Effect of prone positioning in patients with acute respiratory distress syndrome: A meta-analysis

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Objective: **To review the effectiveness of prone position as compared with supine position, with respect to mortality, improvement in oxygenation, number of days on mechanical ventilation, and ventilator-associated pneumonia.**

Data Source: **PubMed, EMBASE, Cochrane database, and a manual review of article bibliographies.**

Study Selection: **Randomized controlled trials comparing ≥6 hrs of prone position with supine position in adult patients with adult respiratory distress syndrome.**

Data Extraction: **Two reviewers independently performed assessment of abstracts and study quality. Data were combined in a meta-analysis using random-effect models.**

Main Findings: **Five studies were identified. We did not find any significant differences in intensive care unit mortality (three studies, 466 patients; odds ratio, 0.79; 95% confidence interval [CI], 0.45–1.39), 28- to 30-day mortality (three studies, 1,231 patients; odds ratio, 0.95; 95% CI, 0.71–1.28), and 90-day mortality (four studies, 1,271 patients; odds ratio, 0.99; 95% CI, 0.77–1.27). However, prone position showed significant reduction in mortality in patients with higher illness severity (two studies, 113 patients; odds ratio, 0.29; 95% CI, 0.12–0.70). Prone positioning also showed significant and persistent improvement in the Pa_{O_2}/F_{IO_2} ratio in early (12 hrs to 2 days) (four studies, 866 patients; weighted mean difference, 51.5; 95% CI, 6.95–96.05), intermediate (4 days) (three studies, 754 patients; weighted mean difference, 43.87; 95% CI, 13.86–73.88), and late (10 days) period (four studies, 833 patients; weighted mean difference, 24.89; 95% CI, 15.3–34.48). There were no significant differences in number of days on mechanical ventilation (two studies, 831 patients; weighted mean difference, −0.42 days; 95% CI, −1.56 to 0.72) or incidence of ventilator-associated pneumonia (three studies, 967 patients; weighted mean difference, 0.78%; 95% CI, 0.40–1.51).**

Conclusion: **Based on the results of this meta-analysis, prone position improves oxygenation in patients with adult respiratory distress syndrome, and in patients with higher illness severity, it also may reduce mortality. (Crit Care Med 2008; 36:603–609)**

Key Words: mechanical ventilation; prone position; acute respiratory distress syndrome; meta-analysis; oxygenation; acute lung injury

Acute respiratory distress syndrome (ARDS) is a diffuse heterogeneous lung disease that results in progressive hypoxemia because of ventilation/perfusion mismatching causing intrapulmonary shunt. It has diverse causes and is associated with high mortality and morbidity (1, 2).

Application of high F_{IO_2} and positive end-expiratory pressure required to maintain oxygenation may induce more damage to the injured lungs, termed *ventilator-induced lung injury*, and contributes to increased morbidity and mortality (3). Mechanisms by which mechanical ventilation induces or augments lung injury include overstretching of the lung and repeated opening and closing of small airways (shear stress phenomena) (4–6). This ventilator-induced lung injury will manifest as diffuse alveolar damage (7–9), with release of cytokines and bacterial translocation (10).

Patients with ARDS ventilated in the supine position develop atelectasis in the dependent regions of the lung (11). This may be due to lung edema, airway secretions, surfactant deficiency, and from cardiac and abdominal compression (12, 13). Perfusion to these regions is maintained, resulting in intrapulmonary shunt and severe hypoxemia.

Since 1974, when Bryan (14) proposed prone position (PP) to improve oxygenation, many studies have demonstrated its effect on gas exchange (15–22). The mechanisms responsible for this improvement in oxygenation are not completely understood. It may recruit atelectatic regions and minimize ventilator-induced lung injury when used early in the course of acute respiratory failure (23–25). Despite this improvement in oxygenation, studies with PP have not shown a clear survival benefit.

Therefore, we performed a meta-analysis to compare the effectiveness of PP with supine position (SP) with respect to mortality, improvement in oxygenation, number of days on mechanical ventilation, and the incidence of ventilator-associated pneumonia (VAP).

METHODS

Design. A comprehensive literature search was performed in PubMed, EMBASE, Cochrane Library, by hand searching bibliographies of retrieved articles, and by contacting the authors of relevant articles. In the Cochrane Library, we searched both the Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials.

