Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis

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Abstract Background: Prone position ventilation for acute hypoxemic respiratory failure (AHRF) improves oxygenation but not survival, except possibly when AHRF is severe. Objective: To determine effects of prone versus supine ventilation in AHRF and severe hypoxemia \( \text{partial pressure of arterial oxygen (PaO}_2\text{/inspired fraction of oxygen (FiO}_2\text{)} <100 \text{ mmHg}} \) compared with moderate hypoxemia \( 100 \text{ mmHg} \leq \text{PaO}_2\text{/} \)
FiO₂ ≤ 300 mmHg). Design: Systematic review and meta-analysis.

Data Sources: Electronic databases (to November 2009) and conference proceedings. Methods: Two authors independently selected and extracted data from parallel-group randomized controlled trials comparing prone with supine ventilation in mechanically ventilated adults or children with AHRF. Trialists provided subgroup data. The primary outcome was hospital mortality in patients with AHRF and PaO₂/FiO₂ <100 mmHg. Meta-analyses used study-level random-effects models. Results: Ten trials (N = 1,867 patients) met inclusion criteria; most patients had acute lung injury. Methodological quality was relatively high. Prone ventilation reduced mortality in patients with PaO₂/FiO₂ <100 mmHg [risk ratio (RR) 0.84, 95% confidence interval (CI) 0.74–0.96; p = 0.01; seven trials, N = 555] but not in patients with PaO₂/FiO₂ >100 mmHg (RR 1.07, 95% CI 0.93–1.22; p = 0.36; seven trials, N = 1,169). Risk ratios differed significantly between subgroups (interaction p = 0.012). Post hoc analysis demonstrated statistically significant improved mortality in the more hypoxemic subgroup and significant differences between subgroups using a range of PaO₂/FiO₂ thresholds up to approximately 140 mmHg. Prone ventilation improved oxygenation by 27–39% over the first 3 days of therapy but increased the risks of pressure ulcers (RR 1.29, 95% CI 1.16–1.44), endotracheal tube obstruction (RR 1.58, 95% CI 1.24–2.01), and chest tube dislodgement (RR 3.14, 95% CI 1.02–9.69). There was no statistical between-trial heterogeneity for most clinical outcomes. Conclusions: Prone ventilation reduces mortality in patients with severe hypoxemia. Given associated risks, this approach should not be routine in all patients with AHRF, but may be considered for severely hypoxemic patients.

Keywords Acute lung injury · Prone position · Hypoxia · Randomized controlled trial · Systematic review · Meta-analysis

Introduction

Acute lung injury (ALI) and the more hypoxemic subgroup of acute respiratory distress syndrome (ARDS) may occur after many primary or secondary pulmonary injuries, leading to a common syndrome characterized by hypoxemia, pulmonary congestion, and decreased pulmonary compliance. This syndrome is associated with substantial mortality [1, 2], morbidity [3, 4], and costs [5]. Mechanical ventilation usually corrects tissue hypoxemia [6] but also may be complicated by ventilator-induced lung injury. Although lower tidal volume [7] reduces ventilator-induced lung injury, mortality in patients with ARDS remains high [1, 2].

Mechanical ventilation of patients with ALI in the prone position, first suggested in 1974 [8], optimizes both lung recruitment and ventilation–perfusion matching [9]. Collapse due to gravity of ventral lung segments in the prone position is less than that of dorsal lung segments in the supine position [10, 11], while lung perfusion in the prone position is more evenly distributed [12]. Other potentially important improvements include enhanced postural drainage of secretions [13] and decreased alveolar overdistension [14], cyclic alveolar collapse, and ventilator-induced lung injury [15].

Multicenter randomized trials [16–18] and systematic reviews [19–23] have failed to demonstrate that prone ventilation improves overall mortality in patients with acute hypoxic respiratory failure, despite the strong physiological rationale. Subgroup analyses have suggested a mortality benefit in patients with severe hypoxemia [16] or with higher severity of illness [16, 21, 22]. However, these analyses are limited by reporting bias due to lack of subgroup data from most trials [21, 22], limited numbers of patients and events [16, 21, 22], and omission of appropriate statistical tests to detect subgroup differences [24].

The objective of this systematic review, performed in collaboration with prone ventilation trialists, was to determine whether prone ventilation reduces mortality compared with supine ventilation in patients with acute hypoxic respiratory failure and severe hypoxemia. We reasoned that patients with severe hypoxemia would be the most likely to benefit from prone ventilation because the main effect of prone ventilation is to improve oxygenation [19], and clinicians use this technique primarily for refractory hypoxemia [25]. Furthermore, the proposed protective effects of prone ventilation occur due to lung recruitment, and patients with more severe hypoxia have more recruitable lung [26]. A priori, we hypothesized that prone ventilation would reduce mortality in severely hypoxemic patients, defined by baseline ratio of partial pressure of arterial oxygen (PaO₂) to inspired fraction of oxygen (FiO₂) <100 mmHg, but not in patients with moderate hypoxemia (100 mmHg ≤ PaO₂/FiO₂ ≤ 300 mmHg). We chose a threshold PaO₂/FiO₂ of 100 mmHg to identify severe hypoxemia because this value was used to stratify patients in the most recent randomized controlled trial (RCT) of prone ventilation [27] and because bedside clinicians can readily determine whether a patient’s PaO₂/FiO₂ is above or below this threshold.
Methods

Study identification

We updated our previous search [19] using systematic methods (Appendix) to identify RCTs of mechanical ventilation in the prone compared with supine position in patients with ALI, ARDS, and acute hypoxemic respiratory failure [28]. We identified all relevant trials using the following techniques: electronic searches of MEDLINE, EMBASE, and CENTRAL, (from inception to November 2009); manual searches of reference lists from included studies and review articles; manual and electronic searches of conference proceedings of the American Thoracic Society (1994–2009), Society of Critical Care Medicine (1994–2009), European Society of Intensive Care Medicine (1994–2009), American College of Chest Physicians (1994–2009), and the International Symposium on Intensive Care and Emergency Medicine (1997–2009); and contact with primary investigators. Finally, we searched for unpublished and ongoing trials in clinicaltrials.gov and controlled-trials.com [29]. No language restrictions were applied [30].

