Systematic Review

Effect of Prone Positioning on Clinical Outcomes of Non-Intubated Subjects with COVID-19: A Comparative Systematic Review and Meta-Analysis

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Effect of Prone Positioning on Clinical Outcomes of Non-Intubated Subjects with COVID-19: A Comparative Systematic Review and Meta-Analysis

Azizullah Beran; MD¹, Mohammed Mhanna; MD¹, Omar Srour; MD¹, Hazem, Ayeshe; MD¹, Omar Sajdeya; MD¹, Sami Ghazaleh; MD¹, Asmaa S. Mhanna; MD², Dana Ghazaleh; MD³, Waleed Khokher, MD¹, Aadil Maqsood; MD⁴, Ragheb Assaly; MD⁴

¹Department of Internal Medicine, University of Toledo, Toledo, OH, USA.

²University of Toledo, Toledo, OH, USA.

³University of Minnesota, Minneapolis, MN, USA.

⁴Department of Pulmonary and Critical Care Medicine, University of Toledo, Toledo, OH, USA.

Corresponding author: Azizullah Beran, M.D., Department of Internal Medicine, University of Toledo, 2100 W. Central Ave, Toledo, OH 43606, Tel: 469.348.1347, Email: Azizullah.Beran@utoledo.edu

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Data availability statement: The authors declare that all the data supporting the findings of this study are available within the manuscript.

Abstract

Introduction: Awake Prone positioning (APP) has been recently proposed as an adjunctive treatment for non-intubated coronavirus disease 2019 (COVID-19) patients requiring oxygen therapy to improve oxygenation and reduce the risk of intubation. However, the magnitude of the effect of APP on clinical outcomes in these patients remains uncertain. We performed a comparative systematic review and meta-analysis to evaluate the effectiveness of APP to improve the clinical outcomes in non-intubated subjects with COVID-19.

Methods: The primary outcomes were the need for endotracheal intubation and mortality. The secondary outcome was the length of hospital stay. Pooled risk ratio (RR) and mean difference (MD) with the corresponding 95% confidence intervals (CIs) were obtained by the Mantel-Haenszel method within a random-effect model.

Results: A total of fourteen studies (five randomized controlled trials [RCT] and nine observational studies) involving 3324 subjects (1495 received APP and 1829 did not) were included. There was a significant reduction in the mortality rate in APP group compared to control (RR 0.68, 95% CI 0.51-0.90, $P = 0.008$, $I^2 = 52\%$) with no significant effect on intubation (RR 0.85, 95% CI 0.66-1.08, $P = 0.17$, $I^2 = 63\%$) or length of hospital stay (MD -3.09 days, 95% CI -10.14, 3.96, $P = 0.39$, $I^2 = 97\%$). Subgroup analysis of RCTs showed significant reduction in intubation rate (RR 0.83, 95% CI 0.72-0.97, $P = 0.02$, $I^2 = 0\%$).

Conclusions: APP has the potential to reduce the in-hospital mortality rate in COVID-19 subjects with hypoxia without a significant effect on the need for intubation or length of hospital stay. However, there was a significant decrease in the need for intubation on subgroup analysis of RCTs. More large-scale trials with a standardized protocol for prone positioning are needed to better evaluate its effectiveness in this select population.

Introduction:

Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to significant morbidity and mortality globally ¹. Acute respiratory distress syndrome (ARDS) occurs in 20-41% of patients with severe COVID-19 ². Prone positioning is known to improve oxygenation and mortality in mechanically ventilated and intubated patients with moderate-to-severe ARDS ³. Prone positioning improves oxygenation by reducing ventilation-perfusion (V/Q) mismatch and reducing the intrapulmonary shunt ⁴.

Utilizing awake prone positioning (APP) has been recently proposed as an adjunctive treatment for spontaneously breathing non-intubated COVID-19 patients requiring oxygen therapy to reduce the risk of intubation ⁵. Most published studies showed significant improvement in oxygenation parameters such as the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO₂/FiO₂), PaO₂, and oxygen saturation (SpO₂) after APP sessions ⁴⁻⁶. Several single-arm meta-analyses have evaluated the effect of APP on oxygenation parameters and pooled the overall mortality and intubation rates in subjects who underwent APP without a control group⁷. However, the magnitude of the effect of APP on clinical outcomes (e.g., the risk of endotracheal intubation or mortality) in subjects with COVID-19 remains uncertain. Therefore, we performed a comparative meta-analysis to evaluate the effectiveness of APP to improve the clinical outcomes in subjects with COVID-19.

