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EDITORIAL

Strategies to reduce pulmonary complications after esophagectomy

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Abstract

Esophagectomy, the surgical removal of all or part of the esophagus, is a surgical procedure that is associated with high morbidity and mortality. Pulmonary complications are an especially important postoperative problem. Therefore, many perioperative strategies to prevent pulmonary complications after esophagectomy have been investigated and introduced in daily clinical practice. Here, we review these strategies, including improvement of patient performance and technical advances such as minimally invasive surgery that have been implemented in recent years. Furthermore, interventions such as methylprednisolone, neutrophil elastase inhibitor and epidural analgesia, which have been shown to reduce pulmonary complications, are discussed. Benefits of the commonly applied routine nasogastric decompression, delay of oral intake and prophylactic mechanical ventilation are unclear, and many of these strategies are also evaluated here. Finally, we will discuss recent insights and new developments aimed to improve pulmonary outcomes after esophagectomy.

Key words: Esophagectomy; Complications; Pneumonia; Acute lung injury; Acute respiratory distress syndrome

Core tip: Pulmonary complications following esophagectomy significantly contribute to postoperative morbidity and mortality. Over the years many strategies aimed at reducing pulmonary complications have been investigated. In the current article, we discuss these strategies, specifically minimally invasive surgical techniques; anti-inflammatory therapies and optimization of patient performance.

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INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer related mortality, and its incidence is increasing rapidly[1]. For patients with loco-regional disease the best chance for long-term survival is offered by a transthoracic esophagectomy after neoadjuvant therapy[2-4]. However, esophagectomy is considered to be one of the most invasive and complex gastrointestinal procedures with a high post-operative morbidity and mortality[5]. Concentration of surgical treatment in high volume centers and improvements in perioperative care have led to significant reductions in postoperative mortality and improved long-

term survival[5,6].

Respiratory complications are most common after esophagectomy, with up to a 60% incidence rate; respiratory failure due to pulmonary complications remains the major cause of postoperative morbidity and mortality after esophagectomy[7,8]. A wide range of perioperative strategies have been introduced in order to reduce these pulmonary complications. In this editorial we will discuss several of these strategies.

DEFINITIONS

The most severe pulmonary complications following esophagectomy are pneumonia, adult respiratory distress syndrome (ARDS) and acute lung injury (ALI). Pneumonia is the most common complication and is significantly associated with need for re-intubation, prolonged hospital stays and in hospital mortality[9]. Although ARDS and ALI have been clearly defined during American-European consensus conferences, criteria for pneumonia differ widely[10-12]. In a recent systematic review, pneumonia rates were reported by 56 studies and defined by 18 studies. However, 16 different definitions were used, resulting in a wide range of reported pneumonia rates (between 1.5% and 38.9%). Consequently, this variation makes it difficult to compare study results[10]. Therefore, generating a consensus on the definition of pneumonia after esophagectomy is an important step in improving the quality and comparability of research. Despite the heterogeneity in definitions, several interesting strategies to reduce pulmonary complications after esophagectomy have been described.

OPTIMISATION OF PERFORMANCE STATUS

Nutrition

Improvement of performance status of patients undergoing esophagectomy is important in reducing pulmonary complications. Adequate enteral nutrition is an important tool to achieve this in the pre-operative and postoperative phase. When nutrition is inadequate, leading to malnutrition, this is associated with expiratory muscle weakness and pulmonary complications after major upper abdominal surgery[13]. Preoperative malnutrition also increases the risk for overall complications after esophagectomy (OR = 3.50, 95%CI: 1.89-6.49)[14]. Furthermore, when all patients undergoing esophagectomy receive preoperative intensive nutritional support by a dietician, fewer postoperative complications are observed (OR = 0.23, 95%CI: 0.05-0.97)[15]. This is supported by another prospective cohort study that investigated preoperative nutritional support for malnourished patients[16]. Despite the fact that preoperative nutritional support seems a logical and promising strategy to prevent postoperative pulmonary complications, clear evidence is lacking.

An important role for nutrition also exists in the postoperative phase. Early enteral nutrition after gastrointestinal surgery improves patient recovery and reduces morbidity and mortality[17]. However, commonly a nil-by-mouth regimen is still applied after esophagectomy. The rationale for this regimen is the concern that early oral intake would result in vomiting with subsequent aspiration pneumonia. Furthermore sequelae of anastomotic leakage are thought to be more severe if leaked fluids contain food besides to saliva. However, benefits of a nil-by-mouth regimen are theoretical and evidence is lacking[18].

Jejunal tube feeding can be started early to ensure enteral nutrition following esophagectomy. Compared to total parenteral nutrition or fasting this reduces postoperative pneumonia rates by 50% or more[19,20]. Drawbacks are frequent dislocation of nasojejunal tubes, and serious complications such as leakage[21].