Study eligibility

Two investigators independently evaluated retrieved studies for possible inclusion and resolved differences by consensus [31]. We included studies if they (1) enrolled mechanically ventilated adults or postneonatal children with acute hypoxemic respiratory failure (defined by \( \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg} \)); (2) randomly assigned patients to two or more groups, including a treatment group ventilated in the supine position, with an intervention period of at least 48 h in duration; and (3) reported any of our primary or secondary outcomes (see below).

Trials allocating patients in alternating fashion or by hospital registry number (quasirandomization) or trials with co-interventions (such as high-frequency oscillation or nitric oxide) specified as part of the intervention and applied equally to both groups were also eligible. We excluded randomized crossover trials in which patients received both treatment and control interventions in random order. We also excluded short-term trials in which the intervention was applied for \( \leq 48 \text{ h} \), because we believed that outcomes would be minimally affected by applying the intervention for such a short duration.

We included trials in which prone positioning was used early (within 72 h after initiation of mechanical ventilation for acute hypoxemic respiratory failure) and as late or rescue therapy (72 h after initiation of mechanical ventilation), and trials in which prone ventilation was applied intermittently (for a predefined period of time each day) or continuously (without interruption for the duration of the study period).

Data extraction and study quality

Two reviewers independently abstracted data on study methods, details of prone ventilation (including duration of prone ventilation per day and total duration of the intervention period) and general mechanical ventilation, and study outcomes. Disagreements were resolved by consensus.

We abstracted data on: method of randomization and allocation concealment, number of postrandomization withdrawals and losses to follow-up, and crossovers between assigned groups [32]. Allocation concealment was assessed according to the criteria of the Cochrane Collaboration [33]. We also determined whether studies were stopped early for benefit [34] or for other reasons such as harm or futility. Since blinding of caregivers, patients, and family members is impossible in a trial evaluating prone ventilation, we determined whether outcome assessors were blinded to the diagnosis of ventilator-associated pneumonia (VAP) and whether important co-interventions such as weaning, sedation and paralysis, steroids, and use of rescue therapies for hypoxemia (inhaled nitric oxide, high-frequency oscillation, extracorporeal oxygenation) were standardized or equally applied in treatment and control groups.

The authors of included trials collaborated in this systematic review by reviewing original trial data, providing previously unpublished data for subgroups of patients, and clarifying data and methods.

Outcomes

The primary outcome was mortality in the subgroup of patients with severe acute hypoxemic respiratory failure, defined by baseline \( \text{PaO}_2/\text{FiO}_2 < 100 \text{ mmHg} \), compared with mortality in patients with \( 100 \text{ mmHg} \leq \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg} \). For each study, mortality was determined at hospital discharge or, if not available, at the longest duration of follow-up. Secondary outcomes included mortality stratified according to the same threshold \( \text{PaO}_2/\text{FiO}_2 \) but limited to patients with ALI/ARDS; and in all patients, duration of mechanical ventilation, ventilator-free days to day 28, and adverse events (VAP, pressure ulcers, endotracheal tube obstruction, unplanned extubation, unplanned removal of central venous catheters or arterial lines, unplanned removal of chest tubes, pneumothoraces, and cardiac arrests). We also considered the effect on \( \text{PaO}_2/\text{FiO}_2 \) ratio on the first, second, and third calendar day after randomization in all patients. We measured the oxygenation effect of prone positioning by comparing the mean \( \text{PaO}_2/\text{FiO}_2 \) ratio
measured in the prone group with the closest available recorded measurement in the supine group. Where more than one measurement was taken we chose the measurement closest to the end of the proning session on that day.

We analyzed patients according to assigned group for all outcomes.

Statistical analysis

We aggregated outcome data at the trial level and performed statistical calculations with Review Manager (RevMan) 5.0 (2009; The Cochrane Collaboration, Oxford, UK) and STATA 9.2 (2006; StataCorp, TX, USA) using random-effects models. Random-effects models incorporate both within-study and between-study variation and provide more conservative treatment estimates when heterogeneity is present. We reported continuous outcomes using mean differences (a measure of absolute change) and ratios of means (a measure of relative change [35]), and binary outcomes as risk ratios (RR). For the primary outcome, we performed a z test of interaction between the RR for mortality in the subgroup of patients with PaO$_2$/FiO$_2$ <100 mmHg and the RR in the subgroup of patients with PaO$_2$/FiO$_2$ ≥100 mmHg, which tests the null hypothesis that the treatment effect in each subgroup is the same. In a post hoc analysis, we conducted similar comparisons of the more versus less hypoxemic subgroups using PaO$_2$/FiO$_2$ thresholds ranging from 80 to 200 mmHg, in increments of 10 mmHg. All statistical tests were two sided. We considered \( p < 0.05 \) as statistically significant in all analyses and report individual trial and summary results with 95% confidence intervals (CIs).

We assessed between-study heterogeneity for each outcome using the \( I^2 \) measure [36, 37]. We considered statistical heterogeneity to be low for \( I^2 = 25–49\% \), moderate for \( I^2 = 50–74\% \), and high for \( I^2 ≥ 75\% \) [37].