Methods:***Data sources and search strategy***

We performed a comprehensive search for published studies indexed in PubMed/MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to August 30, 2021. We also performed a manual search for additional relevant studies using references of the included articles. The following search terms were used: ("prone positioning" or "prone position") and ("COVID-19" or "SARS-CoV-2"). The search was not limited by language, study design, or country of origin. Supplementary Table 1 describes the full search term used in each database searched.

Inclusion and exclusion criteria

All published studies (randomized controlled trials (RCTs) and observational studies) that compared APP versus the control group in non-intubated COVID-19 subjects and reported one of the following outcomes: endotracheal intubation, mortality, and length of hospital stay were eligible for inclusion. All the studies that did not report endotracheal intubation or mortality rates were excluded, such as a study by Kharat et al.⁸ Only adult subjects aged 18 years or older were eligible for inclusion. We excluded single-arm studies, case reports, reviews, commentaries, preprints (not peer-reviewed), and abstracts.

Data extraction

The following data were extracted from the studies: first author name, publication year, country of origin, study design, number of subjects, follow-up duration, subject location, outcomes measures including rates of intubation, mortality, and length of hospital stay. We also extracted details of APP, oxygen and non-invasive respiratory support, and subjects' baseline comorbidities, including body mass index (BMI), hypertension, diabetes mellitus, and chronic obstructive lung disease (COPD). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines to select the final studies. Two investigators (MM and AB) independently performed the search and shortlisted the studies for final review. Discrepancies were resolved by a third reviewer (OS). We did not contact the authors of the studies.

Outcomes

The primary outcomes of our study were the need for endotracheal intubation and mortality between the APP and control groups of non-intubated subjects with COVID-19. The secondary outcome was the length of hospital stay between the two groups.

Statistical analysis

We performed a meta-analysis of the included studies using Review Manager 5.3 (Cochrane Collaboration, Copenhagen, The Nordic Cochrane Centre) and Comprehensive Meta-Analysis (Biostat, Englewood, USA). The median and interquartile range were converted to mean and SD where applicable⁹. The random-effects model was used to calculate the pooled risk ratio (RR) and mean difference (MD) with the corresponding confidence intervals (CI) for proportional and continuous variables, respectively. A *P*-value <0.05 was considered statistically significant.

The heterogeneity of the effect size estimates across the studies was quantified using the Q statistic and I^2 ($P < 0.10$ was considered significant). A value of I^2 of 0–25% indicates insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity, and 76–100% high heterogeneity ¹⁰.

Subgroup and sensitivity analyses for endotracheal intubation and mortality

We performed a subgroup analysis of RCTs for endotracheal intubation. To confirm the robustness of the results, sensitivity analysis for endotracheal intubation and mortality using leave-one-out meta-analysis was performed to see if it had a significant influence on the result of the meta-analysis.

Bias assessment

The Jadad composite scale was used to assess the methodological quality of the RCTs based on randomization, blinding, and withdrawals ¹¹. The scale ranged from 0 to 5 points ¹². Studies with a total score >3 were considered high quality, while moderate quality if a score of 3 and low quality if <3 . The Newcastle Ottawa Quality Assessment Scale (NOS) was used to assess the quality of the observational studies based on the selection of the study groups, comparability of study groups, and ascertainment of exposure/outcome ¹². Studies with a total score >6 were considered high quality, while moderate quality if a score of 6 and low quality if <6 . Publication bias was assessed qualitatively by visually assessing the funnel plot and quantitatively using Egger's regression analysis. Two authors (AB and MM) independently assessed each study for bias. Discrepancies were resolved by a third reviewer (OS).

