

^d Senior Consultant, Institute of Critical Care Medicine, Max Super Speciality Hospital, New Delhi 110017, India
^e Deputy Medical Superintendent, Max Super Speciality Hospital, New Delhi 110017, India
^f Consultant, Institute of Critical Care Medicine, Max Super Speciality Hospital, New Delhi 110017, India

* Corresponding author.
 E-mail address: devenjuneja@gmail.com (D. Juneja).

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Analytic review and meta-analysis of awake prone positioning in patients with Covid-19



Revisión analítica y meta-análisis de pronóstico en pacientes con Covid-19

Dear Editor,

SARS-CoV-2 virus (Covid-19) is an infectious disease where most cases have mild symptoms, while few have pneumonia with respiratory failure. Because prone positioning (PP) improves survival in patients with acute respiratory distress syndrome (ARDS), its use has been recommended in Covid-19 patients. PP has shown more homogenous distribution of ventilation and decreasing shunt in dorsal regions and dead space in ventral regions in mechanically ventilated COVID-19 patients. However, the impact of PP in awake patients has not been well defined. Our aim was to perform a meta-analysis to assess the impact of awake prone positioning (APP) on intubation rate, mortality and gas exchange in Covid-19.

A systematic search was performed in MEDLINE, CENTRAL, Web of Science and Lilacs on August 20th, 2021. We used a strategy that combined keywords and descriptors and screened the reference list of all the available articles. Two groups of keywords linked by the Boolean "OR" operator were included. Covid-19; SARCov2, SARSCoV-2; SARS-CoV-2; COVID; novel coronavirus; coronavirus disease; coronavirus-2019 (first group) and prone positioning; awake prone positioning; self-proning; awake prone position; early

awake prone; awake proning (second group). Subsequently, both groups were joined by the Boolean operator AND. Only randomized controlled trials (RCTs) that compared the use of APP with usual care in patient with acute respiratory failure due to COVID-19 were included. No language restrictions were imposed. Two authors screened the studies for eligibility (disagreements were resolved by a third author).

We contacted investigators for unreported data. Cochrane Collaboration tool to assess risk of bias was used. The following variables were evaluated: age, sex, setting, interventions (respiratory support, time session of APP) and outcomes. The primary outcome was intubation rate and secondary outcomes were mortality and oxygenation. We combined the studies through a meta-analysis with dichotomous data as risk ratios (RRs) and continuous data as mean differences (MDs). We assessed the variation in the results by drawing a forest plot and statistical heterogeneity through the I^2 test at a 95% confidence interval (CI95). According to statistical heterogeneity, fixed-effects model ($I^2 < 20\%$) or a random-effects model ($I^2 \geq 20\%$) were used. Analyses were performed with Review Manager version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark). The quality of the evidence was assessed according to GRADE (Grading of Recommendations Assessment, Development, and Evaluation criteria guidelines).

Of the 1041 citations, after discarding the duplicates, we identified 59 potentially relevant studies where 51 studies were discarded and eight RCT were included (Fig. 1 ESM).¹⁻⁸ The age of the patients ranged between 49 and 66 years (66.7% male).

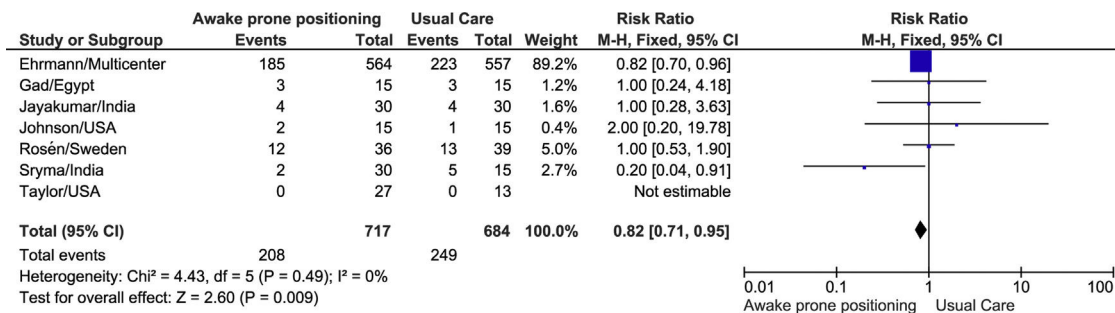


Figure 1 Intubation rate. Forest plot of comparisons between APP and UC.