The following keywords were used: "prone position" combined with "acute respiratory distress syndrome", "acute lung injury", "ARDS", "ALI", or "mechanical ventilation".

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The search was confined to randomized controlled trials with human adults. The search was performed in November 2006.

Two reviewers (AHA, CMM) independently selected the studies to be included in the review using the following inclusion criteria: adult mechanically ventilated intensive care unit (ICU) patients comparing PP and SP. PP had to be used for a minimum of 6 hrs. The study had to report at least one of the following outcomes: mortality, improvement in oxygenation, number of days receiving mechanical ventilation, and incidence of ventilator-associated pneumonia. With respect to mortality, we extracted ICU mortality, mortality at 28 days, and mortality at 90 days. Because the earliest included study had reported a benefit in the subgroup with higher illness severity, we also extracted this information if possible. Oxygenation was assessed as the absolute change in the Pa_{O_2}/F_{IO_2} ratio from baseline to early (12 hrs to 2 days), intermediate (day 4), and late (day 7–10) periods. If data were not available or could not be derived from the publication, we attempted to contact the corresponding author by e-mail.

Both reviewers assessed the methodologic quality of each included trial based on the method described by Jadad et al (26). In particular, reviewers examined details of the randomization methods, using four ratings for quality of allocation concealment (27): 1) adequate concealment of the allocation; 2) uncertainty about adequate concealment of allocation; 3) allocation definitely not adequately concealed; 4) allocation concealment not used.

Discrepancies in ratings were resolved through discussion between the reviewers.

Data Analysis. All data were entered and analyzed using RevMan (Review Manager, version 4.3.1 for Windows, Copenhagen, The Cochrane Collaboration, 2003). The synthesis of data were performed using a random effect model. For dichotomous outcomes, odds ratios (OR) were calculated. For continuous outcomes, weighted mean difference (WMD) was calculated. All effect measures are reported with 95% confidence intervals (CIs).

To assess heterogeneity of treatment effects across studies, I^2 statistics were computed. I^2 measures the extent of inconsistency among the studies results, and the outcome is interpreted as a percentage of total variation across studies that are due to heterogeneity rather than chance (28). A value of 0% indicates that all variability in effect estimates is due to chance rather than to heterogeneity. Larger values show that most of the variability is due to heterogeneity rather than chance. Due to the small number of studies, we did not perform any analysis for possible publication bias.

RESULTS

From the literature search, 63 studies were identified. Five of these fulfilled the inclusion criteria and included a total of 1,316 patients (Gattinoni et al. [29], Guerin et al. [30], Mancebo et al. [31], Papazian et al. [32], Voggenreiter et al. [33]). The other studies were excluded for various reasons (Fig. 1). Four studies compared sessions of variable times of ≥6 hrs of PP with SP (29, 30, 31, 33). One study compared a single session of PP with SP in combination with high-frequency oscillation ventilation (32).