Results:

Study selection

A total of 1048 studies were retrieved by our search strategy. Among these, 57 were eligible for systematic review. Subsequently, we excluded 44 studies because of the following: subjects were intubated, absence of control group, lack of appropriate outcome, or lack of appropriate control. Eventually, 14 studies^{5, 6, 13-24} met our inclusion criteria and were included in the meta-analysis. Figure 1 shows the PRISMA flow chart that illustrates how the final studies were selected.

Quality and publication bias assessment

Quality assessment scores of the RCTs and observational studies are summarized in Supplementary table 2. All the included studies were of moderate or high quality. Four RCTs^{6, 20, 22, 23} were of moderate quality, and one RCT¹⁷ was of high quality. Six observational studies^{5, 13, 15, 16, 19, 21} had a total score >6 , indicating that they were of high quality. Three observational studies^{14, 18, 24} scored 6, indicating that they were of moderate quality.

There was a visible asymmetry in the funnel plot of the studies that reported both the need for endotracheal intubation and in-hospital mortality, which may suggest the presence of publication bias (Figure 4). However, Egger's regression analysis did not demonstrate statistically significant publication bias ($P = 0.54$ and $P = 0.91$ for endotracheal intubation and mortality, respectively).

Study and subjects' characteristics

Tables 1 and 2 show the study and subject characteristics of the studies included in the meta-analysis. All the included studies were published between 2020 and 2021 and included spontaneously breathing non-intubated subjects with laboratory-confirmed COVID-19. Based on country of origin, three studies originated from the United States; five studies originated from Europe (Italy, France, Spain, and Sweden), three studies from Asia (China and India), two studies from South America (Brazil, Mexico, and Ecuador), and one multinational study (meta-trial from 6 countries: Canada, Ireland, France, Mexico, Spain, and USA). Regarding the design of included studies, five were RCTs and nine were observational cohort studies (six studies were retrospective cohort, and three were prospective cohort).

A total of 3324 subjects (1495 received APP and 1829 did not) were included, with males representing 69.8% of the total subjects. The follow-up period across the studies ranged from 14 to 90 days. The assessment of the risk of bias is presented in Supplementary table 2. All nine observational studies scored ≥ 6 on the Newcastle-Ottawa Scale, and all five RCTs scored ≥ 3 , representing a low risk of bias (Supplementary table 2).

Outcomes

Need for endotracheal intubation

Table 2 summarizes the outcomes of the individual studies included in the meta-analysis. Across the 13 studies^{5, 6, 13-20, 22-24} that reported the intubation rate, 27% of subjects who received APP required intubation compared to 29.8% in subjects who did not receive APP. The need for endotracheal intubation was similar between APP and control groups (RR 0.85, 95% CI 0.66-1.08, $P = 0.17$), the statistical heterogeneity was moderate with I^2 of 63% (Figure 2A). However, on subgroup analysis of RCTs, the need for intubation significantly reduced in APP group versus control (RR 0.83, 95% CI 0.72-0.97, $P = 0.02$, $I^2 = 0\%$) (Figure 3). To assess the stability of the results of our meta-analyses, we performed a 1-study removed sensitivity analysis. Removal of Zang et al. moved the overall effect to favor APP with an RR of 0.80 (95% CI: 0.64-0.99), suggesting that Zang et al. was partly the reason for the moderate between-study heterogeneity. (Supplementary figure 1).

Mortality

Thirteen studies^{5, 6, 13, 14, 16-24} reported the mortality rate. The mortality rate was 17.9% in the APP group compared to 25.7% in the control group. There was a statistically significant difference in the mortality rate between the two groups (RR 0.68, 95% CI 0.51-0.90, $P = 0.008$) and the statistical heterogeneity was moderate with I^2 of 52% (Figure 2B). A leave-one-out sensitivity analysis showed consistent results (Supplementary figure 2).

Length of hospital stay

Six studies^{6, 14, 16, 17, 19, 23} reported the length of hospital stay. There was no significant difference with regards to the length of hospital stay (MD -3.09 days, 95% CI -10.14, 3.96, $P = 0.39$, $I^2 = 97\%$) (Figure 2C).

Discussion:

Prone positioning for treating ARDS is a well-known strategy to improve oxygenation; it is recommended for 16 hours daily in mechanically ventilated and intubated subjects with ARDS with PaO_2/FiO_2 ratio less than 150 mmHg³. However, the evidence regarding the utility of APP in non-intubated subjects is limited.