To assess publication bias we examined funnel plots of treatment effect versus study precision and assessed statistically using Begg’s rank correlation test [38] and modified Macaskill’s regression test [39]. Given the low power of these tests, we assumed a more liberal level of significance (\( p < 0.10 \)) to indicate publication bias.

Fig. 1 Flow diagram for studies included in this review. ALI acute lung injury, ARDS acute respiratory distress syndrome, RCT randomized controlled trial
Results

Literature search

We identified 2,683 citations from searches of electronic bibliographic databases and 18 citations from other sources. We retrieved 52 records for detailed evaluation, of which 10 trials [16–18, 27, 40–45] met criteria for inclusion in our review (Fig. 1). One study [40] was verified to be randomized after contacting authors [46, 47]. We identified eight publications [46–53] whose authors provided duplicate or supplementary data. We excluded five trials [54–58] in which the intervention period was less than 48 h and identified one ongoing study that would meet inclusion criteria [59]. Reviewers had perfect agreement for study inclusion. The largest trial (n = 802) [17] enrolled patients with acute hypoxemic respiratory failure (PaO2/FiO2 ≤300 mmHg), including ALI/ARDS (n = 413). One other trial [45] enrolled patients requiring mechanical ventilation with Glasgow coma score ≤9, for which we included only patients with PaO2/FiO2 ≤300 mmHg at baseline. All other trials reporting mortality enrolled exclusively patients with ALI/ARDS.

Study characteristics and methodological quality

The ten included trials (Table 1) [16–18, 27, 40–45] enrolled 1,867 patients (median 77 per trial, range 16–802). One trial (n = 102) enrolled children [41]. Most trials enrolled patients within 72 h after the development of hypoxemic respiratory failure [18, 27, 40–43, 45], but two studies did not limit the duration of acute hypoxemic respiratory failure prior to enrolment [16, 17]. The median PaO2/FiO2 at baseline was 122 (range 100–243) mmHg. Patients in the included trials were ventilated in the prone position for a median of 14 h per day (range 4–24 h), and prone ventilation was continued either for a prespecified duration [40, 44] or until prespecified clinical improvements [16–18, 27, 41–43, 45] (median duration of proning 4.7 days, range 4–10 days).

The included trials had relatively high methodological quality (Table 1). Eight trials concealed allocation [16–18, 27, 40–43, 45], one trial [40] did not conceal allocation [46, 47], and another enrolled alternating patients [44]. All trials analyzed outcomes for patients by assigned group. Seven studies were terminated prematurely after meeting prespecified criteria for futility [41] or because of slow recruitment [16, 18, 40, 42, 43, 45]. For the trials that reported mortality, vital status was known at the end of follow-up for all patients in three trials [40, 41, 43] and losses were less than 5% of those randomized in six trials (12/802 [17], 6/142 [18], 6/344 [27], 2/42 [42], 2/53 [45], 7/304 [16]). Seven trials reported crossovers between groups; these involved <6% of randomized patients for five trials (12/304 [16], 4/102 [41], 5/136 [18], 2/40 [42], 20/342 [27]), and 12% (6/51[45]) and 32% (251/791[17]) in two trials. Five trials mandated low-tidal-volume ventilation (6–8 ml/kg body weight) [27, 40–43], and five trials [18, 27, 40, 41, 43] used mechanical ventilation guidelines or protocols during the study period. Protocols for sedation [18, 41, 42, 44] and for weaning from mechanical ventilation [17, 18, 41, 42] were used in four trials each. Blinded assessment [45] or independent adjudication [17] for VAP was used in two of seven trials that reported this outcome [17, 18, 40, 42–45].

Quantitative data synthesis

Mortality

Seven [16–18, 27, 40–42] of ten trials provided mortality stratified by baseline PaO2/FiO2 and were included in the primary analysis. Two trials [43, 45] could not be included in the analysis because only one patient [43] or no patients [45] had PaO2/FiO2 <100 mmHg, and one trial did not report mortality [44]. The seven trials [16–18, 27, 40–42] in the primary analysis had the lowest baseline PaO2/FiO2 (median 113 mmHg, range 100–152 mmHg), and all but one trial [41] followed patients to hospital discharge [18, 40, 42, 43, 45] or at least 90 days [16, 17, 27]. Prose ventilation significantly reduced all-cause mortality (Fig. 2) in patients with baseline PaO2/FiO2 <100 mmHg (RR 0.84, 95% CI 0.74–0.96; p = 0.01; N = 555) but not in patients with baseline PaO2/FiO2 ≥100 mmHg (RR 1.07, 95% CI 0.93–1.22; p = 0.36; N = 1,169). The test for interaction between these subgroups was statistically significant (p = 0.012), indicating that treatment effects differed significantly in subgroups with severe and moderate baseline hypoxemia.3 Considering all patients together, regardless of severity of hypoxemia, there was no effect on mortality (RR 0.97, 95% CI 0.88–1.07; p = 0.54; N = 1,786). In the severely hypoxemic subgroup, the number of patients needed to prone to prevent one death was 11 (95% CI 6–50, calculated from a random-effects risk difference model).

Since two trials [17, 45] included patients with acute hypoxemic respiratory failure but without ALI/ARDS, we also analyzed mortality limited to patients with ALI/ARDS. Results were similar, although the interaction p value (0.06) was not statistically significant: RR 0.85, 95% CI 0.74–0.98, p = 0.02 in patients with baseline PaO2/FiO2 <100 mmHg (N = 495), and RR 1.04, 95% CI 0.89–1.22, p = 0.60 in patients with baseline PaO2/FiO2 ≥100 mmHg (N = 852).

