Review Article

Role of nebulisation in perioperative period for lung cancer surgeries - a narrative review

Abstract

One lung ventilation (OLV) is required for surgical intervention in patients with lung cancer. One lung ventilation is needed for better exposure and maintenance of ventilation and oxygenation. One lung ventilation for lung surgeries are associated with changes in respiratory mechanics. Also, OLV may lead to lung injury to both the ventilated lung and the collapsed lung and is associated with hypoxia during the procedure. Various strategies like pulmonary rehabilitation, lung recruitment are required in perioperative period to optimize lung function. In spite of these strategies, hypoxic events occur during the OLV. We review the helpfulness of inhaled bronchodilators for improved oxygention in the perioperative period after lung surgery requiring OLV.

Keywords: One lung ventilation; Nebulization; Bronchodilators; Oxygenation; Lung rehabilitation; Lung recruitment

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Introduction

Surgical removal of lung cancer is one of the modality for lung cancer management in addition to radiation therapy and chemotherapy. The surgical removal could be done via open or thoracoscopic guided technique. Both these techniques require one lung ventilation (OLV) for better exposure, maintenance of ventilation and oxygenation. OLV is associated with lung injury to both the ventilated lung and the collapsed lung causing hypoxic events.[1] Hence, comprehensive pulmonary rehabilitation is required in perioperative period to optimize and recruit lung to maintain oxygenation in perioperative period, especially when OLV is required intraoperatively.

Changes during OLV for lung surgery

OLV is associated with changes in the lung and gas exchange. OLV induces inflammation due to multiple reasons including hypoxia, hypoxic pulmonary vasoconstriction, alveoli closure/distension, overdistension and compression of alveolar vessels in the ventilated lung and oxidative stress related injury.[2] Furthermore, surgical manipulation itself can trigger inflammation. It is characterised by increased number of inflammatory infiltrates, such as alveolar macrophages, granulocytes and elevated concentrations of proinflammatory cytokines including tumour necrosis factor-a (TNF-a), interleukin-6 (IL-6) and interleukin-8 (IL-8), and the anti-inflammatory cytokine interleukin-10 (IL-10). One of the serious respiratory response to OLV is lung injury and it has been reported that acute lung injury/acute respiratory distress syndrome occurs in approximately 3.7% of patients after lobectomy.[3] During OLV, nuclear factor kappa-B (NF-kB) pathway can be activated by ischemia – reperfusion injury in alveolar epithelial cells and vascular endothelial cells of both ventilated and collapsed lungs, thus inducing inflammatory molecule expression.[4] This leads to epithelial and endothelial cell damage resulting in increased vascular permeability and albumin leakage.

The epithelial adrenergic signalling pathways which regulate transport through Na+ channel needed for clearance of excess intraalveolar fluid, are altered in acute lung injury. The incidence of acute lung edema following thoracic surgery varies between 2% and 5%, and is responsible for the majority of operative deaths.[5] Ischemia reperfusion injury can damage alveolar capillary membrane causing fluid extravasation which can be further increased by heart failure and fluid overload. Other risk factors for postoperative lung edema are advanced age, pre-existing cardiopulmonary disease, prior chemoradiotherapy, extensive lung resection and one lung ventilation with high tidal volumes.[6] There may be reduced lymphatic clearance due to disruption of lymphatic channels during surgical dissection, prior chemoradiotherapy and sampling of lymph nodes.

Role of nebulisation for OLV for lung surgery

Nebulisation is based on the concept of local drug delivery which is proposed as a method of delivering high drug concentration to the target site. The peculiar characteristic of respiratory system including its large surface area, thin alveolar epithelium, vascularity, rapid absorption, lack of first-pass metabolism makes the drug absorption efficient when administered through nebulaization.[7] Secondly lungs represent most richly perfused organs in the body receiving the entire cardiac output. Thus, nebulized drugs are better absorbed from alveoli and efficeintly distributed even to distal tissues of the lungs.[8]

Bronchospasm is one of the common intraoperative complication of OLV and may be related to hypoxemia and surgical injury. It may persist till reexpansion of collapsed lung. OLV related decrease in lung compliance together with bronchospasm results in decreased ventilatory capacity, increased airway resistance and increased lung injury.

