Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis


CRD summary
This well-conducted review of individual patient data concluded that higher levels of positive end-expiratory pressure (PEEP) may be associated with lower hospital mortality in patients with acute respiratory distress syndrome, but that higher levels of PEEP were unlikely to benefit and may be harmful to patients with less severe lung injury. This conclusion is likely to be reliable.

Authors' objectives
To evaluate the association of higher versus lower positive end-expiratory pressure (PEEP) with patient-important outcomes in adults with acute lung injury or acute respiratory distress syndrome (ARDS) who received ventilation with low tidal volumes; and to investigate whether these associations differ between pre-specified subgroups.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions from 1996 to January 2010. Search terms were reported. The proceedings of six relevant professional bodies were handsearched from 2004 to 2010. References of identified studies, editorials and reviews were checked. Experts in the field were contacted.

Study selection
Randomised controlled trials (RCTs) that compared higher with lower levels of PEEP in critically ill adults aged over 16 years and with a diagnosis of acute lung injury or ARDS were eligible for inclusion. A difference of at least 3cm of water in the first three days following randomisation was required between groups. Trials were required to use a target tidal volume of less than 8mL/kg of predicted body weight in both ventilation strategies. Follow-up until death or for at least 20 days was required. The primary outcome was hospital mortality measured to at least 60 days. Secondary outcomes were death before discharge from the intensive care unit (ICU), pneumothorax with need for chest tube drainage within 28 days, death following pneumothorax with need for chest tube drainage within 28 days, time to unassisted breathing within 28 days, days with unassisted breathing between days one and 28, use of rescue therapy, death following rescue therapy and use of neuromuscular blockers, vasopressors and corticosteroids.

Included patients had a mean age of 56 years. Approximately 38.5% were women. Patients had been in ICU care for a mean of one (higher PEEP) or two (lower PEEP) days and intubated for a mean of one day prior to randomisation. Fifty percent of patients had injuries caused by pneumonia. Two trials titrated PEEP levels to oxygenation; the third study used measurements of plateau pressure.

Two reviewers independently assessed the papers for inclusion in the review.

Assessment of study quality
Individual patient data (IPD) from each trial were checked against reported results. Queries were resolved with the appropriate member of the trial team. These aspects of study level validity were assessed: allocation concealment, blinding of outcome assessment and data analysis, proportion of loss to follow-up and early stopping prior to enrolment of planned sample size. The overall quality of the evidence was assessed using the GRADE system. Two independent reviewers were involved in the process.

Data extraction
Protocols, case report forms and unedited databases were requested from investigators of all eligible trials and IPD were collated. Outcome definitions and data analyses were standardised. The ratio of partial pressure of oxygen to fraction of inspired oxygen was used to assess whether patients had ARDS, with the threshold for diagnosis set at up to 200mmHg. Two reviewers carried out the data management independently.
Methods of synthesis
Relative risks (RR) with 95% confidence intervals (CI) were calculated using log-binomial regression. A multivariable hierarchical model with prognostically significant baseline patient characteristics and trial and recruiting hospital variables was used. A number of other variables including the presence of ARDS were added singly to the model as fixed effects. Cox regression models were used for the outcomes of time to hospital death and time to unassisted breathing. Heterogeneity between trials was assessed using a likelihood ratio test. Further pre-specified sensitivity analyses and post-hoc exploratory analyses were described in the paper.

Results of the review
Data from 2,299 patients in three RCTs were included in the review. All three trials used concealed allocation, blinded data analysis and achieved complete follow-up for the primary outcome and so were considered to be high quality. There was also baseline similarity between groups on important prognostic variables.

There was no statistically significant effect of the level of PEEP on hospital mortality (RR 0.94, 95% CI 0.86 to 1.04). There were statistically significant benefits of higher pressure for the outcomes of death in the ICU (RR 0.87, 95% CI 0.78 to 0.97), institution of rescue therapies for profound hypoxemia (RR 0.64, 95% CI 0.54 to 0.75) and rate of death following rescue therapy (RR 0.65, 95% CI 0.52 to 0.80). There were no statistically significant differences for the outcomes of pneumothorax, death following pneumothorax, use of vasopressors or unassisted breathing days up to day 28.

There was a statistically significant interaction between baseline presence of ARDS and with treatment effect (p=0.02). Patients with ARDS showed a statistically significant benefit of higher PEEP on the primary outcome of hospital mortality (RR 0.90, 95% CI 0.81, 1.00, p=0.049) as well as statistically significantly better performance on achieving unassisted breathing. In contrast, patients without ARDS showed a trend towards a harm from higher PEEP on hospital mortality (RR 1.37, 95% CI 0.98 to 1.92, p=0.07); this pattern was replicated for a range of secondary outcomes.

The results of further exploration of heterogeneity were reported.

Authors' conclusions
Data suggested that higher levels of PEEP may be associated with lower rates of hospital mortality in patients who met criteria for ARDS, but that such a benefit was unlikely in patients with less severe lung injury. It was possible that higher levels of PEEP may in fact be harmful to patients with less severe lung injury.

CRD commentary
The review question and the inclusion criteria were clear and specific. The authors searched several relevant databases and other sources without language restriction, which minimised the risk of relevant studies being excluded and publication and language biases being introduced into the review. The authors used methods to reduce reviewer bias and error at all stages of the review process and used appropriate measures to verify IPD and assess study validity. The decision to use meta-analysis was reasonable and the use of pre-specified potential effect modifiers to explore heterogeneity was informative. The authors' conclusions clearly reflect the results of the review and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that clinicians should bear in mind the possible harm when considering use of higher PEEP in patients with less severe acute lung injury, although higher levels were supported in patients with ARDS. For these patients PEEP could be titrated.

Research: The authors stated that investigators in clinical trials should consider the possible contribution of trial data to prospective meta-analysis, particularly with regard to consideration of termination of a trial.

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