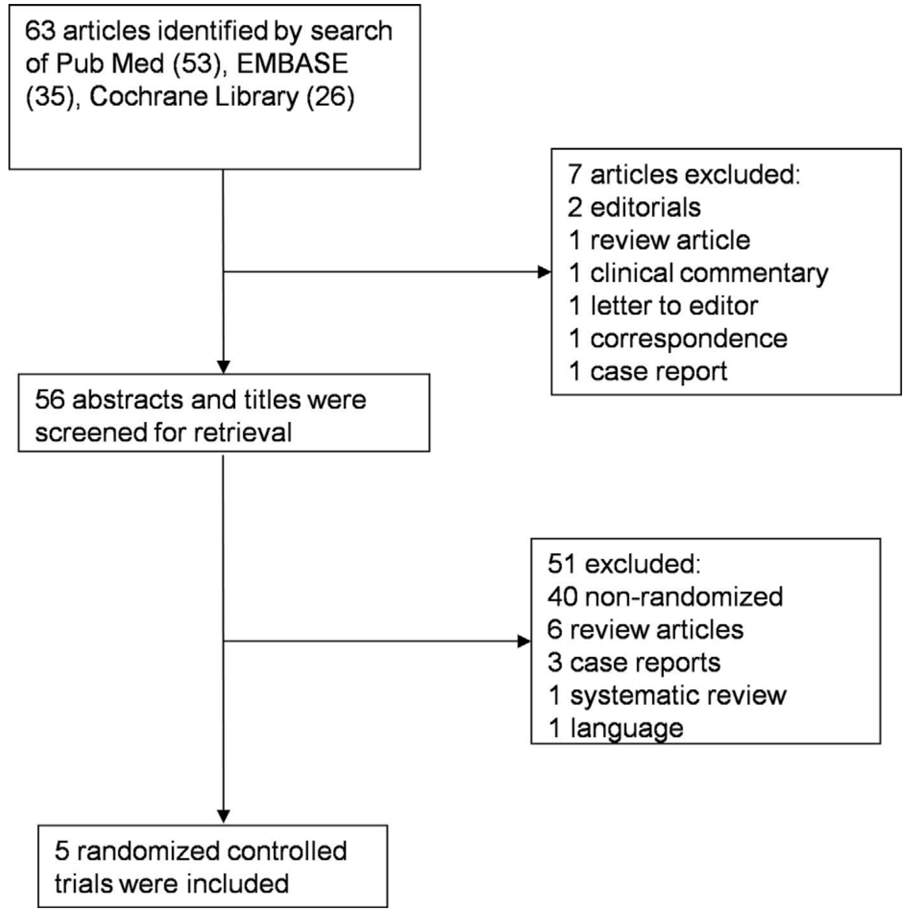

Figure 1. Literature search flow diagram.

The method of concealment for all included studies was ranked adequate (grade A) (Table 1). Two studies used central randomization (29, 33). Three studies performed concealment using sealed opaque envelopes (30–32). Treatment was not blinded due to the type of intervention. In one study (Guerin et al. [30]), 11 patients were excluded from the analysis (two participants were lost to follow-up, five patients due to secondary refusal to participate, three due to inclusion errors, and one had previously been enrolled in the study). Another study (Mancebo et al. [31]) excluded six patients (four patients lost to follow-up, and two patients had missing data). No patients were excluded from analysis in the other three studies (29, 32, 33).

Guerin et al. (30) allowed patients randomized to SP to cross over to PP based on physiologic variables chosen at the time of study design. They analyzed these patients in the originally assigned group (intention to treat).

Sample size varied from 39 to 780 patients in the included studies. Baseline characteristics of both groups in all the studies were not significantly different.

Mortality. Three studies reported ICU mortality (29, 31, 32) (Table 1, Fig. 2). There was no significant difference in ICU mortality for those patients treated with PP vs. SP (pooled OR, 0.79; 95% CI, 0.45–1.39). Three studies reported 28- to 30-day mortality (29, 30, 31). There were no significant differences in 28- to 30-day mortality (pooled OR, 0.95; 95% CI, 0.71–1.28). Four studies examined 90-day mortality (29, 30, 31, 33). There were no significant differences in mortality between the groups (pooled OR, 0.99; 95% CI, 0.77–1.27).

In *post hoc* analysis, the studies by Gattinoni et al. (29) and Mancebo et al.

Table 1. Studies on prone positioning in acute respiratory distress syndrome

Study	Gattinoni et al. (29), 2001	Guerin et al. (30), 2004	Mancebo et al. (31), 2006	Papazian et al. (32), 2005	Voggenreiter et al. (33), 2005
Patients, n	304	791	136	39	40
Quality[a]	A	A	A	A	A
Prone positioning					
Time after diagnosis	Varied	<24 hrs	<24 hrs	<24 hrs	Varied
Duration	7 hrs/day	8.6 hrs/day	20 hrs/day	12 hrs	11 hrs/day
ICU mortality rate (%)					
SP	73/152 (48.0)		35/60 (58.3)	5/13 (38.5)	
PP	77/152 (50.7)		33/76 (43.4)	3/13 (23.1)	
28- to 30-day mortality rate (%)					
SP	70/152 (46.1)	121/378 (32.0)	32/60 (53.3)		
PP	74/152 (48.7)	134/413 (32.4)	30/76 (39.5)		
90-day mortality rate (%)					
SP	84/152 (55.3)	160/378 (42.3)	32/60 (53.3)		3/19 (15.8)
PP	89/152 (58.6)	179/413 (43.3)	32/76 (42.1)		1/21 (4.8)
Mortality rate in SAPS II >50					
SP	16/33 (48.5)		9/11 (81.8)		
PP	9/47 (19.2)		15/22 (68.2)		
Early changes in oxygenation (SD)					
SP		27 (68.9)	10 (89.7)	4 (52.69)	37 (63.74)
PP		38 (67.7)	86 (79.5)	101 (53.3)	65 (74.81)
Intermediate changes in oxygenation (SD)					
SP		51 (71.38)	15 (84.5)		27.7 (78.9)
PP		77 (71.79)	83 (73.54)		71 (75.5)
Late changes in oxygenation (SD)					
SP	44.6 (68.2)	51 (66.98)	23 (90)		66.5 (89.1)
PP	63 (66.8)	78 (72.86)	67 (76.64)		80.7 (77.3)
Total ventilator days (SD)					
SP		14.1 (8.6)			33 (23)
PP		13.7 (7.8)			30 (17)
VAP rate (%)					
SP		91/378 (24.1)	9/60 (15)		17/19 (89.5)
PP		85/413 (20.6)	14/76 (18.4)		13/21 (61.9)

