Prone positioning in hypoxemic respiratory failure: meta-analysis of randomized controlled trials

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CRD summary
The review found that prone positioning did not appear to affect overall mortality associated with hypoxaemic respiratory failure compared with supine positioning, although it may benefit the most severely-ill patients. The review was well conducted and the authors' conclusions appear reliable.

Authors' objectives
To evaluate the effect of prone positioning on clinical outcomes in patients with hypoxaemic respiratory failure.

Searching
MEDLINE, Current Contents and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to January 2007 for studies in any language. Search terms were reported. Reference lists of relevant studies and reviews were also checked.

Study selection
Randomised controlled trials (RCTs) that compared prone with supine positioning in the management of adults with hypoxaemic respiratory failure were eligible for inclusion. Trials were required to report intensive care unit mortality (primary outcome), hospital mortality, clinical outcomes or complications of both positions. Outcomes were defined in detail in the review. Trials reporting only gas exchange, haemodynamics or respiratory mechanics were excluded.

Participants in the included trials were adults undergoing mechanical ventilation, most of whom had acute lung injury or acute respiratory distress syndrome. The mean Simplified Acute Physiology Score II varied across trial groups, ranging from 38 to 46.1 (where reported). The proportion of cases in which hypoxaemic respiratory failure was caused by pneumonia varied across trial groups, ranging from 14 to 62%. The time interval from diagnosis to initiation of prone positioning also differed across trials. The mean daily duration of prone positioning (where reported) ranged from seven to 17 hours (daily mean); the overall duration ranged from two days to at least 10 days. Trials differed as to whether participants receiving co-interventions (e.g. nitric oxide) were eligible.

Two reviewers independently selected the studies.

Assessment of study quality
Trials were allocated 1 point for specifying each of the following: randomisation, random sequence generation, allocation concealment, double blinding, and information on withdrawals or drop-outs (maximum 5 points). Trials were designated as high quality (more than 2 points) or low quality (2 points or fewer).

Two reviewers independently assessed study validity.

Data extraction
Odds ratios (ORs) were extracted or calculated for dichotomous outcomes and mean differences for continuous outcomes, with 95% confidence intervals (CIs). Data were analysed both by intention-to-treat and per protocol (including only clinically evaluable participants who had not crossed over from one study arm to the other).

Two reviewers independently extracted the data, resolving differences by consensus or by referral to a third reviewer.

Methods of synthesis
Trials were combined to calculate pooled odd ratios and 95% confidence intervals for dichotomous data, using the
Mantel-Haenszel fixed-effect and DerSimonian and Laird random-effects models. For continuous data weighted mean differences (WMDs) and 95% confidence intervals were calculated. Heterogeneity was assessed using the $\chi^2$ and $I^2$ tests. Fixed-effect models were presented, although it was planned to use random-effects if there was significant statistical heterogeneity. Publication bias was not formally assessed as there were too few trials. A post-hoc subgroup analysis investigated intensive care unit mortality in the most severely-ill group (as defined in the review).

**Results of the review**

Four RCTs were included (n=1,271 patients, range 40 to 791). Three were high quality trials (scoring 3 out of 5 points) and one low quality trial (scoring 2 points).

There was no statistically significant difference between the prone and supine position groups in overall intensive care unit (ICU) mortality (four RCTs). However among the most severely-ill patients, the prone position was associated with significantly lower ICU mortality (OR 0.34, 95% CI 0.18 to 0.66; two RCTs; n=195 patients).

There was no statistically significant difference between the prone and supine position groups in ventilator-associated pneumonia (three RCTs), ICU length of stay (one RCT), duration of mechanical ventilation (two RCTs) or pneumothorax (two RCTs).

In the prone positioning group, there was a significantly higher rate of new or worsening pressure sores (OR 1.49, 95% CI 1.17 to 1.89; three RCTs; n=1,135 patients).

There was no significant statistical heterogeneity for any analysis.

All results presented above were by intention-to-treat.

**Authors' conclusions**

Prone positioning did not appear to affect overall mortality among patients with hypoxaemic respiratory failure, although a benefit for the most severely-ill patients could not be excluded.

**CRD commentary**

The objectives and inclusion criteria of the review were clear and relevant sources were searched for studies in any language. It was unclear whether the search was limited by publication status, but there were insufficient studies to assess the potential for publication bias. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently select studies, assess validity and extract the data.

Appropriate statistical techniques were used to combine the trials and assess for heterogeneity. The authors acknowledged the potential for bias in the review arising from the small amount of data and from differences between the trials; they were suitably cautious in interpreting their main findings.

The review was well conducted and the authors’ conclusions appear reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that explicit guidelines on the use of prone positioning would facilitate its implementation and decrease associated potential safety risks.

**Research:** The authors stated that a multi-centre study should be conducted among patients with severe hypoxaemic respiratory failure, with prone positioning started early for up to 20 hours per day, adequate treatment duration, well-defined outcomes, and protocols for ventilation and care practices. They noted that such a study was currently in progress.

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