Drugs and their mechanism of action in nebulisation

The most commonly used drugs are glucocorticoids such as budesonide and B2 agonists salbutamol. Earlier studies have shown that glucocorticoid are helpful in attenuating ventilation induced inflammatory response and also for ischaemia-reperfusion injury.[9] Compared to systemic glucocorticoids, such as dexamethasone and hydrocortisone, budesonide nebulization offers the unique benefits due to its local effects. During nebulization, the nebulizer unit

breaks the liquid into micro-particles, which are directly inhaled into the lower respiratory tract and rapidly absorbed by the pulmonary mucosa, thus increasing the local drug concentration. It also hydrates the airways, which dilutes airway secretions and facilitates their discharge. It increases lung compliance and efficacy of ventilation by decreasing the airway resistance. It is possible that the glucocorticoid inhibits NF-kB activation and protein 1 expression, thus decreasing proinflammatory cytokine expression in epithelial and endothelial cells as well as recruitment of inflammatory infiltrates.[10] Budesonide can also inhibit T cell-mediated epithelial inflammation in vitro.[11]

The B adrenergic agonists can accelerate the resolution of alveolar edema and decrease lung vascular injury by enhancing salt and water transfer across the alveolar and distal airways.[12] After B adrenergic stimulation intracellular concentration of Calcium increases, thus increasing cyclic adenosine monophosphate generation which upregulates cation channels. The release of proinflammatory cytokines, chemotaxis and neutrophil degranulation is also reduced.[13] B agonists may partially restore alveolar-capillary permeability by inhibiting endothelial cell contraction and reducing intercellular gaps.[14]

Salbutamol directly activates myocardial and vascular B adrenergic receptors, following systemic reabsorption leading to positive inotropic effect and increase in cardiac output thus increasing lung fluid clearance and reverse blood oxygenation abnormalities by lowering the capillary hydrostatic pressure within the lung and simultaneously increasing the mixed venous oxygen saturation.[15]

Literature review

Ju et al.[16] conducted a study on 100 patients scheduled for lobectomy. The patients were randomized to pre-operative nebulised budesonide or saline group.[16] The authors collected bronchoalveolar lavage fluid samples from the collapsed or the ventilated lung at two points (before one-lung ventilation and 30min after re-expansion). They estimated the levels of serum and bronchoalveolar lavage fluid cytokines in these samples. When compared, budesonide group has reduced both peak (mean (SD) 3.7 (0.4) vs 2.5 (0.2)kPa) and plateau pressures (mean (SD) 3.1(0.2) vs 2.2 (0.1)kPa as compared to saline group ($p<0.001$). Also, lung compliance was better in the budesonide group as compared to saline group ($p<0.001$). Budesonide nebulisation lead to redcution in tumour necrosis factor-a, Interleukin-1b, Interleukin-6 and Interleukin-8 levels in bronchoalveolar lavage fluid. The interleukin-10 was increased at 30 min after re-expansion. He concluded that inhaled budesonide pre-operatively has a beneficial effect on respiratory and ventilatory mechanics after OLV for thoracic surgery. It was associated with a decrease in proinflammatory cytokines and an increase in the anti-inflammatory cytokine IL-10.

Li et al.[17] studied lung protective effects of budesonide nebulisation during perioperative period of thoracolumbar fusion.[17] Forty patients who underwent spinal fusion for the treatment of thoracolumbar degenerative disorders were randomly allocated into a budesonide intervention group and a control group. The control group received routine supportive therapy while budesonide group, in addition, also received budesonide nebulization (1-mg budesonide/2-mL saline, twice daily) from 1 day preoperatively till third postoperative day. They observed that the incidences of pulmonary symptoms and complications were higher in the control group than in the budesonide group. The budesonide group showed remarkably less reduction from baseline in PaO2 and SpO2 as compared with the control group ($P<0.05$). These findings indicate that budesonide nebulization perioperatively has a pulmonary protective effect.

Licker et al.[18] studied the effect of aerosolized salbutamol for pulmonary edema resolution after lung resection surgeries.[18] They observed that nebulization with salbutamol (5mg) led to reduction in lung water volume, improved hemodynamics, and oxygenation. Also, lung edema in the early postoperative period was lesser. Manocha et al.[19] reviewed retrospective chart of 86 mechanically ventilated patients with acute lung injury who had received inhaled salbutamol.[19] The cohort was divided into two groups high dose salbutamol (>2.2mg/day) and low dose group (<2.2mg/day). The groups were compared for days alive and free of acute lung injury and other organ dysfunction. They concluded high dose inhaled salbutamol group had significantly more days alive and free of acute lung injury than low dose inhaled salbutamol group.