ICU, intensive care unit; SP, supine position; PP, prone position; SAPS II, Simplified Acute Physiology Score; VAP, ventilator-associated pneumonia.
[a]Quality, allocation concealment was adequate (A), unclear (B), inadequate (C), or not used (D).

(31) reported mortality for patients with SAPS II of >50. The study by Gattinoni et al. (29) showed a significant improvement in mortality at 10 days (19.4% for PP vs. 48.5% for SP [relative risk, 0.4; 95% CI, 0.19–0.85]). The study by Mancebo et al. (31) found a nonsignificant improvement in ICU mortality in this subgroup, with 68% (15 of 22 patients) for PP vs. 82% (nine of 11 patients) for SP. The pooled results showed a significant decrease in mortality in this subgroup (OR, 0.29; 95% CI, 0.12–0.70) (Fig. 3).

Oxygenation. Four studies reported changes in oxygenation (PaO_2/FIO_2 ratio) during the early period (30–33). The pooled results showed a statistically significant WMD of 51.5 (95% CI, 6.95–96.05) favoring the PP group (Fig. 4). Three studies reported oxygenation changes in the intermediate period (30, 31, 33). There was a significant improvement in oxygenation favoring the PP group, with a pooled WMD of 43.87 (95% CI, 13.86–73.88) (Fig. 4). Four studies reported oxygenation changes in the late period (29, 30, 31, 33). The pooled results showed a significant improvement in oxygenation, with a WMD of 24.89 (95% CI, 15.3–34.48) favoring the PP group (Fig. 4, Table 1).

Total Ventilator Days. Two studies reported the total number of days on ventilator (30, 33) (Table 1). There was no significant difference in length of ventilator days between PP and SP groups (pooled WMD, −0.42 days; 95% CI, −1.56 to 0.72) (Fig. 5).

Incidence of VAP. Three studies reported VAP as a complication (30, 31, 33) (Table 1). There was no significant difference in the incidence of VAP in PP groups as compared with SP groups, with an overall WMD of 0.78% (95% CI, 0.40–1.51) (Fig. 6).

DISCUSSION

In this systematic review and meta-analysis, we identified five randomized controlled studies that assessed the effect of PP as compared with SP on mortality and improvement in oxygenation in patients with ARDS. Overall, PP did not reduce mortality significantly, but it does improve oxygenation. Within this population, PP may have a positive effect on mortality in patients with higher illness severity.

Individually, each of these studies had some limitations, primarily related to sample size and power. Two studies were stopped prematurely because the caregivers were unwilling to continue randomizing patients to PP (29) or due to decreased motivation of investigators and limited funding (31), and two studies had small sample sizes (32, 33). One study allowed crossover of patients from SP to PP (30), although they did use an intention-to-treat analysis. Two studies (29, 30) applied higher tidal volumes than is current practice because these studies were done before publication of the ARDSNet study (34).

