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Clinical Investigation

CLINICAL INVESTIGATION

The impact of the acute respiratory distress syndrome on outcome after oesophagectomy†

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Abstract

Background: The Acute Respiratory Distress Syndrome (ARDS) is a serious complication of major surgery and consumes substantial healthcare resources. Oesophagectomy is associated with high rates of ARDS. The aim of this study was to characterize patients and identify risk factors for developing ARDS after oesophagectomy.

Methods: A secondary analysis of data from 331 patients gathered during the Beta Agonists Lung Injury Prevention Trial was undertaken. Characteristics and outcomes of patients with early (first 72 h postoperatively) and late (after 72 h) ARDS were determined. Linear and multivariate regression analysis was used to study the differences between early and late ARDS and identify risk factors.

Results: ARDS was associated with more non-respiratory organ failure (early 44.1%, late 75.0%, no ARDS 27.6% $P<0.001$), longer ICU stay (mean early 12.1, late 20.2, no ARDS 7.3 days $P<0.001$) and longer hospital stay (mean early 18.1, late 24.5, no ARDS 14.2 days $P<0.001$) but no difference in mortality or quality of life. Older patients (OR 1.06 (1.00 to 1.13), $P=0.045$) and those with mid-oesophageal tumours (OR 7.48 (1.62–34.5), $P=0.010$) had a higher risk for ARDS.

Conclusions: Early and late ARDS after oesophagectomy increases intensive care and hospital length of stay. Given the high incidence of ARDS, cohorts of patients undergoing oesophagectomy may be useful as models for studies investigating ARDS prevention and treatment. Further investigations aimed at reducing perioperative ARDS are warranted.

Key words: oesophageal neoplasms; oesophagectomy; one-lung ventilation; respiratory distress syndrome, adult

† Trial registration numbers. The Beta Agonist Lung Injury Prevention Trial: International Standardised Randomised Control Trial Register ISRCTN47481946 and European Database of Randomised Controlled Trials EudraCT 2007-004096-19.

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Editor's key points

- Acute Respiratory distress syndrome (ARDS) has a high morbidity and mortality.
- In this secondary analysis, outcomes and risk factors in patients developing ARDS early (within three days) or late (four–28 days) after oesophagectomy were compared.
- ARDS was associated with higher morbidity, longer ICU and hospital stays but no increase in mortality.
- There was no difference in mortality or quality of life between early and late ARDS but the data may be underpowered to detect this.

The Acute Respiratory Distress Syndrome (ARDS) frequently complicates the recovery from major surgery.[1] It is associated with high mortality[2–4] and although this has improved with time,[5] it remains an important cause of death and morbidity. Management of patients with ARDS consumes substantial healthcare resources.[6] The definitions of ARDS were updated in 2013, with the removal of the term acute lung injury (ALI).[7] The term ARDS is used here to describe patients with ALI and ARDS.

The outcome of ARDS varies according to the underlying disease process responsible. In a recent study, where overall hospital mortality in ARDS was 41.1%, mortality was 43.6% in patients with ARDS caused by aspiration, 40.6% by pneumonia and 21.4% by severe trauma.[2] Major thoracoabdominal surgery, especially when combined with sepsis, is a common cause of ARDS with high associated mortality.[1]

Oesophagectomy carries a high risk for both mortality and morbidity, particularly pulmonary complications.[8] Tandon and colleagues[9] in 2001 reported rates of ARDS of 38.3%, with a mortality rate in patients developing severe ARDS of 50%. Another study comparing open oesophagectomy to hybrid procedures (laparoscopic abdominal and open thoracic resection), reported major pulmonary complications in 43% of the open group and 15% in the hybrid group, in whom the incidence of ARDS was also lower. Out of 280 patients, 21 cases of ARDS were reported and ARDS was diagnosed in six of the 12 patients who died.[10] Others have reported a respiratory complication rate of 27.4% and increased length of hospital stay, in patients who developed pulmonary complications after oesophagectomy.[11]

