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REVIEW

Mortality in mechanical ventilation in prone position in patients with acute respiratory distress syndrome

Mortalidad en ventilación mecánica en posición prono en pacientes con síndrome de distrés respiratorio aguda

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ABSTRACT

Introduction: prone ventilation has been shown to improve oxygenation and lung mechanics in patients with acute respiratory distress syndrome, but I consider it necessary to delve deeper into the relationship between the prone position and mortality.
Objectives: to evaluate whether the prone position decreases the risk of mortality in adult patients with acute respiratory distress syndrome vs. supine ventilation, in a global and segmented manner, as well as to know the main adverse effects related to it.
Material and methods: A meta-analysis of randomized controlled clinical trials comparing patients in the prone vs. supine position was performed with a search in Pubmed, Embase, Cochrane Library and LILACS, and mortality, hospital stay, days of mechanical ventilation and adverse effects were evaluated.
Results: seven randomized controlled clinical trials were included in the analysis. The prone position showed a non-significant tendency to decrease mortality when analyzed globally. When stratified by subgroups, a significant decrease in the risk of mortality was found in patients: 1) ventilated with low tidal volume, 2) prolonged prone position, and 3) established before 48 hours of disease progression in severe hypoxemia. The adverse effects related to prone position were the development of pressure ulcers and orotracheal tube obstruction.
Conclusion: prone position ventilation is a safe strategy and reduces mortality in patients with severe oxygenation impairment. It should be established early, for prolonged periods, and associated with a protective ventilation strategy.

Keywords: Respiratory Distress Syndrome; Adult; Prone Position; Meta-Analysis.

RESUMEN

Introducción: la ventilación en posición prona ha demostrado mejorar la oxigenación y la mecánica pulmonar en pacientes con síndrome de dificultad respiratoria aguda pero considero necesario profundizar sobre la relación entre la posición prono y la mortalidad.
Objetivos: evaluar si la posición en prono disminuye el riesgo de mortalidad en pacientes adultos con síndrome de distres respiratorio agudo vs. ventilación en posición supina, de manera global y segmentada así como también conocer los principales efectos adversos relacionados con la misma.
Método: se realizó un metaanálisis de ensayos clínicos controlados aleatorizados que compararon pacientes en posición prona vs. Supina con búsqueda en Pubmed, Embase, Cochrane Library y LILACS.y se evaluó la mortalidad, estancia hospitalaria, días de ventilación mecánica y efectos adversos.
Resultados: siete ensayos clínicos controlados aleatorizados fueron incluidos en el análisis. La posición prono

mostró una tendencia no significativa a disminuir la mortalidad al analizarlo de manera global. Al estratificar por subgrupos se encontró una disminución significativa en el riesgo de mortalidad en pacientes: 1) ventilados con volumen corriente bajo, 2) pronación prolongada y 3) instauración antes de 48h de evolución de la enfermedad en hipoxemia severa. Los efectos adversos relacionados con la pronación fueron el desarrollo de úlceras por presión y la obstrucción del tubo orotraqueal.
Conclusión: la ventilación en posición prono es una estrategia segura y disminuye la mortalidad en los pacientes con compromiso severo de la oxigenación, debe ser instaurada tempranamente, durante periodos prolongados y asociada a una estrategia de ventilación protectora.

Palabras clave: Síndrome de Dificultad Respiratoria del Adulto; Posición Prona; Metaanálisis.

INTRODUCTION

Clinical studies have shown that patients with acute respiratory distress syndrome (ARDS) account for approximately 5 % of all hospitalized patients on mechanical ventilation.[1,2,3,4,5,6] Most studies have shown that patients with mild ARDS (PaO2/FiO2 200-300) account for only 25 % of cases, with the remaining 75 % corresponding to patients with moderate or severe ARDS.[7,8] ARDS is associated with a hospital mortality rate of approximately 40 %.[9] Mortality varies according to the severity of the oxygenation deficit. In the Berlin clinical definition study (2012), mortality was 27 % in patients with mild ARDS, 32 % in moderate ARDS, and 45 % in those with severe ARDS.[10] Although deterioration in oxygenation is a risk factor for mortality in ARDS, patients generally die from multiple organ failure, and only a minority (13-19 %) die from refractory hypoxemia.[11,12] Although mortality has declined in recent decades (due to protective ventilation and limiting plateau pressure), other strategies or treatments must be found to reduce mortality significantly.