Although our review did not find an overall improvement in survival, we did find that the subgroup of patients with higher severity of illness had reduced mortality in the PP group as compared

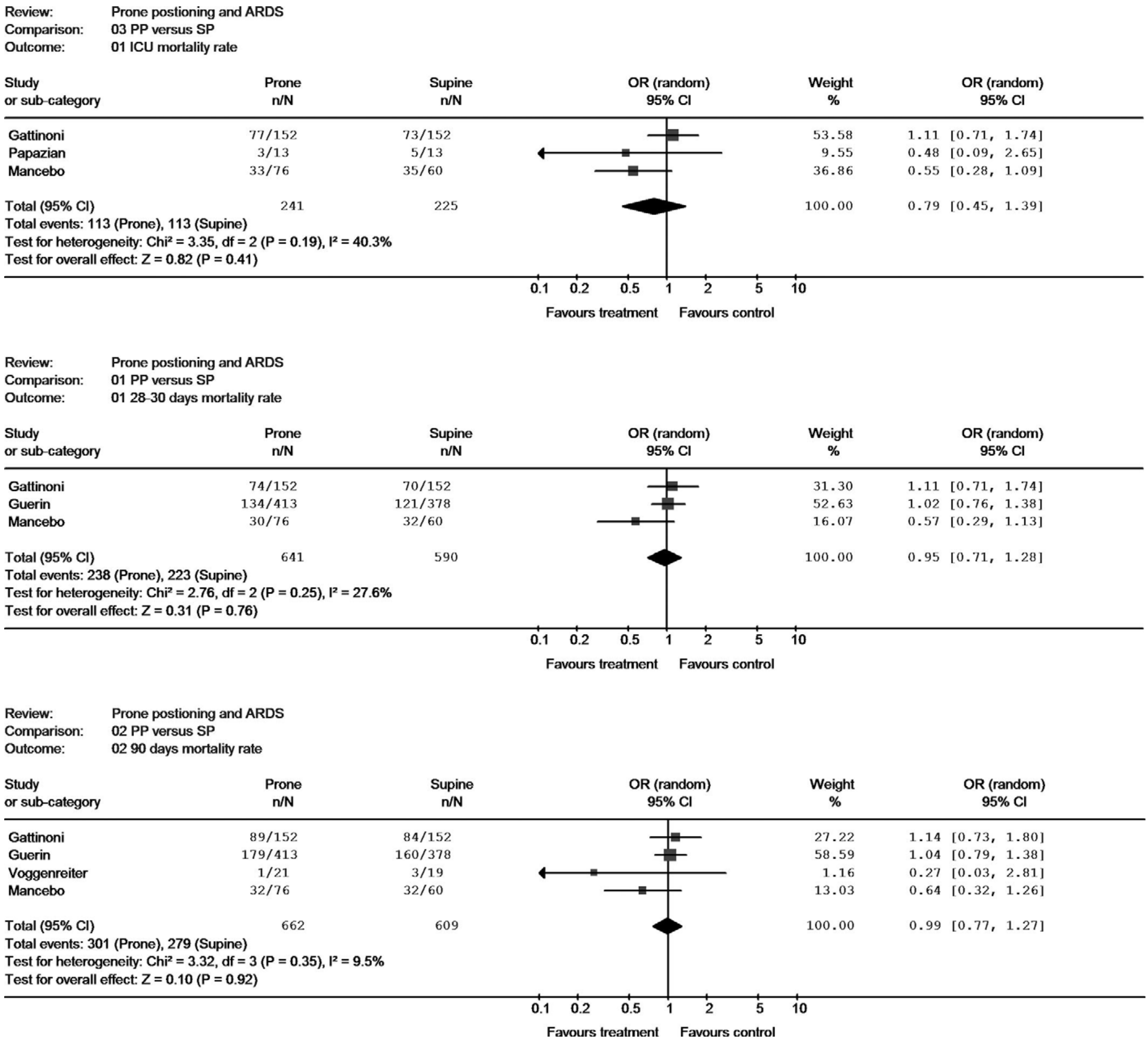

Figure 2. Comparison of prone position (*PP*) and supine position (*SP*) for intensive care unit (*ICU*) (*top*), 28- to 30-day (*middle*), and 90-day (*lower*) mortality rates. Data are shown for each study for prone and supine groups as n (number of deaths) over N (number in group). *ARDS*, acute respiratory distress syndrome; *OR*, odds ratio; *CI*, confidence interval.

