Prone Versus Supine Position in Intubated COVID-19 Patients With ARDS: A Systematic Review and Meta-Analysis

Dita Aditjaningsih (✉ ditaaditia@gmail.com)

Universitas Indonesia Fakultas Kedokteran <https://orcid.org/0000-0001-6201-2400>

Adhrie Sugiarto

Universitas Indonesia Fakultas Kedokteran

Sidharta Kusuma Manggala

Universitas Indonesia Fakultas Kedokteran

Hansen Angkasa

Universitas Indonesia Fakultas Kedokteran

Ahmad Pasha Natanegara

Universitas Indonesia Fakultas Kedokteran <https://orcid.org/0000-0002-4524-168X>

Research

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Abstract

Background

This review determined the effect of prone positioning in changes of partial pressure of arterial oxygen/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio, partial pressure of carbon dioxide (PaCO_2), mortality rate, ICU length of stay and duration of mechanical ventilation in intubated COVID-19 patients with severe ARDS.

Methods

A computer-aided comprehensive electronic bibliographic search from MEDLINE, EMBASE, and Science Direct were conducted. The search comprised the articles written in English and intubated adults (≥ 18 years old) patients with COVID-19. The primary outcome was comparing $\text{PaO}_2/\text{FiO}_2$ ratio between prone and supine position group. Secondary outcomes were PaCO_2 , ICU discharge, and mortality rate. Review Manager version 5.4 (The Cochrane Collaboration) was used for statistical analyses of the included studies.

Results

A total of 7 articles were determined to be eligible, consisting of 1403 intubated COVID-19 patients with ARDS that showed prone position was associated with a higher $\text{PaO}_2/\text{FiO}_2$ ratio compared to supine position (MD 60.17, 95% CI 46.86 - 73.47; $p < 0.00001$). Four studies reported the PaCO_2 measurement and showed no significant difference between prone and supine position (MD 2.07, 95% CI -2.79 - 6.92; $p < 0.40$). Only two studies reported mortalities, one study had 262 deaths out of 648 patients (40.4%) and one study lost 11 out of 20 patients (55%). One study reported median ICU stay and mechanical ventilation duration (16 days) were significantly longer in prone position group.

Conclusion

This meta-analysis showed that prone position improved $\text{PaO}_2/\text{FiO}_2$ ratio in intubated COVID-19 patients with ARDS.

Background

The World Health Organization (WHO) has declared a public health emergency on coronavirus disease 2019 (COVID-19), a global pandemic that impacted more than 200 countries and over 3.9 million deaths.⁽¹⁾ As of July 2021, there are 2.35 million COVID-19 cases in Indonesia with 61.868 deaths reported.⁽²⁾ The ongoing pandemic has presented clinical management challenges which overwhelmed numerous health systems. The most common signs and symptoms of COVID-19 include fever, dyspnea, cough, sore throat, loss of taste or smell, and fatigue appearing within 2–14 days after exposure to the virus. However, around 67–85% of critically ill patients who were admitted to the intensive care unit (ICU) with COVID-19 developed hypoxemia, acute respiratory distress syndrome (ARDS) that required intubation and the mechanical ventilator.⁽³⁾ In general, respiratory failure with ARDS had poor outcomes, COVID-19 patients with ARDS were no exception.⁽⁴⁾ Some countries reported 61.5% fatality rate, especially those with mechanical ventilators.⁽⁵⁾ In the United Kingdom, 4855 patients with COVID-19 needed advance respiratory support and 57% of them died.⁽⁶⁾

Over the last decades, ARDS interventions have been evaluated, in particular, prone position was an important non-pharmacologic strategy that showed lifesaving potential for invasively ventilated patients with moderate to severe ARDS.⁽⁷⁾ Placing the patient in prone position optimizes the ventilation and decreases the intrapulmonary shunting which facilitates more effective oxygenation due to more uniform alveolar recruitment throughout the lung.⁽⁸⁾ A meta-analysis of prone position in ARDS and acute lung injury showed that prone position during invasive mechanical ventilation improved oxygenation and reduce ICU mortality rate.⁽⁹⁾ The Surviving Sepsis Campaign (SSC) COVID-19 subcommittee and WHO guidelines recommend prone position for the management of COVID-19 associated ARDS.^(10, 11) Numerous studies of awake prone position have been done outside of the ICU to reduce the incidence of intubation and ICU admissions, with the results suggested the prone position improved oxygenation with reduced respiratory effort.