The risks of artificial feeding, combined with the lack of evidence concerning effects of a nil-by-mouth regimen, are reasons to investigate the feasibility and safety of starting oral intake early after esophagectomy. Interestingly, for major upper abdominal surgery early oral intake has already been demonstrated to be feasible and safe[22]. However, further research is needed to provide more evidence in patients undergoing esophagectomy.

Inspiratory muscle training

Another method to optimize performance status is through physical exercise. If postoperatively compromised, respiratory muscle strength will result in reduced lung function and insufficient coughing. This might induce atelectasis, which, acting in combination with postoperative pain and sedation, might result in hypoxia[23]. For this reason, several studies have been performed to prevent postoperative decrease in muscle function by preoperative physiotherapy. For example, a large-scale randomized controlled trial (RCT) demonstrated that inspiratory muscle training (IMT), for two or more weeks before coronary artery bypass graft surgery reduced the incidence of all pulmonary complications from 35% to 18%, and for pneumonia from 16% to 7%[23]. Preoperative IMT is also feasible for patients undergoing esophagectomy, and even preserves postoperative respiratory muscle strength[24,25].

Minimizing irradiated lung volume

Patients with esophageal cancer are mostly treated neoadjuvant with radiotherapy and chemotherapy[4]. However, these multimodality treatments are often correlated with an increase in postoperative pulmonary complications and mortality[26]. An adjustable factor in these treatments is the amount of radiation on the lung. For example, when $\geqslant$ 40% of the lung volume received $\geqslant$ 10 Gy, the incidence of pneumonia and ARDS significantly increased from 8% to 35%[26]. Multivariate analysis of various dosimetric factors has shown that the total amount of lung spared from doses > 5 Gy is significantly correlated with reduced pulmonary complications[27]. Though this correlation is not found in all studies, it seems reasonable to reduce the amount of irradiated healthy lung

Table 1 Advantages of prone positioning

Alveolar recruitment
Improved redistribution of ventilation
Redirection of compressive force of the heart
Better clearance of secretion
Lung retraction not necessary
Shorter operation time
Fewer ports needed

tissue from an oncological viewpoint.

PEROPERATIVE STRATEGIES

Minimally invasive surgery

Minimally invasive surgery has rapidly evolved in recent years. Since minimally invasive approaches reduce factors associated with pulmonary complications (*e.g.*, blood loss, pain, and inflammation), minimally invasive esophagectomy would be especially beneficial with respect to pulmonary complications[28]. Recently, a prospective RCT demonstrated the benefits of a minimally invasive approach regarding pulmonary complications for the first time[29]. Fifty-nine patients undergoing thoracolaparoscopic esophagectomy in prone positioning were compared to 56 patients undergoing open transthoracic esophagectomy in a left semi-lateral position. The pneumonia (clinical diagnosis confirmed by radiologic investigation and a positive sputum culture) rate within the first two postoperative weeks was 9% *vs* 29% in the open group (RR = 0.30, 95%CI: 0.12-0.60). Since a sputum culture is often negative in case of pneumonia, this study may underestimate the true pneumonia rate. However, the observed reduction in postoperative pneumonia by the minimal invasive approach is significant[29].

It is questionable whether the minimally invasive approach, the prone positioning, or a combination of both caused the outcomes in this trial. Traditionally, patients undergo an open transthoracic esophagectomy in a left lateral decubitus position with double lumen tube intubation for one-lung ventilation. However, with the development of minimally invasive, thoracoscopic techniques, patient positioning was no longer restricted to a lateral decubitus position giving rise to minimally invasive, thoracoscopic, prone position techniques[30]. There are several advantages to a prone positioning, including partial or intermittent single lumen ventilation, as opposed to total lung collapse by a double lumen intubation in lateral decubitus position (Table 1). Further, perioperative distribution of pulmonary ventilation and circulation might be improved, leading to better oxygenation[30]. These advantages translate in improved postoperative outcomes, as shown by two studies that demonstrated an advantage of prone positioning compared to left lateral decubitus positioning[31,32].

Despite these advantages, prone positioning has not been adopted widely. Surgeons question whether or not safety is compromised due to the difficulty of an emergency conversion in prone position to left lateral with subsequent difficult airway management. However, a recent systematic review concluded prone positioning to be safe[30]. Furthermore in the previously mentioned trial during thoracoscopic dissection all patients were in prone position[29].

Corticosteroids and neutrophil elastase inhibitors

Pulmonary complications can be reduced by dampening the inflammatory response through medication. Sato *et al*[33] found a pre-operative single dose of methylprednisolone (10 mg/kg) significantly reduced postoperative inflammation and subsequent pulmonary complications (from 30% to 9%). Other studies found similar benefits of methylprednisolone, without observing adverse effects[34].

