

Beta-Agonist Lung injury Trial-2 (BALTI-2): a multicentre, randomised, double-blind, placebo-controlled trial and economic evaluation of intravenous infusion of salbutamol versus placebo in patients with acute respiratory distress syndrome

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Scientific summary

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Scientific summary

Background

Acute respiratory distress syndrome (ARDS) is a common type of respiratory failure in intensive care patients. It is characterised by:

1. acute onset
2. bilateral infiltrates on chest radiographs
3. pulmonary artery occlusion pressure < 18 mmHg (if measured), or absence of clinical signs of left atrial hypertension
4. ratio of partial pressure of oxygen in arterial blood (PaO_2) to the fraction of inspired oxygen (FI_{O_2}) < 200 mmHg (26.7 kPa) [if the PaO_2 – FI_{O_2} ratio is between 200 and 300 mmHg (40 kPa), a less severe grade of disease, acute lung injury, is recognised].

Acute respiratory distress syndrome can be caused by primary lung conditions such as aspiration or pneumonitis, or can arise as a complication of non-pulmonary conditions such as severe sepsis.

Acute respiratory distress syndrome affects 6–8% of all patients admitted to intensive care units (ICUs), and is associated with a high risk of death. Estimates of mortality range from 34% to 61%, and survivors may experience long-term detrimental physical and psychological effects and reduced quality of life. There may be up to 7000 deaths per year in the UK attributable to ARDS.

Acute respiratory distress syndrome has a significant disease burden but there are no established pharmacological treatments. Previous studies, including a 40-patient, Phase II randomised controlled trial (RCT), have suggested that salbutamol may be beneficial for patients with ARDS. We therefore conducted a multicentre Phase III trial to attempt to give a definitive answer to this question.

Objectives

The primary objective of the trial was to assess whether or not an intravenous (i.v.) infusion of salbutamol given at 15 µg/kg ideal body weight (IBW)/hour for up to 7 days reduces 28-day all-cause mortality in patients with ARDS compared with a placebo (0.9% sodium chloride) infusion.

The secondary objectives were:

1. to evaluate the effects of i.v. salbutamol on mortality in ICU, mortality in hospital, ventilator-free days (VFDs), organ failure-free days, length of ICU and hospital stay, mortality up to 12 months after randomisation and health-related quality of life at 6 and 12 months after randomisation
2. to evaluate the safety of i.v. salbutamol for ARDS patients
3. to evaluate the cost-effectiveness of i.v. salbutamol for patients with ARDS
4. to explore whether or not the effects of salbutamol vary between patients of different age, initial disease severity, mortality risk at ICU admission and ARDS aetiology.

Methods

The study design was a multicentre, placebo-controlled RCT conducted in ICUs in the UK. An economic evaluation was conducted alongside the trial. Patients were eligible if they were ≥ 16 years of age, were

intubated and ventilated, fulfilled the American–European Consensus Conference definition of ARDS and were within 72 hours of ARDS onset. They were randomised to receive an i.v. infusion of either salbutamol (15 µg/kg IBW/hour) or placebo (0.9% saline). All study drugs were packaged identically and identified by a unique number. We used a remote telephone randomisation system, with minimisation by centre of recruitment, age and PaO_2 – FIO_2 ratio. The infusion was given for up to 168 hours; it was terminated before 168 hours if the patient recovered or died, if clinically indicated, or if requested by the patient or their relatives.

The primary outcome measure was mortality at 28 days post randomisation. Secondary outcomes were mortality at (first) discharge from ICU, mortality at (first) discharge from hospital, mortality at 12 months, VFDs, organ failure-free days, side effects sufficient to stop study drug treatment, health-related quality of life at 6 and 12 months and lengths of stay in ICU and hospital. Data were collected by staff of participating hospitals up to hospital discharge, and patients were followed up at 6 and 12 months by postal questionnaire. Mortality over 12 months after randomisation was ascertained from the NHS Information Centre, via the Medical Research Information Service.

The target sample size was 1334, which was sufficient to show a statistically significant reduction in mortality with salbutamol from 44% in the placebo group to 35.2% in the control group (risk ratio of 0.80) with 90% power. Analysis (by intention to treat) estimated risk ratios and 95% confidence intervals (CIs) for dichotomous outcomes, mean differences and 95% CIs for continuous outcomes and hazard ratios for survival. Subgroup analyses used interaction tests.

Interim analyses were conducted approximately annually, and supplied confidentially to a Data Monitoring and Ethics Committee (DMEC).

Results

Recruitment took place between November 2006 and March 2010. Recruitment was terminated after the second interim analysis, when the DMEC recommended closing the trial. A total of 46 centres recruited one or more patients to Beta-Agonist Lung injury Trial-2. A further 21 centres obtained approvals but were unable to recruit before the trial was stopped. Recruitment was significantly slower than planned because of delays in starting recruitment at participating centres and smaller numbers of patients being recruited at each centre than anticipated.

A total of 326 patients was recruited. Two withdrew and did not provide primary outcome data. There was an increase in 28-day mortality in the salbutamol group (risk ratio 1.47; 95% CI 1.03 to 2.08) and fewer VFDs and organ failure-free days [differences –2.68 (95% CI –4.67 to –0.70) and –2.30 (95% CI –4.54 to –0.06), respectively]. Twelve-month mortality was similar in the salbutamol and placebo groups (risk ratio 1.09; 95% CI 0.83 to 1.43).

A low proportion of patients were followed up by postal questionnaire at 6 and 12 months. The data suggested that quality of life was lower in the salbutamol group, but no difference or a small benefit to salbutamol was only excluded by the 95% CI for the Short Form questionnaire-12 items physical component score at 12 months.

Health economic analyses showed that costs of care were slightly higher in the salbutamol group and that salbutamol was unlikely to be cost-effective.

Conclusions

Intravenous salbutamol at this dose is not an effective treatment for ARDS and may cause harm.

Trial registration

This trial is registered as ISRCTN38366450.

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