Several studies have suggested the need of outcome measurements after prone position manoeuvre for mechanical ventilated COVID-19 patients. Currently, there are very limited studies comparing prone position and supine position in intubated COVID-19 patients. The aim of this analysis was to determine the changes of partial pressure of arterial oxygen/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio

after prone position compared to supine position in intubated COVID-19 patients with ARDS. This review also examined the changes of partial pressure of carbon dioxide (PaCO_2), mortality rate, ICU length of stay and duration of mechanical ventilation.

Methods

Search Strategy

The systematic review was conducted according to the PRISMA statement. A computer-aided comprehensive electronic bibliographic search from MEDLINE, EMBASE, and Science Direct were conducted on the 7th of July 2021, for articles published in the last 10 years (7th July 2011- 7th July 2021). A gray literature search was not conducted. Boolean phrase, medical subject headings (MeSH), and truncations were used when searching each database. Multiple searches were conducted to ensure all relevant studies were identified. A manual search of the reference list from the articles retrieved for additional relevant studies was also undertaken. The keywords and terms used for the search were "COVID#19", "coronavirus disease 2019", "acute respiratory distress syndrome", "ARDS", "intubated", "prone position", "supine position", "prone*", "TI prone position", "AB prone position", "COVID#19 OR acute respiratory distress syndrome", "coronavirus disease 2019 OR acute respiratory distress syndrome", "COVID#19 OR ARDS", "coronavirus disease OR ARDS", "COVID#19 OR TI COVID#19", "COVID#19 OR intubated OR ARDS", "(COVID#19 OR intubated OR ARDS) AND prone position". The review was not registered.

The systematic review was conducted according to the PRISMA statement.⁽¹²⁾ Intubated COVID-19 patients were determined as the population, prone position as the intervention, supine position as the comparison and $\text{PaO}_2/\text{FiO}_2$ ratio, PaCO_2 , mortality rate, ICU discharge, and duration of mechanical ventilation as the outcome. Potentially relevant articles from the three databases were included. The potential articles then were removed or excluded through a manually-systematic search of duplicate articles and a screening based on the title and abstract. The full-text of the remaining articles was examined based on review criteria predefined and the remaining articles were included in the review. Two authors screened titles and abstracts independently based on the inclusion and exclusion criteria. Studies that met the criteria were coded with "yes" and was retrieved for full text screening. Studies coded with "no" were excluded from the review. Two authors independently screened the full text articles and final included studies were approved by all authors.

Review Criteria

Included studies comprised of articles that was written in English, any other language was not included in the review. The subject must be human, adults (≥ 18 years old) diagnosed with COVID-19, intubated, comparing prone position and supine position, and measure the following outcomes: 1) $\text{PaO}_2/\text{FiO}_2$ ratio, 2) PaCO_2 , 3) mortality rate, 4) ICU length of stay, and 5) duration of mechanical ventilation. Systematic reviews and meta-analyses are excluded from the review, as well as case reports. Other exclusion criteria for the review are case series, editorials, and non-intubated (using high flow nasal cannule or non-invasive ventilation) patients.

Data Extraction

Two independent authors extracted data from the included articles. The data extracted were the type of interventions being compared (prone and supine position), outcome measures, including $\text{PaO}_2/\text{FiO}_2$ ratio, PaCO_2 , mortality rate, ICU discharge, and duration of mechanical ventilation. Other data such as year of publication, study design, sample size, mean age, severity by APACHE II and SOFA score, and duration of prone position were also extracted.