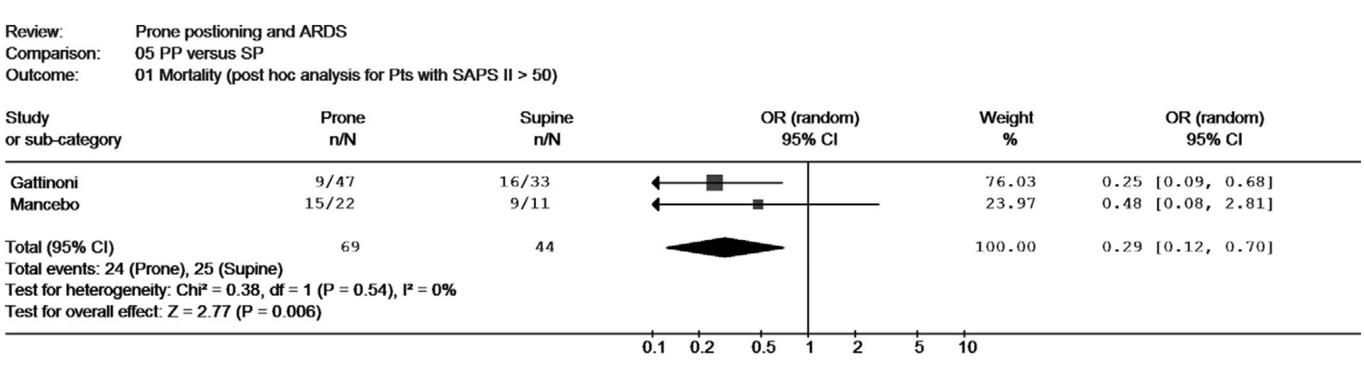

Figure 3. *Post hoc* analysis of comparison of prone position (*PP*) and supine position (*SP*) regarding mortality of subgroup with Simplified Acute Physiology Score (SAPS) II of >50. *ARDS*, acute respiratory distress syndrome; *Pts*, patients; *OR*, odds ratio; *CI*, confidence interval.