In the current COVID-19 pandemic era, a substantial number of COVID-19 patients developed ARDS with an extreme surge in need for respiratory support, intubation, and mechanical ventilation. Hence, every effort was implemented to avoid intubation and mechanical ventilation, given the shortage of human and medical resources²⁵.

One of the proposed strategies to avoid such complications is to implement prone positioning in awake, spontaneously breathing patients in the hope of preventing further respiratory deterioration and the need for advanced respiratory support²⁶.

Several studies have shown significant improvement in oxygenation parameters such as PaO₂/FiO₂, PaO₂, SpO₂, and respiratory rate ²⁷⁻²⁹. Some meta-analyses have investigated the effect of APP on clinical outcomes in non-intubated patients with COVID-19 by pooling the rates of intubation and mortality from single-arm studies which did not have a control group^{7,30}. A meta-analysis by Pavlov et al.³⁰ has pooled the mortality and intubation rates in single-arm studies and showed the pooled intubation rate of 27% among those who underwent APP. However, few studies have evaluated the effects of APP vs. control on clinical outcomes of patients with COVID-19^{13, 14, 18, 19}. To our knowledge, only one comparative meta-analysis by Chua et al.³¹ has been published that evaluated the impact of APP vs. control on intubation and mortality rates in subjects with COVID-19. However, Chua et al.³¹ included a limited number of studies (five studies), and all the included studies were observational (no RCT). Further studies, including RCTs^{6, 20, 23} have been published, and we provide an updated comparative meta-analysis to investigate the effect of APP compared to control on the clinical outcomes, including the need for intubation, in-hospital mortality, and length of hospital stay.

Our meta-analysis demonstrated that APP reduced mortality in non-intubated COVID-19 subjects without a significant difference in the need for endotracheal intubation and length of hospital stay. However, APP showed a significant reduction in the need for intubation when subgroup analysis was restricted to RCTs.

Our meta-analysis results are similar to those from the recent meta-analysis by Chua et al.³¹ which revealed that APP could decrease mortality rate (Odds ratio (OR): 0.35, 95% CI: 0.16-0.75, P = 0.007) without significant effect on intubation rate (OR: 1.20, 95% CI: 0.77-1.86, P = 0.42) in non-intubated COVID-19 patients with hypoxia. However, we further conducted a subgroup analysis of RCTs for intubation, which significantly reduced the need for intubation. Furthermore, sensitivity analysis did not show consistent findings for intubation. This discrepancy might be attributed to the inconsistent protocols of APP utilized in the included studies and to the absence of standardized criteria and indications for intubation³². Thus, we believe that there is an urgent need for guidelines and protocols to guide the practice of APP in COVID-19 subjects. The protocols should include the eligibility criteria to initiate APP,

number of sessions and average time per day, proper follow-up protocols, early identification of complications and treatment failure, and standardized criteria for intubation.

Our study has certain limitations. First, this meta-analysis was mainly based on observational studies and only included five RCTs. Therefore, more large-scale RCTs to investigate the impact of APP on the clinical outcomes of COVID-19 subjects are warranted. Second, moderate heterogeneity was found in the measurement of intubation and mortality. This can be explained by inconsistent follow-up duration among the studies, significant variation in the used respiratory supports, and wide range of frequency and duration of the applied APP protocols, and significant difference in the location of the study (ED vs. hospital ward vs. ICU)³². Third, we were not able to assess the oxygenation parameters before and after APP sessions due to limited reported data. Fourth, the majority of the studies did not assess the APP protocol adherence, and there was a lack of standardized protocol and optimal duration for APP among studies. Lastly, the lack of patient-level data did not allow to control for possible variations in baseline characteristics or adoption of APP.