3Two trials were excluded from this subgroup analysis because only one patient [43] or no patients [45] had PaO2/FiO2 <100 mmHg. Adding data from these two trials to the PaO2/FiO2 <100 mmHg subgroup caused small changes to the pooled effect estimate for this subgroup (RR 1.05, 95% CI 0.92–1.20, p = 0.44; N = 1,230) and test for subgroup interaction (p = 0.019).
Table 1  Characteristics of the randomized controlled trials included in the systematic review

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</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>802</td>
<td>344</td>
<td>304</td>
<td>142</td>
<td>102 children (age 2 weeks to 18 years)</td>
</tr>
<tr>
<td>Enrolment criteria</td>
<td>Hypoxemic acute respiratory failure (413 ALI/ARDS patients)</td>
<td>ARDS with PEEP ≤5 cmH₂O³⁷</td>
<td>ALI/ARDS with PEEP ≤5 cmH₂O³⁷</td>
<td>ARDS with four-quadrant infiltrates on CXR³⁷</td>
<td>ALI/ARDS ³⁷</td>
</tr>
<tr>
<td>Mean enrolment</td>
<td>152</td>
<td>113</td>
<td>127</td>
<td>105</td>
<td>100</td>
</tr>
<tr>
<td>PaO₂/FiO₂ (mm Hg)</td>
<td>8</td>
<td>10</td>
<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Mean enrolment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratified randomization by severity</td>
<td>No</td>
<td>Yes (by PaO₂/FiO₂)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Time after meeting enrolment criteria</td>
<td>&gt;12-24 h</td>
<td>&lt;72 h</td>
<td>Not prespecified</td>
<td>&lt;48 h</td>
<td>&lt;48 h</td>
</tr>
<tr>
<td>Last follow-up</td>
<td>90 days</td>
<td>6 months</td>
<td>6 months</td>
<td>Hospital discharge</td>
<td>Hospital discharge or 28 days</td>
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<tr>
<td>Prone positioning:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned duration</td>
<td>28 h/day until weaning criteria</td>
<td>20 h/day for 28 days</td>
<td>6 h/day for 10 days</td>
<td>20 h/day until weaning criteria</td>
<td>20 h/day until weaning criteria (max. 7 days)</td>
</tr>
<tr>
<td>Actual duration (average)</td>
<td>9 h for 4.1 days</td>
<td>18 h for 8.3 days</td>
<td>7 h for 4.7 days</td>
<td>17 h for 10.1 days</td>
<td>18 h for 4 days</td>
</tr>
<tr>
<td>Prone discontinuation criteria</td>
<td>Clinical improvement ³⁷</td>
<td>FIO₂ 40% and PEEP ≤5 cmH₂O</td>
<td>None</td>
<td>FIO₂ ≤45% and PEEP ≤5 cmH₂O</td>
<td>Spontaneous breathing or OI &lt;6</td>
</tr>
<tr>
<td>Crossover criteria (supine to prone)</td>
<td>PaO₂/FiO₂ &lt;100 for 12 h</td>
<td>PaO₂ ≤55 mmHg on FIO₂ = 1.0 and PEEP ≤15 cmH₂O</td>
<td>No</td>
<td>PaO₂ &lt;60 mmHg on FIO₂ = 1.0 and PEEP ≤20 cmH₂O</td>
<td>No</td>
</tr>
<tr>
<td>Co-interventions:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protective mechanical ventilation</td>
<td>No</td>
<td>Yes (i.e., VT ≤8 ml/kg of PBW ³⁷)</td>
<td>Consensus conference guidelines ³⁷</td>
<td>Yes (i.e., VT ≤10 ml/kg of PBW ³⁷ or ABW)</td>
<td>Yes (i.e., VT ≤6-7 ml/kg of BW ³⁷)</td>
</tr>
<tr>
<td>Weaning protocol</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pre-defined sedation targets</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Concealment of allocation</td>
<td>Sealed opaque</td>
<td>Central</td>
<td>Sealed opaque envelopes</td>
<td>Sealed opaque envelopes</td>
<td>Sealed opaque envelopes</td>
</tr>
<tr>
<td>Randomized patients excluded for all mortality analyses ³⁷</td>
<td>7/385 supine, 4/417 prone</td>
<td>1/175 supine, 1/169 prone</td>
<td>No</td>
<td>2/62 supine, 4/80 prone</td>
<td>No</td>
</tr>
<tr>
<td>Crossover (supine to prone group)</td>
<td>81/378</td>
<td>20/174</td>
<td>12/152</td>
<td>5/60</td>
<td>0/51</td>
</tr>
<tr>
<td>Crossover (prone to supine group)</td>
<td>170/413</td>
<td>0/158</td>
<td>0/152</td>
<td>0/76</td>
<td>4/51</td>
</tr>
</tbody>
</table>

³⁷: No crossover analysis of supine and prone patients is possible.
<table>
<thead>
<tr>
<th>Table 1 continued</th>
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<tbody>
<tr>
<td><strong>Population:</strong></td>
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<tr>
<td>Patients</td>
</tr>
<tr>
<td>Enrolment criteria</td>
</tr>
<tr>
<td>Mean enrolment</td>
</tr>
<tr>
<td>Mean enrolment Pa(_{O_2}/FiO_2) (mm Hg)</td>
</tr>
<tr>
<td>Stratified randomization by severity</td>
</tr>
<tr>
<td>Time after meeting enrolment criteria</td>
</tr>
<tr>
<td>Last follow-up</td>
</tr>
</tbody>
</table>

**Procedures:**

- Planned duration: 20 h/day until weaning criteria
- Actual duration (average): 18 h
- Prose discontinuation criteria: Pa\(_{O_2}/FiO_2>250\) and PEEP ≤ 8 cmH\(_2\)O for 12 h
- Crossover criteria (supine to prone): No