Mechanical ventilation in the prone position has been used for several decades in patients with ARDS to improve oxygenation.[12,13,14] It is now clearly recognized that pronation is associated with significantly enhanced oxygenation indices compared to the supine position; the prone position has also been found to reduce ventilation-associated lung injury.[15] Several clinical trials have been conducted to extrapolate these results to the clinical setting. Still, none have positively impacted patient survival or other aspects, such as oxygenation and reduced risk of injury.[16,17] Meta-analyses and systematic reviews have only suggested a trend toward lower mortality in patients with severe oxygenation compromise when in the prone position.

In recent years, with the COVID-19 pandemic, influenza A (H1N1), and an increase in cases of atypical pneumonia leading to distress, changes have appeared in the pronation strategy and patient inclusion criteria.[17,18,19] The real impact of pronation on mortality, the ventilation strategies to be used, and which patient groups benefit from prone positioning need to be determined.

What is the real impact of prone positioning on mortality in patients with ARDS, and what clinical characteristics determine a better response to this ventilation strategy?

To evaluate the impact of mechanical ventilation in the prone position on mortality and clinical outcomes in patients with acute respiratory distress syndrome (ARDS), especially those with severe oxygenation compromise, considering recent changes in inclusion criteria and ventilation strategies.

METHOD

Meta-analysis of randomized controlled trials, analyzing selected articles from the specific search that meet the inclusion criteria:

- Randomized controlled trials comparing mechanical ventilation in the prone position vs. conventional mechanical ventilation in the supine position in patients who met the criteria for ARDS according to the latest consensus in 2012.
- Patients classified as having acute lung injury (PaO2/FiO2 between 200-300 mmHg) were also included.
- Patients over 16 years of age

Excluding articles that met any of the following exclusion criteria:

- Studies that evaluated a pediatric population (<16 years) were excluded.
- Studies conducted in animals or used APRV ventilation, VAFO, and inhaled nitric oxide.
- Inconclusive studies

The titles and articles identified in the search were screened, and studies that met the inclusion criteria described were selected. Information about the study design, randomization method, participant characteristics, inclusion and exclusion criteria, interventions, and outcomes was extracted. Data from the included studies

were analyzed qualitatively and quantitatively by population, intervention, and outcome. After data collection, statistical calculations, tables, and graphs were used to establish the predominant outcome in the studies analyzed.

RESULTS

Twenty-two references were thoroughly reviewed, seven meeting the study's inclusion criteria.

The total number of patients was 2 119, of whom 1 088 were ventilated in the prone position and 1 031 in the supine position. The severity of the disease and the risk of mortality assessed by SAPS II were similar in the seven studies. All included studies were randomized controlled clinical trials and were analyzed first.

Overall mortality: In the prone group, there were 456 events (41,9 %), and in the supine group, there were 483 (46,8 %), showing a trend in favor of the prone group but without statistical significance with an OR of 0,76 (95 % CI: 0,54-1,06). We then stratified the results of the studies according to:

Mortality and protective ventilation: When evaluating the association between mortality and tidal volume administered, we stratified into two groups based on the use of low tidal volume as part of a protective ventilation strategy and those who used high tidal volume, which appears to be related to the development of ventilation-associated lung injury. Four studies used a tidal volume ≤8cc/kg of ideal weight, showing a 36 % decrease in the risk of mortality, a finding that was not observed when using a tidal volume >8cc/kg with an OR: 1,01 (95 % CI: 0,77-1,32).

Mortality and number of hours per day in the prone position: All studies reported and analyzed data on the duration of prone positioning. In four studies, the number of hours per day increased (18 hours on average), which translated into a significant decrease in the risk of the event in favor of the group of patients who were pronated for more than 12 hours with an OR: 1,01; (95 % CI: 0,77-1,32).