Despite the limitations, our study has significant strengths. First, we included a total of 14 studies with over 3300 subjects with COVID-19. This is by far the largest analysis comparing the effect of APP on clinical outcomes in COVID-19 subjects with hypoxia. Although significant heterogeneity was noted, we performed a subgroup analysis of RCTs and sensitivity analysis to evaluate the robustness of our results. Consistent results were observed on sensitivity analysis for mortality. Despite the presumed heterogeneity, the meta-analysis was undertaken to observe the effect of APP in subjects with COVID-19, as several studies revealed some benefits in terms of mortality and intubation rates. Finally, all the included studies in our study were of moderate or high quality based on quality assessment.

In conclusion, APP has the potential to reduce the in-hospital mortality rate in COVID-19 subjects with hypoxia without a significant effect on the need for intubation or length of hospital stay. However, there was a significant decrease in the need for intubation on subgroup analysis of RCTs. More large-scale trials with a standardized protocol for APP are needed to better evaluate its effectiveness in this select population.

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Figure legends:

Figure 1: PRISMA flow diagram for the selection of studies.

Figure 2: Forest plots comparing awake prone positioning and control regarding: (A) endotracheal intubation, (B) mortality, and (C) length of hospital stay.

Figure 3: Subgroup analysis of RCTs for the need for endotracheal intubation.

Figure 4: Funnel plots comparing awake prone positioning and control regarding: (A) endotracheal intubation and (B) mortality.

Figure 1: PRISMA flow diagram for the selection of studies.

432x396mm (38 x 38 DPI)

Forest plots comparing awake prone positioning and control regarding: (A) endotracheal intubation, (B) mortality, and (C) length of hospital stay.

532x629mm (130 x 130 DPI)

Subgroup analysis of RCTs for the need for endotracheal intubation.

268x73mm (72 x 72 DPI)

Figure 4: Funnel plots comparing awake prone positioning and control regarding: (A) endotracheal intubation and (B) mortality.

651x751mm (130 x 130 DPI)

Table 1: Study characteristics of the included studies.

Study, year	Study design	Country	Total sample size (APP/Control), n	Male, n (%)	Age, mean $\pm$ SD, years	Subject location of APP	Oxygen & non-invasive respiratory support	Details of APP	Follow-up period
Ehrmann, 2021 ²³	RCT	Multinational	1121 (564/557)	746 (66.5)	61.1 $\pm$ 13.7	Ward & ICU	HFNC	151 patients had $\geq$ 8 hours of APP daily	28 days
Ferrando, 2020 ⁵	PC	Spain	199 (55/144)	147 (73.9)	62.6 $\pm$ 12.04	ICU	HFNC	>16 hour/day regardless of APP session numbers	28 days
Jagan, 2020 ¹⁴	RC	USA	105 (40/65)	57 (54.3)	62.1 $\pm$ 16.3	Ward	NR	$\geq$ 1 hour for $\geq$ 5 occasions per day and $\geq$ 1 hour overnight	NR
Jayakumar, 2021 ²⁰	RCT	India	60 (30/30)	50 (83.3)	56.1 $\pm$ 11.6	ICU	SFM, NRM, HFNC, NIV	13 (43%) patients completed mean of $\geq$ 6 hours daily in APP	NR
Johnson, 2021 ⁶	RCT	USA	30 (15/15)	16 (53.3)	57.2 $\pm$ 19.5	Ward	NC	Average 1.6 hours in the first 72 hours	NR
Jouffroy, 2021 ²¹	RC	France	379 (40/339)	291 (76.8)	59(56-64)*	ICU	NIV, CPAP, HFNC, NC, SFM	Two 3-6-hour APP sessions daily	28 days