Review Manager version 5.4 (The Cochrane Collaboration) was used for statistical analyses. A two-sided p -value of <0.05 was denoted as statistically significant. For dichotomous outcomes, odds ratio (OR) was used, while for continuous outcomes, mean difference (MD), along with 95% confidence interval (CI) was used. If the data were presented as median and range/ interquartile range, it was converted to mean and standard deviation.⁽¹³⁾ I-square (I^2) test was used to assess the heterogeneity of studies. I^2 of less than 40% is considered insignificant, 40–60% is considered moderate heterogeneity, and more than 60% were categorized as substantial heterogeneity.⁽¹⁴⁾

Quality Assessment

The qualities of the studies included were independently assessed using Cochrane Risk of Bias Tool for randomized controlled trials (RCTs).⁽¹⁵⁾ The tool examines 7 distinct domains, including randomization procedures, blinding methods, and appropriate data reporting. Points are only rewarded when a criterion is fulfilled. All criteria were scored by the basis of 'High risk of bias' (-), 'Low risk of

bias' (+), and 'Unclear risk of bias' (?). For non-RCTs studies, we used Newcastle Ottawa Scale (NOS).⁽¹⁶⁾ NOS examines three categories, which are Selection, Comparability, and Outcome for cohort studies. While for case-control studies Exposure was examined instead of Outcome. The maximum score a study can obtain was 9. In the cohort segment, a maximum of 1 star for each question within the Selection and Outcome categories and a maximum of 2 stars can be given for Comparability. Meanwhile in the case-control segment, a maximum of 1 star for each question within the Selection and Exposure categories and a maximum of 2 stars for Comparability can be awarded. The cut-off to consider a study for low risk of bias was ≥ 7 , the same as previous studies. GRADE approach was used to examine the certainty of evidence and was conducted by two authors independently.

Results

Search Findings

The combined search using MEDLINE, EMBASE and Science Direct was conducted from 7th of July 2011 – 7th of July 2021. The search yielded 1,729 published studies. Based on the titles, abstract, and duplicates screened, 852 potential articles remained and full-text articles were retrieved. The full-text articles were reviewed based on eligibility criteria, a total of 7 articles were determined to be eligible for inclusion in this review (Figure 1). All of the studies were quality assessed using NOS and had low risk of bias (Table 1).

Characteristics of Included Articles

The seven studies included in this review were cohort studies (Table 2).⁽¹⁷⁻²³⁾ All of the studies were quality assessed using NOS and had low risk of bias (Table 2). The sample size varied with the least having only 9 subjects and the most having 648 which was a multi-centered study. We could not find any randomized controlled trials in this area. All of the recruited COVID-19 patients were from ICUs where the participants were mechanically ventilated. The mean age of all the included studies ranged between 53 and 63 years old. Three included studies calculate APACHE II during the first 24 hours of ICU admission, two out of the three studies calculated both APACHE II and SOFA. Furthermore, two other studies only used SOFA and two studies did not use either of the two scales. The APACHE II varied from an average of 10 to 26.2 and SOFA score ranged from 6.8 to 8.2. The duration of prone position sessions was similar across seven studies, averaging around 16 hours of prone position. The studies recorded PaO₂/FiO₂ ratio on supine position, ranging from a mean of 17.5 as the lowest and 123 as the highest. Three studies mentioned the inclusion criteria regarding to PaO₂/FiO₂ ratio and had a similar cut-off, which was ≤ 150 mmHg.

Table 1 – Quality Assessment of Included Cohort Studies

Newcastle-Ottawa Criteria					
Study	Selection	Comparability	Outcome	Total Score	Overall risk of bias
Astua et al	****	**	**	*****	8 Low
Berrill et al	****	**	**	*****	9 Low
Mittermaier et al	****	**	**	*****	8 Low
Weiss et al	****	**	***	*****	9 Low
Gleissman et al	****	**	**	*****	8 Low
Clarke et al	****	**	**	*****	8 Low
Langer et al	****	**	**	*****	8 Low

Outcome Measures

The combined data of seven studies, consisting of 1403 COVID-19 patients who had severe ARDS and were intubated, showed that prone position group was associated with higher PaO₂/FiO₂ ratio compared to supine position group (MD 60.17, 95% CI 46.86 to 73.47; $p < 0.00001$; Fig. 2). The statistical heterogeneity was observed to be extensive ($I^2 = 87\%$) and the funnel plot resulted in asymmetrical shape, suggestive of publication bias (Fig. 3).

Four studies reported the PaCO₂ measurement during prone position and supine position with 1331 patients combined. It showed no significant difference between prone position and supine position (MD 2.07, 95% CI -2.79 to 6.92; $p < 0.40$; Fig. 4). Heterogeneity was observed as substantial ($I^2 = 95\%$). Quality of evidence using GRADE approach was found to be very low for both analysis (Table 3).