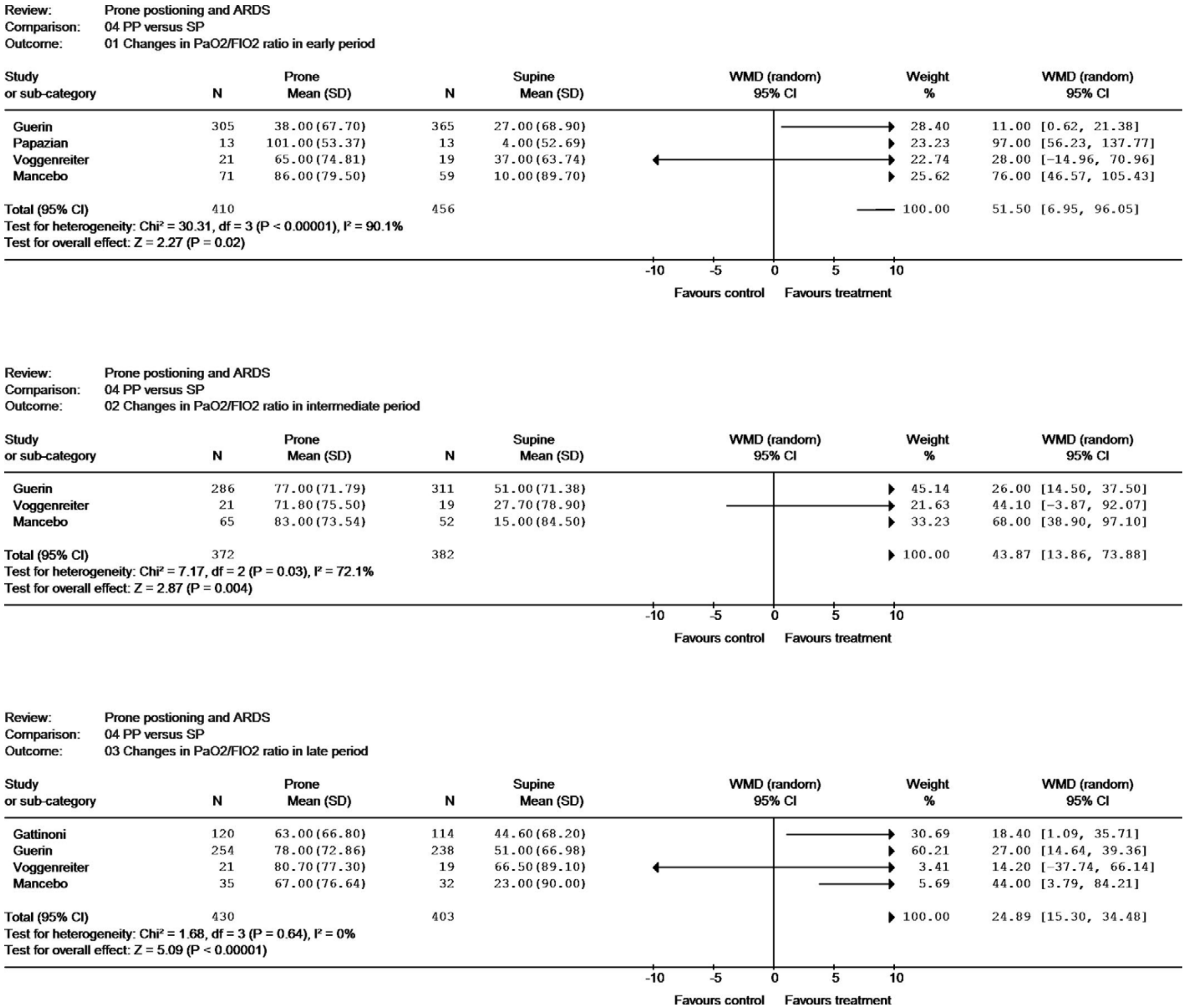

Figure 4. Comparison of prone position (*PP*) and supine position (*SP*) for the oxygenation improvement in early (*top*), intermediate (*middle*), and late (*back*) periods. In contrast to the other figures with rates, the direction for an improvement in oxygenation with supine position favored is to the right (positive values). *ARDS*, acute respiratory distress syndrome; *WMD*, weighted mean difference; *CI*, confidence interval.

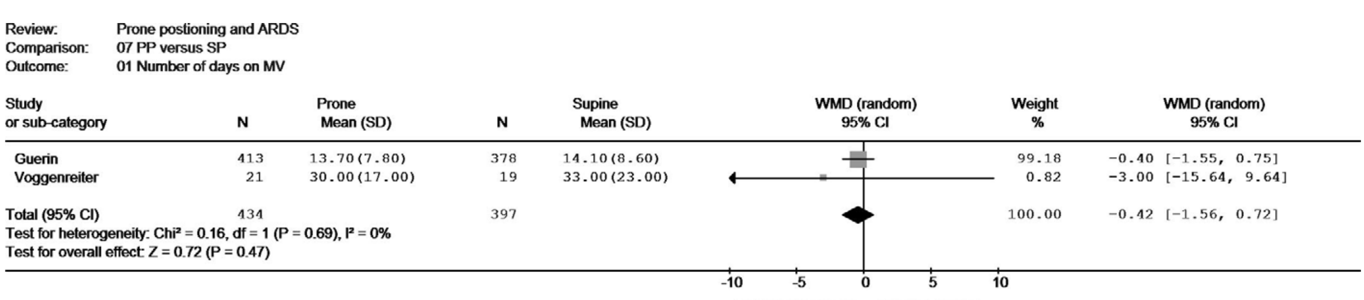

Figure 5. Comparison of prone position (*PP*) and supine position (*SP*) regarding number of days on mechanical ventilation (*MV*). *ARDS*, acute respiratory distress syndrome; *WMD*, weighted mean difference; *CI*, confidence interval.

with the SP group (OR, 0.29; 95% CI, 0.12–0.70) (29, 31). Limitations of this observation are that it is a subgroup analysis, with incomplete data available to confirm similarity of the PP and SP subgroups at baseline. Also, mortality was reported at 10 days for one study and at ICU separation for the other study.