However, even with pre-operative methylprednisolone administration, pulmonary complications occur frequently[35]. This might be caused by the systemic inflammatory response on esophagectomy, leading to accumulation of neutrophils in the lungs. Subsequently local release of neutrophil elastase injures the lung[36]. Since glucocorticoids do not affect the release or function of neutrophil elastase, additional selective inhibition of neutrophil elastase might be beneficial[37]. Indeed, adding a selective neutrophil elastase inhibitor to methylprednisolone improves oxygenation during the first seven postoperative days[38]. Furthermore, perioperative selective neutrophil elastase inhibition prevented ALI after minimally invasive esophagectomy[36].

The results of perioperatively administered methylprednisolone and neutrophil elastase inhibitors are encouraging. However, all trials were conducted in Eastern populations. Because genomic factors might influence results, trials should be conducted in other populations in order to determine whether these results can be extrapolated to all populations.

Protective ventilation

Protective ventilation can reduce the amount of mechanically induced pulmonary injury during esophagectomy. During protective ventilation, tidal volumes are reduced and a moderate positive end-expiratory pressure is applied[39]. This strategy reduces inflammation and improves oxygenation compared to conventional ventilation. Though pneumonia rates have shown to be lower after protective ventilation, this was not significantly different[39].

Goal-directed fluid therapy

Goal directed fluid administration reduces postoperative pulmonary complications in other types of surgery such as major (upper) abdominal and major vascular surgery (RR = 0.7, 95%CI: 0.6-0.9)[40]. With this strategy, fluids are administered to achieve predefined, patient-specific hemodynamic goals, avoiding excessive resuscitation or under-resuscitation as seen with liberal or restrictive fluid administration[40]. Increased volume of perioperative fluid administration increases the risk for pulmonary complica-

tions following esophagectomy[41]. Therefore, it would be interesting to determine if this can be prevented by goal-directed fluid administration. However, because instruments that adequately measure hemodynamic parameters to guide fluid administration are invasive or difficult to use, they are not commonly applied. As a consequence several simple, minimally invasive instruments have been developed. Further research should first compare these devices in order to determine which impacts outcomes most[42].

POSTOPERATIVE STRATIEGIES

Strategies to reduce pulmonary complications that are applied postoperatively are analgesia, prolonged postoperative ventilation, and nasogastric decompression. Adequate postoperative analgesia is important after esophagectomy, because postoperative pain from thoracic and upper abdominal wounds compromises pulmonary function, coughing, and mobilization, resulting in atelectasis and pneumonia. In patients undergoing esophagectomy, thoracic epidural analgesia is more effective then intravenous opioid analgesia[43]. Furthermore, thoracic epidural analgesia facilitates early extubation and reduces the risk for respiratory failure, overall pulmonary complications and mortality[9,44].

Postoperative pain, aspiration and airway edema were the main rationale for routinely performing prolonged postoperative ventilation for many years. Mechanical ventilation could cause barotrauma, ventilator acquired pneumonia and endotracheal tube related problems. Early extubation, based on individual clinical factors, does not increase pulmonary complications[45]. After early extubation, routine bronchoscopic clearance of secretions was associated with reduced mortality, possibly due to preventing of postoperative pulmonary complications[44]. However, further studies are needed to substantiate this retrospectively found effect.

Another commonly applied strategy to reduce pulmonary complications due to postoperative aspiration is routine nasogastric decompression. However, a recent meta-analysis showed that after major upper abdominal surgery this strategy increased pulmonary complications (OR = 1.49, 95%CI: 1.01-2.21)[46]. Routine insertion of a nasogastric tube six to ten days following a esophagectomy is not beneficial compared to early removal of the nasogastric tube (second day postoperative)[47]. Furthermore, the commonly used single lumen nasogastric tube does not reduce aspiration compared to the situation in which no tube is routinely inserted[48,49]. In addition, routine nasogastric decompression failed to reduce pneumonia rates[48,49]. However, trials that have investigated routine nasogastric tube insertion did not specifically investigate pulmonary complications, highlighting a need for a trial to detect a clinically significant reduction in pulmonary complications is needed.

CONCLUSION

Pulmonary complications are an important problem after esophagectomy. However, many advances have been made in recent years. Proven effective strategies are minimally invasive surgery, thoracic epidural analgesia and early enteral nutrition. Perioperative methylprednisolone and neutrophil elastase inhibitor administration can be added to these strategies if their benefits are confirmed in additional studies.

Preoperative optimization of performance status, prone positioning and targeted fluid therapy are promising for further research. While new interventions are extensively investigated before application, it seems unjust to apply invasive interventions without proven benefits. Therefore several commonly applied strategies (*e.g.*, routine nasogastric decompression, delay of oral intake, prophylactic mechanical ventilation) are currently being re-evaluated.

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