Out of seven studies, only two studies mentioned mortalities whereas five other studies did not report. Langer et al had 262 deaths out of 648 patients (40.4%) and Weiss et al lost 11 out of 20 patients (55%). In addition, this study reported mechanical ventilation duration with median of 16 days (interquartile range 10-30) were significantly longer in prone position group compared to supine position group.

Two studies, Langer et al and Mittermaier et al, displayed ICU length of stay. However, Mittermaier et al did not compare between prone position and supine position. The study analysed 23 samples and divided into 3 subgroups, one of which prone position analysis. There were overlapping of samples between the subgroups Sample found that the average length of stay (in days) was 50.4 with standard deviation of 34.9. The study reported One study compared the two groups and reported that patients in prone position had a significantly longer stay in the ICU with median of 16 days (interquartile range 11-28).

Table 3 – Certainty assessment using GRADE approach

Certainty Assessment (GRADE approach)										
Studies	Design	No. of patients		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect (95% CI)	Certainty
		PP	SP							
PaO ₂ /FiO ₂	Cohort	828	575	not serious	substantial ^a	not serious	not serious	very serious ^b	MD 60.17 [46.86, 73.47]	very low
7 studies										
PaCO ₂	Cohort	785	546	not serious	substantial ^a	not serious	not serious	very serious ^b	MD 2.07 [-2.79, 6.92]	very low
5 studies										

CI: Confidence interval; MD: Mean difference

^a Substantial heterogeneity

^b Funnel plot suggested of publication bias

Discussion

The PaO₂/FiO₂ ratio is an integral component to diagnose ARDS. It is one of the key parameters in the Berlin criteria.⁽²⁴⁾ The severity of the disease can be based on the ratio starting from 200-300 mmHg as mild, 100-200 as moderate, and <100 as severe conditions. Furthermore, some cohort studies linked the mortality percentage with PaO₂/FiO₂ levels, thus, making it become a valuable diagnostic, prognostic and clinical management tool.⁽²⁵⁾ Several studies have proven that prone position helped improve the ventilation-perfusion ratio due to expansion of the collapsed dorsal lung, reduction of the pleural pressure gradient and resulted in more homogenous distribution of the lung stress and strain.^(23, 26) The PROSEVA study concluded that the 28-day mortality for severe ARDS patients assigned to prone position group was 16% and the unadjusted 90-day mortality was 23.6% compared to those in supine position, which were 32.8% and 41% respectively.⁽²⁷⁾ Since the pandemic began large numbers of hospitalized COVID-19 patients fulfilled the criteria of ARDS, which required invasive mechanical ventilation and a high level of patient care.^(2, 6, 17) Numerous studies recommended prone positioning to help improve oxygenation and decrease work of breathing. This study demonstrated that COVID-19 patients with ARDS were associated with a higher PaO₂/FiO₂ ratio in the prone position group compared to supine position group. The findings of this meta-analysis parallel to prior studies, suggesting that prone positioning may improve oxygenation of injured lungs. The included articles were all cohorts, as there are no randomised controlled trials (RCTs) studies available, and were quality assessed using NOS which seven of the studies had a low risk of bias. However, the heterogeneity was substantial and the funnel plot suggested publication bias.

Additionally, this review also examined PaCO₂ levels between the two groups and found that there was no significant association between the prone position with PaCO₂ level, and that was not parallel to the prior studies.^(27–31) Altered ventilation-perfusion ratio is a fundamental cause of abnormal gas exchange, which a low ratio induces hypoxemia and a high ratio induces hypercapnia.⁽²⁸⁾ Under normal physiology, PaCO₂ is the primary control for air exchange, specifically for the minute ventilation or amount of air exchanged in the lungs per minute.^(26, 29) It is responsible for affecting the pH, if there is an increase in PaCO₂ then the pH will decrease and increase minute ventilation. Whereas, a decrease in PaCO₂ will increase pH and decrease minute ventilation.^(27, 30) A study conducted in 2003 by Gattinoni et al showed a reduction of PaCO₂ level in ARDS patients in response to prone position. It stated that prone positioning reduced areas of distended lungs and the physiological dead-space, therefore it reduced shunts and resulted in reduction in PaCO₂.⁽³¹⁾ We included four cohort studies with low risk of bias to measure the outcome in PaCO₂ level, and found the heterogeneity was extensive. The possible mechanism that proning did not significantly affect the level of PaCO₂ was prone position using pressure-controlled ventilation would have a reduction of the chest wall compliance that reduced the tidal volume and minute ventilation.⁽³²⁾ Furthermore, prone position using volume-controlled ventilation would have the increased pleural pressure that reduced the venous return and affected the regional perfusion and increased the dead space.⁽³²⁾ Langer and colleague called it the CO₂-non responders.⁽²²⁾