**Co-interventions:**

- Protective mechanical ventilation: Yes (i.e., Vt 6-8 ml/kg of IBW\(^a\))
- Weaning protocol: Yes (i.e., Vt 6-8 ml/kg of IBW\(^a\))
- Pre-defined sedation targets: No

**Concealment of allocation:**

- Randomized patients excluded for all mortality analyses\(^g\): 1/20 supine, 1/22 prone
- No
- No
- 2/28 supine, 0/25 prone
- Not applicable

**Crossover (supine to prone group):**

- 2/19
- 0/19
- 0/11
- 3/26 (1/9 hypoxic)
- 0/8

**Crossover (prone to supine group):**

- 0/21
- 0/21
- 0/11
- 3/25 (1/12 hypoxic)
- 0/8

**Effective number of patients:**

- Not reported

**Abbreviations:** ABW, actual body weight; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CXR, chest x-ray; FiO\(_2\), fractional concentration of inspired oxygen; IBW, ideal body weight; OI, oxygenation index; Pa\(_{O_2}\), partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; SAPS, Simplified Acute Physiology Score; VT, tidal volume.

\(^a\) according to the criteria of the American-European Consensus Conference (69)

\(^b\) Defined by 1 major (relative improvement of Pa\(_{O_2}/FiO_2≥30\%\) after randomization, with FiO\(_2≤60\%\)) and at least 1 minor criterion (PEEP ≤ 8 cmH\(_2\)O, no sepsis, cause of acute respiratory failure under control, stable or improving chest x-ray, and <3 organ dysfunction, including lung dysfunction).

\(^c\) predicted body weight was calculated as 50 = 0.91 (height in centimeters - 152.4) for male patients and as 45.5 = 0.91 (height in centimeters - 152.4) for female patients [7].

\(^d\) average over first 2 days only; average number of days prone not available

\(^e\) ideal body weight was calculated as [height in centimeters – 80] x 0.7 for male patients and as [height in centimeters – 70] x 0.6 for female patients

\(^f\) ideal body weight was determined in the years of age using the National Center for Health Statistics growth charts. Predicted weight charts for sex, stature beyond 3 years of age was generated by identifying the 50th percentile weight associated with age then linking that data to the 50th percentile. See http://wwww.cdc.gov/nchs/nhanes/growthcharts/clinical_charts.htm.

\(^g\) refers to patients randomized to receive prone position ventilation and either never prone or prone position changes were discontinued prior to meeting prone weaning criteria. In addition, 41/152 patients in Gattinoni (16) and 34/168 patients in Taccorre (27) randomized to receive prone ventilation missed one or more sessions. The number of sessions missed per patient in these studies is unavailable.
We found no evidence of statistical heterogeneity for all mortality analyses ($I^2 = 0\%$). Neither Begg’s rank correlation test ($p = 0.52$) nor the modified Macaskill’s regression test ($p = 0.37$) suggested publication bias.

Post hoc analyses using varying PaO$_2$/FiO$_2$ thresholds (Fig. 3) suggested improved mortality in the more severely hypoxemic subgroup using PaO$_2$/FiO$_2$ thresholds up to approximately 140 mmHg to define this subgroup.

**Oxygenation and nonmortality clinical endpoints**

On days 1–3 after randomization, prone ventilation increased PaO$_2$/FiO$_2$ ratio in seven trials [16, 18, 27, 40–42, 44], by 27–39% (Fig. 4). Prone ventilation also reduced VAP (RR 0.81, 95% CI 0.67–1.00, $p = 0.05$; two trials that followed up patients for 6 months [16, 27]. Baseline PaO$_2$/FiO$_2$ values were unavailable for one patient in the prone group in one trial [40] and one patient in the supine group in another trial [42]. Weight is the contribution of each study to the overall risk ratio. CI confidence interval, $I^2$ percentage of total variation across studies from between-study heterogeneity rather than chance, $n/N =$ number of deaths/number of patients randomized.

**Adverse events (Table 2)**

Prone positioning increased the risk of pressure ulcers (RR 1.29, 95% CI 1.16–1.44, $p < 0.00001$; seven trials [16, 18, 40, 41, 43, 45], $N = 1,279$), endotracheal tube obstruction.

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**Study or sub-category** | **Prone** | **Supine** | **Risk Ratio** | **Weight %** | **Risk Ratio** |
---|---|---|---|---|---|
**All Patients** | | | | | |
Gattinoni 2001 | 92/148 | 87/149 | 27.67 | 1.96 (0.80, 1.28) |
Beuret 2002 | 4/12 | 4/9 | 0.81 | 0.75 (0.25, 2.22) |
Guerin 2004 | 179/413 | 159/377 | 36.18 | 1.03 (0.87, 1.21) |
Curley 2005 | 6/51 | 4/51 | 0.53 | 1.00 (0.26, 3.78) |
Voggenreiter 2005 | 1/21 | 3/19 | 0.20 | 0.30 (0.03, 3.66) |
Mancebo 2006 | 38/76 | 37/60 | 10.47 | 0.81 (0.60, 1.10) |
Chan 2007 | 5/11 | 6/11 | 1.33 | 0.83 (0.26, 2.97) |
Fernandez 2008 | 8/21 | 10/19 | 1.97 | 0.72 (0.36, 1.45) |
Taccone 2009 | 79/166 | 91/172 | 20.84 | 0.90 (0.73, 1.11) |
Subtotal (95% CI) | 410/919 | 401/867 | 100.00 | 0.97 (0.88, 1.07) |