Mortality and onset of pronation: Just as the number of hours per day of pronation is important, so too does the timing of pronation appear to be important. Greater benefit is found when patients are pronated within the first 48 hours after the start of mechanical ventilation, with an OR of 0,49 (95 % CI: 0,35-0,68).

Mortality and severity of hypoxemia: The studies were stratified according to the severity of hypoxemia, which was classified as moderate (PaO2/FiO2: 100-200) and severe. Five studies reported patients with moderate hypoxemia, and two studies reported severe hypoxemia. The group with severe oxygenation compromise showed a clear benefit with pronation, with an OR of 0,51 (95 % CI: 0,36-1,25).

Prone position, intensive care stay, and days on mechanical ventilation: Four studies reported intensive care stay, and five studies recorded days on mechanical ventilation. No differences in outcomes were found between the two groups studied.

Prone position and adverse effects: Pressure ulcers (34 %) were the most frequently reported adverse event, followed by ventilator-associated pneumonia (21,4 %), endotracheal tube obstruction (14,6 %), accidental extubation (10,9 %), loss of venous access (10,9 %), pneumothorax (5,8 %), and endotracheal tube displacement (3,7 %). The prone position was associated with a higher and statistically significant risk of orotracheal tube obstruction (OR: 2,19; 95 % CI: 1,55-3,09) and the development of pressure ulcers (OR: 1,53; 95 % CI: 1,21-1,94). No differences were found in the other events described. No differences.

DISCUSSION

The study's primary objective was to evaluate the impact of mechanical ventilation in the prone position on mortality in patients with ARDS in a global and stratified manner, as well as its adverse effects. When evaluating the results overall, we found a non-significant trend toward a decrease in the risk of mortality in favor of the prone group. However, when analyzing the studies individually, we found that the most recent clinical trials incorporated some changes in both the inclusion criteria and the pronation protocol based on the analysis of the probable causes of the unfavorable results in the early studies: first, the inclusion of more severely compromised patients with a PaO2/FiO2 level <200; second, the prolongation of pronation time to >16 hours per day; third, the use of protective ventilation strategies with a tidal volume <8 cc/kg of ideal weight, maintaining a plateau pressure <30 cmH2O, and titration of an optimal PEEP level. When evaluating the studies on a timeline, a trend toward progressively favoring the prone group is observed, with Guérin et al. showing a striking reduction in mortality risk in favor of pronation.[21,22] However, when stratifying the results by subgroups, we found interesting results that support the theory on the evolution and refinement of the prone position ventilation strategy.

First, the use of low tidal volume (<8cc/kg ideal body weight) in patients with ARDS became widespread after the publication of the ARDS network study. This intervention showed a reduction in mortality risk, probably related to the generation of less mechanical stress on the alveolar membrane by preventing overdistension and improving alveolar stability. When associated with recruitment capacity and homogenization of ventilation distribution, flow, and airway pressures attributed to pronation, it is likely also to achieve an additive effect in preventing and reducing ventilation-associated lung injury.[23,24] Therefore, when evaluating the subgroup

of patients in whom a tidal volume <8 cc/kg ideal body weight was used, a significant decrease in the risk of mortality was found compared to the group that used a higher tidal volume, results that could be attributed to the decrease in ventilation-associated lung injury. Second, the degree of alveolar recruitment in the prone position is another element to be analyzed. ARDS is characterized by disruption of the alveolar-capillary barrier, with increased permeability, flooding, and alveolar edema, also associated with depletion of pulmonary surfactant, leading to instability and alveolar collapse. Lung involvement is heterogeneous, with well-aerated lung regions that participate in gas exchange and other areas that are collapsed due to the pressure imposed by interstitial edema and alveolar flooding, mechanisms that explain the decrease in lung volume in these patients.[25,26] Pronation allows these alveolar areas to be recruited, redistributing and homogenizing ventilation, decreasing intrapulmonary shunt, and improving oxygenation, ventilation, and lung mechanics. However, the degree of recruitment depends on factors such as the severity of lung involvement, the duration of pronation, and the time elapsed from lung injury to patient pronation.[27,28]

Although the prone position can effectively increase oxygenation several days after the onset of the disease, its use during the early phase showed better results. During this phase, all conditions that favor the effectiveness of pronation are present, such as alveolar edema, reversible collapse, and the absence of structural lung alterations.[29] In this phase, the risk of ventilation-associated lung injury reduction probably exceeds that obtained in the late stages of ARDS, in which the damage has already been inflicted.

