traditional large V_T and volume-controlled ventilation, the application of small V_T and PEEP through pressure-controlled ventilation was associated with a lower incidence of postoperative lung dysfunction and satisfactory gas exchange.**

Trial registry: **Australian New Zealand Clinical Trials Registry; No.: ACTRN12609000861257; URL: www.anzctr.org.au**

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Abbreviations: ALI = acute lung injury; CV = conventional strategy group; OLV = one-lung ventilation; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; PV = protective strategy group; S_{pO_2} = oxygen saturation by pulse oximeter; VILI = ventilator-induced lung injury; V_T = tidal volume; ZEEP = zero end-expiratory pressure

The important aspects of ventilator-induced lung injury (VILI) are volutrauma, barotrauma, atelectrauma, and oxygen toxicity. The protective ventilation strategy, which addresses these issues by using a small V_T with positive end-expiratory pressure (PEEP), limited airway pressure, and low F_{IO_2}, has gained wide acceptance as a ventilation strategy and has been shown to reduce VILI in patients with ARDS.[1-3]

It is uncertain whether the instigation of mechanical ventilation can induce some degree of structural injury to normal lungs.[4-6] Recently, the safety issue of conventional methods for one-lung ventilation (OLV) has been raised because of the possibility for VILI using a large tidal volume (V_T) in lung resection surgery. Conventional methods for OLV often use a V_T of 8 to 12 mL/kg (the same V_T for two-lung ventilation) to prevent atelectasis,[7,8] and systemic oxygenation is optimized by increasing F_{IO_2} to 1.0 to create a buffer should ventilation and oxygenation become difficult. PEEP is usually not applied because it can

direct more blood flow to the nonventilated lung and cause shunt aggravation.[7-9] However, this approach to OLV is not an evidence-based guideline and has a potential for volutrauma, barotrauma, atelectrauma, and oxygen toxicity. Several studies have shown some correlations between OLV and cumulative oxidative stress,[10] proinflammatory cytokine release,[11] and tissue damage on histologic analysis.[12] Furthermore, a retrospective analysis of contributing factors for acute lung injury (ALI) after lung resections has identified the increased duration of OLV as one of the main risk factors.[13]

With the significant contributions of standardization of surgical techniques and advances in anesthetic management, lung resection surgery is now considered as a relatively safe procedure; however, various degrees of postoperative pulmonary complications still remain a matter of great concern.[14] We, therefore, reasoned that because VILI could contribute to postoperative respiratory complications, a lung-protective ventilatory strategy during OLV might reduce these complications.

To date, several observational studies have identified duration of OLV, VT, and the level of inspiratory airway pressure as risk factors for postresection ALI-ARDS in thoracic surgery.[13,15,16] From these reports, recent recommendations have suggested using smaller VT and PEEP during OLV.[17] However, there have been no prospective randomized trials assessing the impact of a standardized protective ventilatory regimen on intraoperative safety and on the occurrence of lung complications. Therefore, this study was performed to test the hypothesis that protective ventilation strategies can more effectively reduce postoperative pulmonary complications compared with conventional strategies, while providing safe OLV in patients undergoing lung resection surgery.

Materials and Methods

Study Population

Approval for the study was obtained from our institutional review board. Written informed consent for enrollment in the trial was obtained from each patient.

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From January to May 2009, all patients with American Society of Anesthesiology physical status 1 to 2 and scheduled for an elective lobectomy in our hospital were subjected to the study. An exclusion criterion consisted of the patient's refusal to take part in the study. As a result, a total of 122 patients were initially enrolled in the study. Patients were randomized into the conventional ventilation group (the CV group) or the protective ventilation group (the PV group) via a computer-generated random number table using a sealed envelope assignment.

Anesthesia and Surgery

Before anesthesia, a thoracic epidural catheter was inserted at the level of the thoracic segment from T4-5 to T6-7. Continuous infusion was started 15 min after OLV at a rate of 4 mL/h through the thoracic epidural catheter and was maintained for 2 to 3 days by patient-controlled epidural analgesia (hydromorphone 8 mg + 0.2% ropivacaine 375 mL + normal saline 121 mL; bolus 1.5 mL, lockout time 15 min, basal infusion 4 mL/h). Patients who refused or failed to control epidural analgesia received IV patient-controlled analgesia (fentanyl 1,500 μg + ketorolac 180 mg + normal saline 64 mL; bolus 1 mL, lockout time 15 min, basal infusion 1 mL/h).

Intraoperative monitoring included a three-lead ECG, BP cuff, and measurements of oral temperature, oxygen saturation by pulse oximetry (Spo_2), expired CO_2, arterial pressure, and urine output. The trachea was intubated after administering propofol (2 mg/kg), rocuronium (0.6 mg/kg), and fentanyl (2 μg/kg). Anesthesia was maintained with inhaled sevoflurane in a 1:1 mixture of oxygen and air. After anesthesia induction, all patients received an arterial catheterization for continuous arterial BP measurement and arterial blood gas sampling. Blood gas tension analysis was performed immediately with standard blood gas electrodes (Rapidlab 1265; Bayer Healthcare; Leverkusen, Germany).

Four surgeons experienced in major lung resections, each of whom performs more than 100 major lung resection surgeries per year, conducted each operation and were unaware of the strategy used. Lobectomies were performed through a standard posterolateral or anterolateral muscle-sparing thoracotomy or video-assisted thoracic surgery.

Standardized fluid replacement consisted of 10 mL/kg lactated Ringer solution preoperatively, followed by 6 mL/kg/h perioperatively. If mean arterial pressure was <70 mm Hg for >5 min, an additional fluid challenge was achieved with 10 mL/kg hydroxyethyl starch.

After surgery, all patients were extubated, admitted to the ICU, and monitored for at least 24 h. After extubation, patients were observed with supplemental oxygen for 30 min followed by return to room air. Supplemental oxygen was continued if patients showed an Spo_2 value $<95\%$. Postoperative fluid management for 24 h was 1 mL/kg/h. Bedside mobilization was tried at postoperative 6 h and continued if patients did not show decrease of Spo_2 to $<90\%$ and increase of heart rate >20-30/min. Nothing by mouth was discontinued usually 6 to12 h after operation. Patients were cared for by attending physicians in the ICU not involved in the protocol and blinded to the allocated group.

Study Protocol of Each Ventilator Strategy

After tracheal intubation with a left- or right-sided standard double-lumen tube (Broncho-Cath 35F or 37F; Mallinckrodt Medical, Ltd; Athlone, Ireland) under fiberoptic bronchoscopy, mechanical ventilation was initiated with an anesthesia ventilator (Aestiva/5; Datex-Ohmeda, GE Healthcare; Helsinki, Finland) connected to a circle system. Gas flow and airway pressure were measured at the proximal end of the endotracheal tube with a standard monitor for ventilatory measurement (Datex-Ohmeda, GE Healthcare).