Conclusion

One lung ventilation for lung surgeries are associated with changes in respiratory mechanics. Thus respiratory rehabilitation and optimization prior to surgery is essential. The addition of inhaled bronchodilators may be useful for improved oxygention in the perioperative period after lung surgery.

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Conflicts of interest

The authors declare there is no conflict of interests.

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References

1. Zingg U, ForbergerJ, Frey DM, et al. Inflammatory response in ventilated left and collapsed right lungs, serum and pleural fluid, in transthoracic esophagectomy for cancer. *Eur Cytokine Netw*. 2010;21(1):50–57.
2. Misthos P, Katsaragakis S, Milingos N, et al. Postresectional pulmonary oxidative stress in lung cancer patients:the role of one–lung ventilation. *Eur J Cardiothorac Surg*. 2005;27(3):379–382.
3. Kutlu CA, Williams EA, Evans TW, et al. Acute lung injury and acute respiratory distress syndrome after pulmonary resection. *Ann Thorac Surg*. 2000;69(2):376–380.
4. You Z, Feng D, Xu H, et al. Nuclear factor kappa–B mediates one lung ventilation–induced acute lung injury in rabbits. *J Invest Surg*. 2012;25(2):78–85.
5. Licker M, Widikker I, Robert J, et al. Operative mortality and respiratory complications after lung resection for cancer:impact of chronic obstructive pulmonary disease and time trends. *Ann Thorac Surg*. 2006;81(5):1830–1837.
6. Licker M, De Perrot M, Spiliopoulos A, et al. Risk factors for acute lung injury after thoracic surgery for lung cancer. *Anesth Analg*. 2003;97(6):1558–1565.
7. Labiris NR, Dolovich MB. Pulmonary drug delivery. Part I:physiological factors affecting therapeutic effectiveness of aerosolized medications. *Br J Clin Pharmacol*. 2003;56(6):588–599.
8. Deffebach ME, Charan NB, Lakshminarayan S, Butler J (1987) The bronchial circulation. Small, but a vital attribute of the lung. Am Rev Respir Dis 135(2):463–481.
9. Kumar S, Allen DA, Kieswich JE, et al. Dexamethasone ameliorate renal ischemia–reperfusion injury. *J Am Soc Nephrol*. 2009;20(11):2412–2425.

10. Mittelstadt PR, Ashwell JD. Inhibition of AP–1 by the glucocorticoid inducible protein GILZ. *J Biol Chem*. 2001;276:29603–29610.

11. McKay DM, Brattsand R, Wieslander E, et al. Budesonide inhibits T cell–initiated epithelial pathophysiology in an in vitro model of inflammation. *J Pharmacol Exp Ther*. 1996;277(1):403–410.

12. Groshaus HE, Manocha S, Walley KR, et al. Mechanisms of receptor stimulation–induced improvement of acute lung injury and pulmonary edema. *Crit Care*. 2004;8(4):234–242.

13. Zhang H, Kim YK, Govindarajan A, et al. Effect of adrenoreceptors on endotoxin–induced cytokines and lipid peroxidation in lung explants. *Am J Respir Crit Care Med*. 1999;160(5 Pt 1):1703–1710.

14. Allen MJ, Coleman RA. B2–Adrenoceptors mediate a reduction in endothelial permeability in vitro. *Eur J Pharmacol*. 1995;274(1–3):7–15.

15. Bremner P, Woodman K, Burgess C, et al. A comparison of the cardiovascular and metabolic effects of formoterol, salbutamol and fenoterol. *Eur Respir*. 1993;6(2):204–210.

16. Ju NY, Gao H, Huang W, et al. Therapeutic effect of inhaled budesonide (Pulmicort® Turbuhaler) on the inflammatory response to one–lung ventilation. *Anaesthesia*. 2014;69(1):14–23.

17. Li W, Zhao Y, Sun Z, et al. Lung protective effects of budesonide nebulization during perioperative period of thoracolumbar fusion. *J Thorac Dis*. 2014;6(12):1800–1807.

18. Licker M, Tschopp JM, Robert J, et al. Aerosolized salbutamol accelerates the resolution of pulmonary edema after lung resection. *Chest*. 2008;133(4):845–852.

19. Manocha S, Gordon AC, Salehifar E, et al. Inhaled β2agonist salbutamol and acute lung injury:an association with improvement in acute lung injury. *Crit Care*. 2006;10(1):R12.

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