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BRIEF REPORT

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Prone positioning in acute respiratory distress syndrome: a multicenter randomized clinical trial

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Abstract *Objective:* We examined the effect on survival of prone positioning as an early and continuous treatment in ARDS patients already treated with protective ventilation. *Design and setting:* Open randomized controlled trial in 17 medical-surgical ICUs. *Patients:* Forty mechanically ventilated patients with early and refractory ARDS despite protective ventilation in the supine position. *Interventions:* Patients were randomized to remain supine or be moved to early (within 48 h) and continuous ($\geq$ 20 h/day) prone position until recovery or death. The trial was prematurely stopped due to a low patient recruitment rate. *Measurements and results:* Clinical characteristics, oxygenation, lung pressures, and hemodynamics were monitored. Need for sedation, complications, length of MV, ICU, and hospital stays, and outcome were recorded. PaO_2/FIO_2 tended to be higher in prone than in supine patients after 6 h (202 ± 78 vs. 165 ± 70 mmHg); this difference reached statistical significance on day 3 (234 ± 85 vs. 159 ± 78). Prone-

related side effects were minimal and reversible. Sixty-day survival reached the targeted 15% absolute increase in prone patients (62% vs. 47%) but failed to reach significance due to the small sample. *Conclusions:* Our study adds data that reinforce the suggestion of a beneficial effect of early continuous prone positioning on survival in ARDS patients.

Keywords Prone positioning · Mechanical ventilation · Acute respiratory distress syndrome · Randomized controlled trial · Survival · Acute lung injury

Introduction

Acute respiratory distress syndrome (ARDS) remains one of the most devastating ICU conditions, due not only to the high mortality rate but also to the high resource consumption and the long-term functional and neuropsychological consequences [1]. Despite extensive knowledge gained about the pathophysiology of the syndrome, targeted treatments have been elusive. Thus the ICU approach largely consists of supportive treatment and avoiding the side effects of invasive therapies such as mechanical ventilation, sedatives, paralytic agents, and oxygen [2–7]. Reducing tidal volume demonstrated a survival advantage in the milestone study of the ARDS Network [8] and is now a common clinical guideline. However, higher positive end-expiratory pressure (PEEP) failed to show significant benefits for these patients [9].

A different strategy for improving ventilatory treatment with suggested benefits for hypoxemic patients is prone positioning. Physiological studies agree in describing improved oxygenation after prone positioning in most patients [10–14], but randomized clinical trials have failed to prove significant reductions in mortality with prone positioning [15–17]. Nevertheless, we cannot rule out the effectiveness of prone positioning due to severe methodological faults in these studies. Some studies positioned patients prone for a few hours per day and for only a few days, irrespective of the clinical effect obtained. Selecting patients with mild respiratory failure may explain the nonsignificant results in others. A recent randomized controlled trial by Mancebo et al. [18] applying prone positioning in severe ARDS patients as an early and continuous treatment found a clinically relevant 25% relative reduction in mortality; however, the small sample size precluded the statistical significance of these results.

We hypothesized that prone positioning may have beneficial effects when used early and continuously in ARDS patients. We aimed to conduct a randomized controlled trial with enough power to determine the survival advantage of prone positioning in ARDS patients.

Material and methods

An open randomized controlled trial was started in September 2003 in 17 Spanish ICUs after approval of every center's ethics committee. Inclusion criteria were: intubated adult patients within 48 h of ARDS diagnosis as defined by the Consensus Conference [19]. Although ventilatory settings, mainly PEEP, were not protocolized before ARDS diagnosis, protective ventilation was a widely established clinical approach. Exclusion criteria were: severe hypotension needing vasopressors (cardiovascular SOFA score 3 or –4), traumatic brain injury, unstable pelvic or spinal column fractures precluding safe prone positioning, moribund condition, and enrollment in another trial. After informed consent was obtained, patients were randomized via a centralized call center that hosted the computer-generated random sequence. Randomization was stratified according to the level of severity (Simplified Acute Physiology Score, SAPS II ≤ 49 vs. > 49, as suggested by Gattinoni et al. [17]) and the type of ARDS (pulmonary vs. extrapulmonary).

After randomization a protocolized ventilatory pattern was set using tidal volume of 6–8 ml/kg ideal body weight with PEEP based on FIO_2 requirements as in the ARDS Network [8] study. Plateau pressure (Pplat) was limited to 30 cmH_2O and respiratory rate up to 35 to achieve normocapnia as far as possible. After 1 h with these settings the selected position, prone or supine, was applied and maintained up to 20 h per day. Prone patients were turned supine when oxygenation improved for longer than 12 h, i. e., PaO_2/FIO_2 ratio higher than 250 at PEEP of 8 cmH_2O or lower. Crossover was allowed only in cases of life-threatening hypoxemia after 6 h in the position selected by the protocol. Sedation and weaning were also protocolized (see Electronic Supplementary Material). The clinical characteristics of the patients at the time of randomization shown in Table 1 confirm a well-balanced distribution between supine and prone groups. After the protocolized ventilatory adjustment, oxygenation improved, mainly due to the higher PEEP applied accordingly with the ARDS Network table, but no patients escaped the inclusion criteria.