Ni, 2020 ¹⁵	PC	China	52 (17/35)	32 (61.5)	62±12	Ward	HFNC, NC, mask, NIV	≥4 hours per day for 10 days	14 days
Padrao, 2020 ¹⁸	RC	Brazil	166 (57/109)	112 (67.5)	58.1±14.1	ED	NC, venturi mask, NRM	58% had >4 hours per session, 2 APP sessions per day	15 days
Perez-Nieto, 2021 ²⁴	RC	Mexico and Ecuador	827 (505/322)	600 (72.6)	54.3 (14.2)	Ward & ICU	LFNC, HFNC, NRM	Median APP time was 12 (IQR: 8–24)	NR
Prud'homme, 2021 ¹³	RC	France	96 (48/48)	68 (70.8)	61.5±14.8	Ward	NC, HFNC	Mean 6.9±5.2 days (32 patients prone for 3-8 hours/day and 16 prone >8 hours/day)	14 days
Rosen, 2021 ²²	RCT	Sweden	75 (36/39)	55 (73.3)	63.7±14	Ward & ICU	HFNC, NIV	Median 9 hours daily (4.4–10.6)	30 days
Taylor, 2020 ¹⁷	RCT	USA	40 (27/13)	27 (67.5)	56.7±14.1	Ward	NC, MFNC, BiPAP	NR	30 days
Tonelli, 2021 ¹⁶	RC	Italy	114 (38/76)	80 (70.2)	67(32-80)*	ICU	HFNC, CPAP, NIV	Varied from 1 to 4 sessions daily	30 days
Zang, 2020 ¹⁹	PC	China	60 (30/30)	39 (65)	64.8±9.9	NR	HFNC, NIV	Mean 13.4 hours of APP (range 6-30)	90 days

Abbreviations: APP: awake prone positioning, BiPAP: bilevel positive airway pressure, CPAP: continuous positive airway pressure, HFNC: high-flow nasal cannula, ICU: intensive care unit, IQR: interquartile range, LFNC: low-flow nasal cannula, MFNC: median-flow nasal cannula, n: sample size, NC: nasal cannula,

NIV: non-invasive ventilation, NRM: non-rebreather mask, NR: not reported, PC: prospective cohort, RCT: randomized controlled trial, RC: retrospective cohort, SD: standard deviation, SFM: simple face mask, USA: United States.

*Median (interquartile range).

Table 2: Subject characteristics and outcomes of the included studies in the meta-analysis.

Study, year	BMI, median (IQR) or mean±SD, kg/m ²		COPD, n		HTN, n		DM, n		Intubation, n		Mortality, n		Length of hospital stay, median (IQR) or mean±SD, days	
	APP	Control	APP	Control	APP	Control	APP	Control	APP	Control	APP	Control	APP	Control
Ehrmann, 2021²³	NR		NR		NR		176	173	185	223	117	132	16.4±10.5	16.5±9.7
Ferrando, 2020⁵	27.3 (25.1-29.4)	26.8 (24.8-31.2)	4	6	20	60	9	23	22	60	6	13	NR	
Jagan, 2020¹⁴	31.3 (26.4-37.5)	28 (24.9-34.4)	5	11	24	36	18	25	4	18	0	16	NR	
Jayakumar, 2021²⁰	28.2±5.7	25.8±2.6	NR		13	9	13	19	4	4	3	2	NR	

Johnson, 2021⁶	32.9 (27.5-39.4)	29.3 (24.4-32.9)	NR		NR		NR		2	1	2	0	4.7 (2.8-8.2)	4.6 (3.1-5)
Jouffroy, 2021²¹	28.5 (26-31)	28 (25-32)	3	17	13/175	175	11	103	NR		96	4	NR	
Ni, 2020¹⁵	NR		3	3	7	10	4	7	0	1	NR		35 (27-52)	35 (28-43)
Padrao, 2020¹⁸	33±58	56±51	3	4	27	62	22	36	33	53	6	22	NR	
Perez-Nieto, 2021²⁴	NR		NR		119	166	121	194	119	130	100	120	NR	
Prud'homme, 2021¹³	27±5	28±5	7	8	15	18	7	12	7	8	4	6	NR	
Rosen, 2021²²	28 (25-30)	29 (27-33)	4	2	17	21	14	11	12	13	6	3	NR	
Taylor, 2020¹⁷	29 (26-39)	31 (28-38)	6	3	NR		10	5	0	0	0	0	6 (3-12)	5 (2-9)
Tonelli, 2021¹⁶	26 (19-36)	28 (20-37)	6	11	NR		8	14	7	30	5	17	20 (3-41)	24 (3-45)
Zang, 2020¹⁹	NR		NR		6	17	3	9	8	4	10	28	8 (4-16)	27 (16-54)

Abbreviations: APP: awake prone positioning, BMI: body mass index, COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus, HTN: hypertension,

IQR: interquartile range, n: sample size, NR: not reported, SD: standard deviation.