Two articles mentioned mortality, Weiss et al showed 55% and Langer et al showed 40.4% of patients died in their study. Furthermore, Langer et al compared mortality between prone position versus supine position group, and reported that 112/409 patient's death (28%) in the supine position group.^(22, 23) However, the significance was not calculated by the author.

Langer et al compared ICU length of stay between the groups. For ICU length of stay, prone position patients had a significantly longer median of 16 days (Interquartile range 11–28) compared to median 12 days (Interquartile range 7–21) for the supine position group. This result supported other studies suggesting that prone positioning had longer time to death and in parallel to the beneficial changes of physiological parameters such as PaO₂/FiO₂ ratio.^(33–36) The mechanical ventilation duration was also significantly longer in prone position group compared to supine position group.⁽²¹⁾ The result might represent that prone positioning was applied as a salvage procedure on ARDS patients with more severe conditions. One other included study mentioned ICU length of stay with an average of 50.4 days.⁽²²⁾ However, Mittermaier et al did not compare between prone position and supine position. The study analysed 23 samples and divided into 3 subgroups, one of which prone position analysis. There were overlapping of samples between the subgroups, therefore, no direct comparison of prone position and supine position can be made. Thus, analysis of results from Langer and Mittermaier could not be performed.

This review focused on comparing the benefit of prone position in intubated COVID-19 patients with ARDS. All trials included in this review were observational studies in nature, while RCT studies were not yet available. Other limitations were the high degree in heterogeneity, risk of publication bias, no standardized prone position protocol, and the certainty of the measured outcome was very low.

Conclusion

Based on the results obtained from this meta-analysis, it can be concluded that intubated COVID-19 patients with ARDS had better PaO₂/FiO₂ ratio when in prone position. We found that there was no difference for PaCO₂ in prone position. Other outcomes such as mortality rate, ICU length of stay, and mechanical ventilation days could not be determined. Due to the limited number of studies with small sample size, high heterogeneity of measured outcomes, and very low certainty of evidence, further randomized clinical studies are needed.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Affiliations

Department of Anaesthesia and Intensive Care, Cipto Mangunkusumo General Hospital, Faculty of Medicine, Universitas Indonesia

Dita Aditiansingih, Adhrie Sugiarto, Sidharta Kusuma Manggala, Hansen Angkasa, Ahmad Pasha Natanegara

Universitas Indonesia General Hospital, Faculty of Medicine, Universitas Indonesia

Dita Aditiansingih

Corresponding Author: Dita Aditiansingih, Department of Anaesthesia and Intensive Care, Cipto Mangunkusumo, General Hospital, Faculty of Medicine, Universitas Indonesia & Universitas Indonesia General Hospital, Faculty of Medicine, Universitas Indonesia

Email: ditaaditiaa@gmail.com

Contributions

DA: Conceptualization; Data curation; Methodology; Project administration; Formal analysis; Writing - original draft; Supervision; Validation; Visualization; Writing - review & editing; Investigation. AS: Conceptualization; Data curation; Methodology; Formal analysis; Project administration; Writing - original draft; Investigation. SKM: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Writing - original draft; Writing - review & editing. HA: Data curation; Investigation; Methodology; Software; Visualization; Writing - original draft; Writing - review & editing. APN: Data curation; Software; Methodology; Visualization; Writing - original draft; Writing - review & editing.

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Tables

Due to technical limitations, table 2 is only available as a download in the Supplemental Files section.

Figures

Figure 1

PRISMA diagram of selection process

Figure 2

Forest Plot of Prone PaO₂/FiO₂ ratio

Figure 3

Funnel Plot of PaO₂/FiO₂ ratio

Figure 4

Forest Plot of PaCO₂

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table2CharacteristicsoftheIncludedArticles.xlsx](#)