Data collection included clinical characteristics, severity score (SAPS II and Lung Injury Score), blood gases, hemodynamics and lung mechanics, and Sequential Organ Failure Assessment (SOFA) score. Complications attributable to prone positioning were specifically recorded. Our primary end-point was 60-day survival. Secondary end-points were length of mechanical ventilation and of ICU stay.

Based on an expected 60% mortality in severe ARDS patients, the estimated sample size required to confirm a 15% absolute reduction in mortality with an α error of 0.05 and a power of 80% was 250. At the end of the first

Table 1 Clinical characteristics of the patients before randomization and protective ventilation adjustment

	Supine ($n = 19$)	Prone ($n = 21$)	p-value
Age (years)	55.3 ± 14.6	53.9 ± 17.9	0.8
Sex: female	6 (31%)	9 (43%)	0.5
SAPS II	37.2 ± 11.5	39.4 ± 13.9	0.6
SAPS II > 49	2 (10%)	4 (19%)	0.6
Lung Injury Score	3.1 ± 0.4	3.1 ± 0.4	0.9
Pulmonary ARDS	13 (68%)	13 (62%)	0.7
Ideal body weight (kg)	62.3 ± 9.4	61.5 ± 12.6	0.8
Immune suppression	12 (63%)	11 (52%)	0.5
SOFA (points)	9.0 ± 3.3	9.5 ± 3.2	0.6
Previous noninvasive ventilation	6 (31%)	8 (38%)	0.7
Respiratory variables			
At randomization			
PaO_2 (mmHg)	98.9 ± 34.8	93.4 ± 34.8	0.6
FIO_2	0.84 ± 0.18	0.85 ± .19	0.8
PaO_2/FIO_2 (mmHg)	122.3 ± 39.9	113.8 ± 42.6	0.5
$PaCO_2$ (mmHg)	46.7 ± 8.8	46.3 ± 14.1	0.9
Respiratory rate (breaths/min)	19.3 ± 5.1	19.9 ± 4.2	0.7
Tidal volume (ml/kg)	9.2 ± 2.2	8.6 ± 2.1	0.4
PEEP (cmH_2O)	11.4 ± 3.8	11.1 ± 4.1	0.8
Plateau airway pressure (cmH_2O)	31.7 ± 5.2	30.4 ± 6.1	0.5
Arterial pH	7.30 ± .07	7.33 ± .12	0.3
After ventilatory adjustment			
PaO_2 (mmHg)	120.0 ± 72.2	104.8 ± 39.8	0.4
FIO_2	0.77 ± .16	0.72 ± .18	0.4
PaO_2/FIO_2 (mmHg)	157.8 ± 83.8	153.2 ± 59.4	0.8
$PaCO_2$ (mmHg)	50.6 ± 12.9	48.1 ± 11.2	0.5
Respiratory rate (breaths/min)	25.2 ± 6.2	25.5 ± 7.0	0.9
Tidal volume (ml/kg)	7.1 ± 1.1	7.4 ± 1.1	0.4
PEEP (cmH_2O)	14.2 ± 4.4	12.1 ± 3.1	0.1
Plateau airway pressure (cmH_2O)	29.9 ± 3.9	28.5 ± 4.7	0.3
Arterial pH	7.29 ± .08	7.31 ± .10	0.5

year, only 42 patients had been enrolled, and the rate of enrollment was steadily dropping, and for this reason the Steering Committee decided to stop the study prematurely. One patient was lost in each group, and therefore a total of 40 patients (19 supine, 21 prone) were evaluated. Two supine patients crossed over to prone positioning in the first week, but they died on days 4 and 32, respectively. Variables were compared by analysis of variance with position as the grouping variable and differences at $p \leq 0.05$ considered statistically significant. The time course of respiratory variables in the two groups was compared using two-way analysis of variance for repeated measures.

Results

Patients turned prone demonstrated an apparent increase in PaO_2/FIO_2 within 6 h (202 ± 78 vs. 165 ± 70 mmHg, $p = 0.16$), and this increase reached statistical significance on day 3 (234 ± 85 vs. 159 ± 78, $p = 0.009$) and at lower PEEP (Fig. 1; see ESM). No clinically significant trends were detected in the need for vasoactive or sedative drugs during the study. Clinically relevant complications were minimal (Table 2; see ESM), although pressure sores were very common in prone patients but were always reversible without significant sequelae. Outcome variables are presented in Table 2. No patients died in the ward or within the 60-day interval after ICU discharge. A 15% reduction in mortality was observed in the prone group compared with supine (38% vs. 53%); however, although this difference fits the projected survival advantage, it did not reach statistical significance due to the small sample.