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**PaO$_2$/FiO$_2$ > 100 Subgroup** | | | | | |
Gattinoni 2001 | 57/95 | 52/103 | 28.45 | 1.19 (0.92, 1.53) |
Guerin 2004 | 126/323 | 110/302 | 46.31 | 1.07 (0.88, 1.31) |
Curley 2005 | 3/30 | 2/28 | 0.62 | 1.40 (0.26, 7.37) |
Mancebo 2006 | 16/33 | 16/31 | 7.54 | 0.94 (0.58, 1.53) |
Chan 2007 | 3/4 | 0/4 | 0.25 | 7.00 (0.47, 103.27) |
Fernandez 2008 | 3/12 | 7/14 | 1.96 | 0.50 (0.16, 1.52) |
Taccone 2009 | 40/93 | 43/96 | 17.57 | 0.96 (0.70, 1.33) |
Subtotal (95% CI) | 248/590 | 230/578 | 100.00 | 1.07 (0.93, 1.22) |

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**PaO$_2$/FiO$_2$ < 100 Subgroup** | | | | | |
Gattinoni 2001 | 35/53 | 35/46 | 28.32 | 0.87 (0.67, 1.21) |
Guerin 2004 | 53/90 | 49/75 | 31.56 | 0.90 (0.71, 1.14) |
Curley 2005 | 1/21 | 2/23 | 0.33 | 0.56 (0.05, 6.51) |
Mancebo 2006 | 22/43 | 21/29 | 13.25 | 0.73 (0.49, 1.02) |
Chan 2007 | 2/6 | 6/7 | 1.31 | 0.39 (0.10, 1.25) |
Fernandez 2008 | 5/9 | 2/4 | 1.38 | 0.31 (0.10, 1.25) |
Taccone 2009 | 39/73 | 46/76 | 23.86 | 0.85 (0.64, 1.11) |
Subtotal (95% CI) | 152/295 | 163/260 | 100.00 | 0.84 (0.74, 0.96) |

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**Fig. 2** Effect of prone ventilation on mortality (at hospital discharge or longest duration of follow-up). The z test for subgroup interaction was statistically significant ($p = 0.012$). Trialists verified all overall and subgroup mortality data; overall mortality data differed from the original publication in one case [16]. Patients lost to follow-up were removed from the denominator. Results are unchanged if these patients are retained in the denominator and assumed to be alive at the end of the follow-up period, as done in two trials that followed up patients for 6 months [16, 27]. Baseline PaO$_2$/FiO$_2$ values were unavailable for one patient in the prone group in one trial [40] and one patient in the supine group in another trial [42]. Weight is the contribution of each study to the overall risk ratio. CI confidence interval, $I^2$ percentage of total variation across studies from between-study heterogeneity rather than chance, $n/N =$ number of deaths/number of patients randomized.
Fig. 3 Effect of prone ventilation on mortality in severe and moderate baseline hypoxemic subgroups for a range of PaO2/FiO2 threshold values. Error bars indicate width of 95% confidence interval of relative risk in the severe (black squares) and moderate (white squares) baseline hypoxemic subgroups. * Interaction p value < 0.05, indicating that treatment effects differed significantly in subgroups with severe and moderate baseline hypoxemia at the PaO2/FiO2 threshold. + Treatment effect p value < 0.05, indicating that prone ventilation significantly decreased mortality in the subgroup with severe baseline hypoxemia defined using the PaO2/

Fig. 4 Effect of prone ventilation on PaO2 (partial pressure of arterial oxygen)/FiO2 (inspired fraction of oxygen) on postrandomization calendar days 1–3. Ratio of means = mean PaO2/FiO2 in the prone group (in the prone position)/mean PaO2/FiO2 in the supine group (at the closest available time). Weight is the contribution of each study to the overall ratio of means. CI confidence interval, I² percentage of total variation across studies due to between-study heterogeneity rather than chance

### Table 1: Ratio of Means

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Prone N</th>
<th>Supine N</th>
<th>Ratio of Means (95% CI)</th>
<th>Weight %</th>
<th>Ratio of Means (95% CI)</th>
</tr>
</thead>
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<tr>
<td>Day 1</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Gattinoni 2001</td>
<td>147</td>
<td>148</td>
<td>25.70 1.53 [1.40, 1.69]</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>8</td>
<td>8</td>
<td>12.50 1.39 [1.16, 1.66]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curley 2005</td>
<td>48</td>
<td>51</td>
<td>12.82 1.50 [1.26, 1.79]</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
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<td>59</td>
<td>14.71 1.25 [1.07, 1.47]</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
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<td>11</td>
<td>11</td>
<td>2.89 1.53 [1.00, 2.34]</td>
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</tr>
<tr>
<td>Fernandez 2008</td>
<td>21</td>
<td>15</td>
<td>6.41 1.22 [0.93, 1.61]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taccone 2009</td>
<td>160</td>
<td>169</td>
<td>24.97 1.31 [1.19, 1.44]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td>461</td>
<td></td>
<td></td>
<td>100.00 1.39 [1.29, 1.50]</td>
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<tr>
<td>Heterogeneity: I² = 0%</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
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<td>Gattinoni 2001</td>
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<td>148</td>
<td>24.21 1.35 [1.21, 1.50]</td>
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<td></td>
</tr>
<tr>
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<td>8</td>
<td>12.90 1.38 [1.16, 1.65]</td>
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<td></td>
</tr>
<tr>
<td>Curley 2005</td>
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<td>49</td>
<td>12.47 1.14 [0.95, 1.37]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mancebo 2006</td>
<td>71</td>
<td>59</td>
<td>15.60 1.27 [1.09, 1.49]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan 2007</td>
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<td>7</td>
<td>2.16 2.09 [1.26, 3.46]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fernandez 2008</td>
<td>21</td>
<td>18</td>
<td>7.40 1.18 [0.91, 1.53]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taccone 2009</td>
<td>159</td>
<td>167</td>
<td>25.26 1.20 [1.09, 1.33]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td>456</td>
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<td></td>
<td>100.00 1.27 [1.18, 1.37]</td>
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<tr>
<td>Heterogeneity: I² = 30%</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>95</td>
<td>139</td>
<td>29.04 1.26 [1.13, 1.40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watanabe 2002</td>
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<td>8</td>
<td>14.59 1.46 [1.21, 1.76]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curley 2005</td>
<td>41</td>
<td>47</td>
<td>16.16 1.19 [1.00, 1.42]</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>7</td>
<td>2.74 1.08 [0.66, 1.77]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fernandez 2008</td>
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<td>17</td>
<td>7.58 1.47 [1.10, 1.94]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taccone 2009</td>
<td>153</td>
<td>161</td>
<td>29.90 1.23 [1.11, 1.37]</td>
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<tr>
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<td></td>
<td></td>
<td>100.00 1.27 [1.19, 1.35]</td>
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<td></td>
</tr>
<tr>
<td>Heterogeneity: I² = 0%</td>
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</tr>
</tbody>
</table>
Unplanned extubation or endotracheal tube obstruction 7 (1,351, 184) 1.58 [1.24, 2.01]