Other issues related to the validity of this meta-analysis relate to the possible publication bias and heterogeneity between studies. Our literature review was

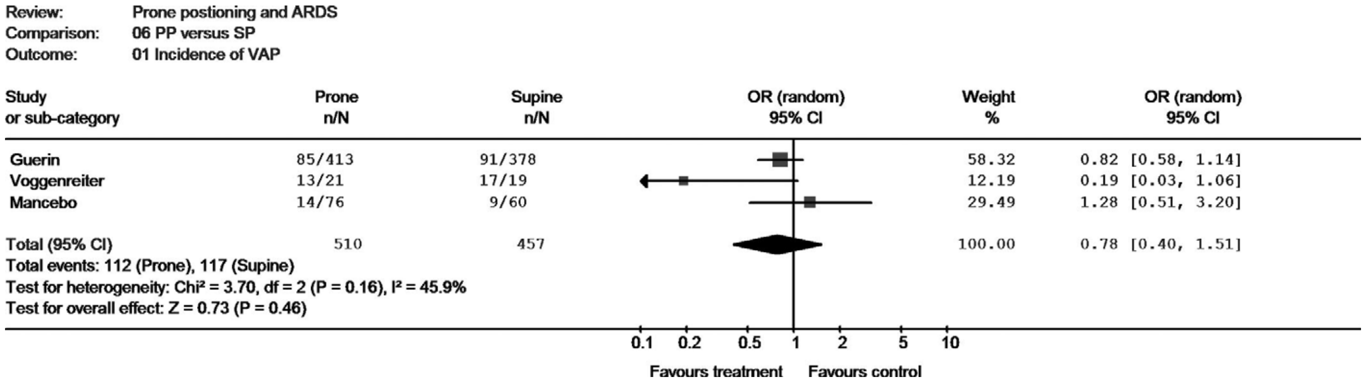

Figure 6. Comparison of prone position (*PP*) and supine position (*SP*) regarding incidence of ventilator-associated pneumonia (*VAP*). *ARDS*, acute respiratory distress syndrome; *WMD*, weighted mean difference; *CI*, confidence interval.

extensive, but the number of studies included is too small to examine using funnel plots to detect publication bias. We used random-effects models to minimize the effect of study heterogeneity, which was not statistically significant in the analyses but may be present, as indicated by a high I^2 statistic for ICU mortality (40%) and by early (90%) and intermediate (72%) changes in oxygenation.

There was clinical heterogeneity in the studies that might account for this statistical heterogeneity and could have affected the results. Three studies applied PP for short periods, ranging from 7 to 11 hrs/day and for up to 10 days (29, 30, 33), and another study used a single 12-hr period of prone ventilation (32). It has been shown in a nonrandomized study that PP applied for longer periods of about 20-hrs has persistent improvement in oxygenation (35), as compared with other studies that used PP for 6–12 hrs (36, 37). One study was limited to ARDS in trauma patients (33). The cause of ARDS may contribute to the results because the response to PP is probably better in secondary causes of ARDS because of diffuse distribution of densities and atelectasis that make it more responsive to recruitment (35, 38–40). Although, we did not examine the interval between onset of ARDS and use of PP, the optimal response and beneficial effect of PP may occur during the early edematous phase of ARDS, when atelectasis and lung edema predominate (41).

All the studies in our review showed significant improvement in oxygenation during the early period of randomization but with variable persistence in individual studies. Our pooled results demonstrated a statistically significant improvement in oxygenation up to 10 days, although the clinical relevance is questionable because the WMD (the absolute change in PaO_2/FIO_2) decreased from 51 at the early period to 25 at 10 days.

VAP continues to be the most common nosocomial infection in the ICU (42–44). Patients who acquire VAP have worse outcomes and have longer ICU and hospital stays (42–46). Many of the human and experimental studies showed a reduced incidence of VAP with PP (47, 48). This could be due to better drainage of airway secretions, reopening atelectatic units in the dorsal region of the lungs, which decreases the favorable media for infection, and decreased bacterial translocation (49). However, this meta-analysis did not show any significant changes in the incidence of VAP with PP.

CONCLUSION

This systematic review and meta-analysis showed beneficial effects of PP on oxygenation in patients with ARDS. Despite the improvement in oxygenation, PP did not improve survival, except perhaps in the more severely ill patients. Because our review of these studies did not identify any major adverse effects of PP, and it is a relatively simple and inexpensive intervention, it should be considered early in the management of patients with ARDS and high illness severity. However, definitive recommendations require that this hypothesis be examined in a properly designed prospective trial. If the pooled OR of 0.29 in this subgroup, with a combined mortality of about 60%, were used to plan a randomized trial, the sample size required is 52 patients in each group.

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