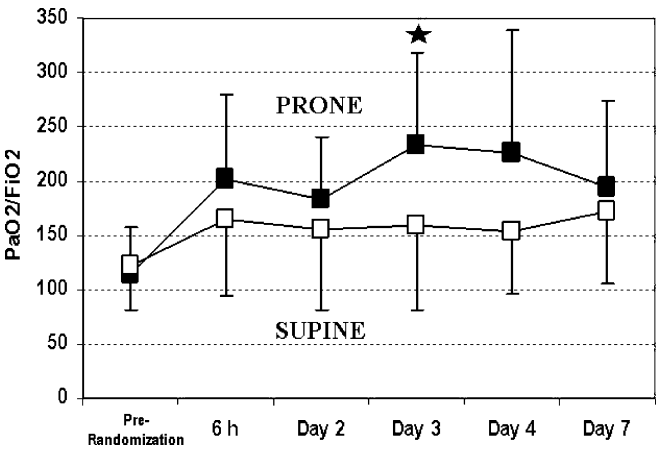

Fig. 1 Mean and SD of PaO_2/FIO_2 in prone and supine groups. The difference did not reach statistical significance until day 3

Table 2 Outcome variables

	Supine ($n = 19$)	Prone ($n = 21$)	p-value
60-day mortality	10 (53%)	8 (38%)	0.3
ICU length of stay (days)	17.5 ± 16.1	14.7 ± 9.7	0.5
Survivors	11.3 ± 7.6	15.9 ± 11.1	0.3
Nonsurvivors	23.0 ± 19.9	12.6 ± 7.2	0.2
Mechanical ventilation length (days)	15.7 ± 16.9	11.9 ± 9.2	0.5
Survivors	7.6 ± 7.6	12.0 ± 10.6	0.3
Nonsurvivors	23.0 ± 19.9	11.9 ± 6.9	0.2
Hospital stay (days)	25.5 ± 17.4	31.3 ± 26.4	0.4
Pneumothorax	1 (5%)	0 (0%)	0.5
Unplanned extubation	1 (5%)	1 (5%)	1.0
Ventilator associated pneumonia	1 (5%)	3 (14%)	0.6

Discussion

The main result of our aborted trial is that the possible survival advantage of prone positioning applied early and continuously in ARDS patients cannot be dismissed and that a new trial with adequate financial support is warranted.

Despite substantial knowledge about the physiological effects of prone positioning in acute respiratory failure only four trials with survival as the major outcome end-point have investigated its use in adults. One study focused on trauma patients [16], two on acute lung injury of varied severity [15, 17], and the fourth on ARDS patients [18]. Moreover, the intensity of treatment (the duration of prone positioning each day and the number of days of treatment) was different each study. We followed the strategy of Mancebo et al. [18] with continuous treatment with very short periods of supine positioning to allow for nursing care and diagnostic procedures, whereas the other studies used prone positioning for periods of only about 6 h or discontinued prone positioning after the first week. Oxygenation in our patients only showed a trend to improvement after 6 h in the prone position, but a statistically significant improvement was evident by day 3, reinforcing the idea that short periods of prone positioning may be insufficient to prove efficacy in patients that would otherwise be classified as responders [11].

The major weakness of our study was the very low recruitment of patients that forced the decision to stop prematurely. The main reasons for our low recruitment rate were medical contraindications of prone positioning and the narrow enrollment period as well as competition from industry-sponsored trials in acute lung injury and septic patients. Mancebo et al. [18] reported the same difficulties in recruitment as the main reason their study failed to attain the power to demonstrate statistically significant differences despite clinically impressive reductions in mortality with prone positioning. Thus our findings should not be regarded as definitively negative as they can be used in future meta-analyses exploring the true effect of prone in ARDS patients.

Our study population consisted of two-thirds of patients with pulmonary ARDS and one-third with extrapulmonary ARDS; this case mix is common in medical-surgical ICUs [18]. The severity of the patients' illness also warrants discussion. Some investigators relate the beneficial effects of treatment in any disease to the mortality rate of the control group, with illnesses with high mortality, as in our case, being more likely to demonstrate benefits [20]. A post-hoc analysis of the Gattinoni et al. [17] data showed that only patients with the most severe forms of ARDS (SAPS II > 49) benefited from prone positioning. This was not the case in the Mancebo et al. [18] study, mainly because the group with SAPS II less than 49 also benefited from prone positioning. Despite adequate block randomization in our study, with 10% of patients having SAPS II higher than 49, the small sample precludes any analysis about a differential effect of prone positioning in this population. Whether switching to the prone position early in the course of ARDS can avoid further ventilator-induced lung injury is yet to be demonstrated, but the lack of efficacy of late prone positioning as a rescue therapy in patients randomized to supine positioning suggests that prone positioning should be applied early to be efficacious.

Our low rate of complications attributable to prone positioning, despite our small sample size, agrees with the previously reported clinical trials [15–18]. We conclude that our study adds data that reinforce the suggestion of a beneficial effect of early continuous prone positioning on survival in ARDS patients.

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