Despite the presence of these variables, the results obtained allow us to establish that the prone position is indicated in patients with severe oxygenation compromise. Furthermore, prolonged periods of prone positioning >12 hours continuous per day (18 hours on average) in patients with severe ARDS is a highly recommended strategy.[30] In moderate ARDS, the clinical recommendation is unclear; however, there is a certain tendency to benefit patients with PaO2/FiO2<140, which, combined with the results of the PROSEVA study, makes it possible to consider this strategy in this group of patients.

Table 1. Summary of study characteristics

Studies/ characteristics	Gatinoni et al.	Guerin et al.	Voggenreiter et al.	Mancebo et al.	Fernández et al.	Taccone et al.	Guérin et al.
Total number of patients	304	791	40	136	40	332	466
Follow-up period	180 days	90 days	90 days	Until discharge	60 days	180 days	90 days
Age (years)	52	62	41	54	54	60	59
Inclusion criteria	PAFI ≤200 with PEEP≥5cmH2O PAFI≤300 with PEEP≥10cmH2O,	PAFI≤300, expected duration of mechanical ventilation>48h	PAFI ≤200 with PEEP≥5cmH2O, PAFI≤300 with PEEP≥5cmH2O,	PAFI≤200 with PEEP≥5cmH2O	PAFI≤200 with PEEP≥5cmH2O	PAFI≤200 with PEEP≥5cmH2O	PAFI≤150 with PEEP≥5 cmH2O, VT6cc/kg
Severity (measures)	127	152	221	146	155	113	100
PAFI	NR	NR	NR	NR	NR	NR	NR
APACHE	NR	NR	11,5	NR	9,3	6,8	10
SOFA	40	45	NR	40,5	38	4	46
SAPS II	Gatinoni et al.	Guerin et al.	Voggenreiter et al.	Mancebo et al.	Fernández et al.	Taccone et al.	Guérin et al.

CONCLUSIONS

Mechanical ventilation in the prone position is a safe and effective therapeutic strategy in adult patients with acute respiratory distress syndrome (ARDS), especially in those with severe oxygenation compromise. Although the overall analysis of the studies included in this meta-analysis showed only a non-significant trend toward reduced mortality, the findings obtained when stratified by subgroups are particularly revealing and clinically relevant.

Evidence indicates that pronation provides a significant benefit in reducing mortality when implemented under specific conditions: when using low tidal volume ventilation (<8 cc/kg ideal body weight), when initiated early (within 48 hours of the start of mechanical ventilation), and when maintained for prolonged periods (more than 12 continuous hours per day). These factors enhance the protective effect of the prone position by reducing mechanical stress and ventilation-associated lung injury, improving ventilation distribution homogeneity, and promoting alveolar recruitment, thereby optimizing gas exchange.

Additionally, the study highlights that, although there are adverse effects related to the prone position, such as the development of pressure ulcers and orotracheal tube obstruction, these events are manageable and do not outweigh the clinical benefits obtained in the appropriately selected groups. No relevant differences were

found between groups in terms of the duration of mechanical ventilation or length of stay in the intensive care unit, reinforcing the idea that the main impact of pronation lies in its effect on survival in contexts of severe hypoxemia.

In summary, the prone position should be considered a first-line intervention in patients with severe ARDS. It is implemented early, sustained, and with protective ventilation strategies. The recommendation still requires more evidence in patients with moderate ARDS, although there is a positive trend in those with intermediate oxygenation indices (PaO2/FiO2 <140). These findings support the need for a protocol-based application based on disease severity to optimize clinical outcomes and reduce ARDS-associated mortality in contemporary medical practice

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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