Discussion

The main finding of our systematic review is that mechanical ventilation in the prone position has a different impact on mortality in patients with acute hypoxic respiratory failure depending on the extent of hypoxemia: it reduces mortality in those with severe hypoxemia, defined by baseline PaO2/FiO2 <100 mmHg, but not in those with less severe hypoxemia. Post hoc analysis demonstrated that the statistically significant difference between the relative risk of death in the more severely hypoxemic subgroup compared with the less severely hypoxemic subgroup was robust across several PaO2/FiO2 thresholds up to approximately 140 mmHg. Other benefits of prone ventilation included significant improvements in oxygenation on days 1–3 and reduced VAP, although there was no decrease in duration of ventilation. The risks of pressure ulcers, endotracheal tube obstruction, and possibly line and tube dislodgement were increased. Results were consistent among trials for mortality and most other clinical outcomes, with low to moderate between-trial differences for oxygenation outcomes, strengthening our findings.

The 16% reduction in the relative risk of death among patients with PaO2/FiO2 <100 mmHg was consistent with our a priori hypothesis that improved oxygenation during prone ventilation would be clinically important in patients at high risk of death from profound hypoxemia. In a post hoc analysis, the first multicenter RCT of prone ventilation [16] showed improved mortality in the quartile of patients with the most severe hypoxemia. The treatment effect, however, did not significantly differ from that in less hypoxemic patients, possibly due to inadequate statistical power. In our meta-analysis, we analyzed mortality stratified by severity of hypoxemia for all trials of prone ventilation which measured this outcome, thereby providing a more robust and powerful analysis.

A physiologic explanation for our finding is that ventilation in the prone position recruits collapsed regions [10, 11] of the lung without increasing airway pressure
and did not use protocols for sedation [16, 18, 41, 42] or hyperinflation [14]. Thus, the delivered tidal volume and peak pressure are dispersed to more alveoli, decreasing the risk of alveolar injury from stretch and strain forces [15]. This lung-protective effect of prone ventilation may be less important in patients with less severe hypoxemic respiratory failure, but appears to be highly relevant for patients with severe hypoxemia (mostly due to ARDS) who are most at risk for alveolar injury from shear and strain forces due to the low ratio of normal to collapsed lung [60]. In severely hypoxic patients, prone ventilation may provide additive benefit to the lung-protective strategy of lowering delivered tidal volumes [7].

A practical question facing clinicians using this intervention is the optimal duration of prone positioning. This issue is difficult to address with the available data. Our post hoc analysis did not show a significant difference in effect on mortality between trials implementing longer versus shorter daily duration of prone ventilation. Furthermore, the analysis was based on subgroups of trials rather than subgroups of patients within trials, and these subgroups differed in several other important ways. Trials using shorter-duration prone ventilation were published earlier (up to 2005), whereas trials using longer-duration prone ventilation were published since 2005. Consequently, the longer-duration trials were more likely to implement treatments such as low-tidal-volume mechanical ventilation [7] that may have contributed to a reduction in mortality. In addition, the more recently completed trials attempted to enrol patients with more severe hypoxemia and earlier in the course of ARDS [18, 27, 40–42]. Finally, performing trial-level subgroup analysis using the mean overall duration of daily prone ventilation in each trial may lead to ecological bias [61], since it cannot be ascertained whether individuals within each trial who received longer durations of prone ventilation actually benefited more than individuals with shorter durations. In contrast, in the primary subgroup comparison of hypoxemia severity, groups of patients with severe and moderate hypoxemia within each trial were analyzed, limiting the potential for ecological bias.

Prone ventilation tended to reduce VAP, possibly through improved drainage of secretions [13]. Nonetheless, the observed reduction in VAP did not hasten weaning from mechanical ventilation. Moreover, as discussed previously [19], most trials did not blind outcome assessors or mandate duplicate independent VAP adjudication [18, 40, 42–44], and did not use protocols for sedation [16, 17, 27, 40, 43, 45] or ventilator weaning [16, 27, 40, 43–45]. Thus, the finding of reduced VAP must be interpreted cautiously.

