The efficacy and safety of prone positional ventilation in acute respiratory distress syndrome: updated study-level meta-analysis of 11 randomized controlled trials

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CRD summary
The prone position, during mechanical ventilation, for patients with acute hypoxaemic respiratory failure, significantly reduced overall mortality. Pressure ulcers and major airway problems occurred significantly more often with the prone position. The findings of the review reflected the evidence, and the conclusions are likely to be reliable.

Authors' objectives
To evaluate the effects of prone versus supine position, on mortality and complications, in patients with acute respiratory distress syndrome.

Searching
PubMed, EMBASE, BioMed Central, trial registers and relevant conference proceedings were consulted in May 2013, with no language restrictions. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) comparing prone versus supine position, for patients with acute respiratory distress syndrome, were eligible for inclusion. Trials of adults with acute hypoxaemic respiratory failure (PaO$_2$/FiO$_2$ of 300mmHg or less; including acute respiratory distress syndrome or acute lung injury), who were on mechanical ventilation support, were eligible. Trials of paediatric patients, and crossover trials that assigned patients to both groups, were excluded. The primary outcome was overall mortality at the longest follow-up. Secondary outcomes were duration of prone position, presence of lung protective ventilation, and adverse events (definitions provided in the article).

The included trials were conducted between 1996 and 2011. The mean age of participants ranged from 41 to 62 years. The duration of prone position and disease severity varied across trials. In three trials, patients had severe acute respiratory distress syndrome. Two trials provided high frequency oscillatory ventilation for all patients in both groups.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
Two reviewers independently assessed the quality of the trials, using the Cochrane risk of bias tool and the Jadad score.

Data extraction
Outcome data were extracted from the trials, independently by two reviewers.

Methods of synthesis
Trial data were combined in meta-analyses, using fixed-effect and random-effects models, to calculate pooled odds ratios. The impact of publication date on the overall effect was assessed in a cumulative analysis. Analyses were conducted on an intention-to-treat basis.

Subgroup analyses and meta-regressions were performed to assess the effects of the duration of prone positioning, lung protective ventilation, patient characteristics, concomitant high-frequency oscillatory ventilation, and adequacy of concealment allocation. The impact of each individual trial was assessed in sensitivity analyses.

Heterogeneity was assessed using $I^2$. Publication bias was assessed by visual inspection of funnel plots, and in Egger and Begg tests.

Results of the review
Eleven RCTs (2,246 patients; range 22 to 802) were included. All trials except one used appropriate methods of randomisation and allocation concealment, and were considered to be at a low risk of bias. Where reported, follow-up
ranged from 28 days to 180 days; two trials assessed events at discharge from the intensive care unit.

Overall mortality was significantly lower in prone-position patients (OR 0.77, 95% CI 0.59 to 0.99; random effects). The results from the fixed-effect model were comparable. There was no evidence of significant heterogeneity ($I^2=33.7\%$). The number-needed-to-treat for the prone position to prevent a death was 16.

Subgroup analyses found that, compared with supine positioning, the odds of death were significantly lower for patients who were in the prone position for more than 10 hours per session (OR 0.62, 95% CI 0.48 to 0.79; eight RCTs), but not for patients who received shorter sessions (three RCTs). Trials using lung protective ventilation reported significant differences favouring prone position (OR 0.62, 95% CI 0.48 to 0.79; eight RCTs); trials without protective ventilation found no difference (three RCTs). Trials of patients with acute respiratory distress syndrome had a statistically significant reduction in mortality (OR 0.62, 95% CI 0.48 and 0.80; seven RCTs); those of a mix of patients with acute respiratory distress syndrome or acute lung injury found no significant difference (four RCTs). Further subgroup and regression results were reported.

The prone position was significantly associated with higher odds of pressure ulcers (OR 1.49, 95% CI 1.18 to 1.89; six RCTs) and major airway problems (OR 1.55, 95% CI 1.10 to 2.17; nine RCTs). There was no evidence of significant heterogeneity ($I^2<33\%$).

**Authors’ conclusions**
The prone position, during mechanical ventilation, for patients with acute hypoxaemic respiratory failure, significantly reduced overall mortality. The effect was greater for patients with acute respiratory distress syndrome, who were prone for over 10 hours per session and received lung protective ventilation. Pressure ulcers and major airway problems were significantly more likely with the prone position.

**CRD commentary**
The review question and selection criteria were clearly reported. Various sources of published and unpublished data were searched. Attempts were made to minimise the risk of reviewer error and bias. Nearly all the trials were considered to be at a low risk of bias. The synthesis methods appear to have been appropriate. There was no evidence of significant heterogeneity.

Multiple subgroup analyses were conducted. Subgroup analyses have limitations, so their results should be interpreted with caution. The sensitivity analyses indicated that removing the most recent trial significantly affected the strength of the pooled estimate. This should be considered when interpreting the review findings.

Despite the limitations, the findings of the review reflected the evidence, and the conclusions are likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that the balance of risks and benefits for each patient should be weighed carefully before using the prone position, especially in intensive care units with less experience of prone positioning.

**Research:** The authors stated that further studies were required to determine the optimal duration for the prone position.

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