Despite a number of studies, no drugs that directly target the underlying pathophysiological mechanisms implicated in the development of ARDS have been identified.[12] In critical care, trials investigating the role of i.v. salbutamol,[13] simvastatin,[14] nitric oxide[15] and exogenous surfactant[16] in treating ARDS have all demonstrated no mortality benefit. The role of steroid administration remains unclear.[17] Reductions in mortality have been demonstrated by trials of lung protective ventilation[18] and neuromuscular blocking drugs.[19] Prone positioning is an effective measure in cohorts with severe ARDS.[20]

Given the limited treatments available, preventative strategies are attractive and could have substantial benefits if implemented in high risk groups, including patients undergoing oesophagectomy.[3] Valid clinical models are imperative for investigating preventative strategies.[21] Patients undergoing one-lung ventilation (OLV), such as occurs in patients undergoing oesophagectomy, provide a potentially useful model for investigating ARDS.

The aim of this study was to undertake a secondary analysis of the multi-centre Beta Agonist Lung Injury Prevention trial to characterize patients developing ARDS after elective oesophagectomy and identify risk factors for the syndrome.

Methods

Between April 2008 and June 2011, 362 adult patients undergoing elective oesophagectomy were enrolled into the BALTI-Prevention trial at 12 academic hospitals in the UK. The results have been published previously.[22] The North American-European Consensus Criteria were used to define ALI/ARDS: (ALI Pa_{O_2}:FI_{O_2}<40.0 kPa; ARDS Pa_{O_2}:FI_{O_2}<26.7 kPa) at the time and for the design of the study.[23]

Baseline characteristics, operative information and postoperative variables were recorded for all participants. Anaesthetists were instructed to follow a low tidal volume and fluid conservative strategy, but otherwise management was left to the individual clinician's discretion. Patients were defined as having ARDS in the presence of hypoxaemia (Pa_{O_2}:FI_{O_2} ratio less than 40.0 kPa), bilateral infiltrates on the chest x-ray and absence of clinical evidence of left atrial hypertension and categorized as having early (day 0–3), late (day 4–28) or no ARDS according to the timing of the first episode of ARDS. The categorization of ARDS was made *a priori* into 'Early' and 'Late', to separate 'primary ARDS' associated with the initial insult of surgery and anaesthesia from that acquired by later complications (secondary ARDS), such as anastomotic leak.

Study outcomes were ventilator free days, organ failure free days, 28 and 90 day mortality and health-related quality of life measured by Euroqol Health Outcome Questionnaire (EQ5D) at 28 and 90 days. Ventilator-free days were as previously defined.[22] Organ failure–free days were defined in a similar manner, with an organ failure–free day being a day without evidence of non-respiratory organ failure. Organ failure was defined by a Sequential Organ Failure Assessment score of four or more.[24] Postoperative pneumonia was recorded if diagnosed by the attending clinicians. As patients had undergone recent upper gastrointestinal surgery, non-invasive ventilation was not used as a standard measure, but was not strictly prohibited. Levels of care were determined according to United Kingdom Department of Health definitions.[25]

Linear regression of secondary outcomes comparing ARDS status was undertaken with and without adjustment for randomization. Linear regression models were then fitted for the secondary outcomes for ARDS status with an interaction term, to examine whether treatment difference depended on observed ARDS status.

Multivariate logistic regression was performed to establish a risk model for ARDS, examining all recorded potential risk factors. A forward stepwise regression model was produced using the specified baseline variables used in the univariate analysis, with P values of 0.05 and P value of 0.1 for subsequent removal from the model.

Multivariate analysis was then fitted for each stage of ARDS, to examine whether the response to different treatments was dependent on baseline characteristics. An unadjusted model was fitted, including terms for treatment allocation, baseline moderation and terms for treatment by moderator interaction. An adjusted model was also produced, containing terms for treatment, moderator and interaction with terms for age and hospital.

Safety outcomes were analysed according to ARDS status. These included respiratory, cardiovascular, surgical and other complications and sepsis. Adverse events were defined as