Unlike other interventions for ARDS, such as high-frequency oscillation [62] and inhaled nitric oxide [63], prone ventilation is readily implemented in any intensive care unit. However, we found that prone ventilation was not without harm, significantly increasing the risks of pressure ulcers, endotracheal tube obstruction, and chest tube dislodgement. Although we did not find differences in pool outcomes of other adverse events, one multicenter trial [27] found significantly increased rates of endotracheal tube and intravenous line dislodgements. Such events can have catastrophic effects in such critically ill patients. For example, in another trial [18] cardiac arrest resulted from dislodgement of a pulmonary artery catheter, which was directly attributed to a prone manoeuvre, highlighting that great care and experienced personnel are required when performing this intervention. Indeed, some ICU personnel remain reluctant to use this technique given its risks and perceived effects on other care practices, such as increased sedation needs and reduced enteral feeding [25, 64]. Our finding that prone ventilation benefits primarily the most severely hypoxic patients, who are uncommonly cared for in many ICUs, challenges caregivers to implement this infrequently performed technique safely [64]. Such patients might be optimally served in higher-volume centres with more experience [65].

Our review has several strengths, including methods to reduce bias and a comprehensive set of relevant clinical and physiological outcomes. Trialists confirmed the primary data, which were analyzed using a predefined statistical plan. The primary hypothesis, that prone ventilation would be of benefit to patients with more severe hypoxemia, was prespecified, biologically plausible, and analyzed using appropriate tests for subgroup effects [66, 67]. However, subgroup analysis should, in general, be hypothesis-generating and confirmed in adequately powered randomized trials, and an ongoing trial targeting the enrolment of 500 patients with PaO2/FiO2 <150 mmHg [59] may provide more definitive data. Unfortunately, over half of the included trials to date were terminated due to slow enrolment. The trials included in this meta-analysis exhibited some methodological diversity (different inclusion criteria, different intervention intensity, etc.); however, for our primary comparison we used patient-level subgroup data, which helps balance out this diversity by producing similar distributions of these trial-specific characteristics in the severe and moderate hypoxic subgroups. In some trials, some of the patients crossed over from the supine to the prone ventilation group or from the prone to the supine group (either missing one or more prone ventilation sessions or discontinuing prone ventilation prior to meeting prone weaning criteria). For example, in the largest trial [17] many patients randomized to the supine ventilation group whose PaO2/FiO2 decreased to <100 mmHg were treated with prone position ventilation. With our intention-to-treat analysis (i.e., analyzing patients by the group to which they were randomized), such crossovers would tend to reduce measured treatment effects, particularly in the severely hypoxic subgroup. Despite this type of analysis, we still found a significant treatment effect in this subgroup, which strengthens the findings.

Our review has other limitations. First, most trials reported PaO2/FiO2 ratio, which is influenced by ventilator
settings and many other factors that are difficult to standardize. An alternative measure, oxygenation index, which incorporates mean airway pressure as a marker of the intensity of mechanical ventilation, was not measured in most trials. However, the finding that a PaO₂/FiO₂ threshold identifies patients whose survival improves with prone ventilation provides predictive validity to this measure and at a minimum demonstrates that prone ventilation may have different effects on patients with more severe hypoxemia compared with less severe hypoxemia. Our post hoc analysis suggested a PaO₂/FiO₂ threshold at which prone ventilation begins to be beneficial of approximately 140 mmHg. However, individual patient data meta-analysis [68] would be a more robust method for identifying such a threshold, since it can adjust for patient-level confounders. Individual patient data meta-analytic techniques would also permit the conduct of time-to-event analyses and exploratory analyses of the optimal intervention duration for prone ventilation. Finally, the small number of available trials, many of which accrued fewer than 30 events, reduced the precision of our pooled effect estimates and may have underestimated heterogeneity.

In summary, our systematic review and meta-analysis found that prone ventilation significantly reduced mortality in patients with severe acute hypoxemic respiratory failure but not in patients with less severe hypoxemia. Prone ventilation improved oxygenation but also increased the risk of adverse events. Although the finding of improved mortality in severely hypoxemic patients is based on a subgroup analysis, clinicians may justifiably consider prone ventilation in these patients.

Acknowledgments The authors would like to thank Ippei Watanabe and Hideyoshi Fujihara (see reference [44]) for providing additional trial data, Elizabeth Uleryk for assistance with the search strategy, and an anonymous reviewer for suggesting the post hoc subgroup analysis using a range of PaO₂/FiO₂ thresholds. Dr. Friedrich is a clinician–scientist of the Canadian Institutes of Health Research (CIHR). Dr. Curley was funded by the National Institutes of Health/National Institute of Nursing Research (NIH/NINR) (Grant No. RO1NR05336).

Conflict of interest statement Dr. Gattinoni received a fee of 1,500 USD 5 years ago for one meeting at KCI Medical Products headquarters, as a member of an advisory board. The other authors declare no financial or other conflicts of interest to disclose. None of the funding agencies had any involvement in the study. The authors declare that they had full control of all primary data and that they agree to allow the journal to review their data if requested.

Appendix: Literature search

The following databases were searched in OVID on November 14, 2009: MEDLINE (1950 to present), EMBASE (1980 to week 46, 2009), and Cochrane Central Register of Controlled Trials (fourth quarter 2009).

MEDLINE
1. (pron$ adj4 position$).mp.
2. clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs.
3. 1 and 2

EMBASE
4. (pron$ adj4 position$).mp.
5. random:.tw. or clinical trial:.mp. or exp health care quality/
6. 1 and 2

Cochrane Central Register of Controlled Trials
7. (pron$ adj4 position$).mp.

MEDLINE, 1,491 records
EMBASE, 807 records
CENTRAL, 385 records
Total records retrieved, 2,683
Number after duplicates manually removed, 1,870
Retrieved for more detailed evaluation, 52

Notes: "$" retrieves unlimited suffix variations. The “.mp.” extension includes the title, original title, and abstract fields in all databases, in addition to the subject heading of “prone position” in MEDLINE. Filters for MEDLINE [70] (line 2) and EMBASE [71] (line 5) are based on published sensitive strategies for retrieving randomized trials.

References