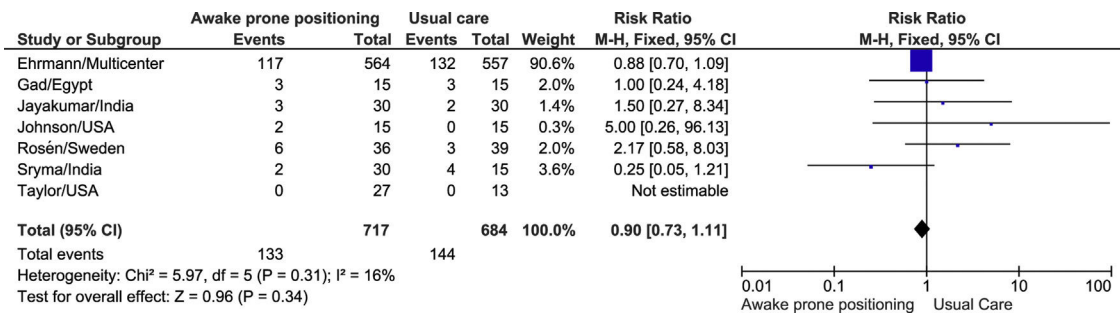


Figure 2 Mortality. Forest plot of comparisons between APP and UC.

Four studies were conducted in the ICU,^{1–3,6} three in the medical ward^{4,5,8} and one study did not report the setting.⁷ The largest study was conducted in six countries: France, USA, Canada, Mexico, Spain, Ireland.¹ The other studies were carried out in Egypt (one),² India (two),^{3,7} Sweden (two)^{5,6} and USA (two).^{4,8} The number of participants ranged from 30^{2,4} to 1121.¹ APP time varied between 1 and 16 h between the studies, and the supplemental oxygen used (high-flow nasal cannula, nonrebreathing mask, nasal cannula and no invasive ventilation) was variable in both groups.

All studies were at high risk of bias due to performance bias (blinding of patients and staff) and most studies did not detail the orotracheal intubation criteria.

For the meta-analysis, we pooled seven studies because one study did not present outcomes.⁵ We found significant differences in the intubation rate in favor to the APP group [RR: 0.82 (CI95% 0.71–0.95), I²: 0%, Fig. 1], but no differences in mortality [RR: 0.90 (CI95% 0.73–1.11), I²: 16%, Fig. 2]. Regarding the intubation rate, we performed sensitivity analysis, excluding the study with the greatest weight¹ [RR: 0.84 (CI95% 0.52–1.35), I²: 9%, Fig. 2 ESM], where we found that the benefit is not maintained.

Five studies, using different assessment of oxygenation (SaO₂/FiO₂,^{1,5,8} SaO₂² and ROX index⁷), describes a positive impact of APP in gas exchange. In turn, two studies (which assessed PaO₂/FiO₂ ratio) show a decrease in oxygenation.^{3,4} In the remaining study, oxygenation was not evaluate.⁶ Due to the different assessments of oxygenation, no meta-analysis was performed.

The quality of the evidence according to GRADE for the outcomes intubation rate and mortality was ranked as very low. We downgrade for risk of bias (performance bias) and imprecision (due to the number of participants and the wide confidence interval).

This study shows a significant decrease in the intubation rate, without a relevant effect on mortality, in Covid-19 patients supported with APP compare to usual care. It should be noted that the quality of the evidence is low in both results. In addition, our sensitivity analysis (excluding the largest study) showed no benefit.

In addition, the current data do not allow us to draw conclusions regarding the benefit in oxygenation, although most studies show an improvement in oxygenation with APP.^{1,2,5,7,8} Only two studies found no improvement in oxygenation,^{3,4} where the authors detail it as an unexpected finding, arguing the low adherence to the protocol³ or the

late assessment of oxygenation (48 or 72 post APP)⁴ as possible explanations.

To our knowledge, this is the first meta-analysis showing the benefit of APP in interventional studies. Although four previous reviews found significant decrease in the intubation rate and mortality, those results were obtained through meta-analysis of proportions (without a control group), including observational studies and with considerable statistical heterogeneity.^{9,10}

The main limitations of this metanalysis are: (1) the clinical heterogeneity observed with the intervention in terms of session time and oxygenation supplementation; (2) the lack of additional well designed and large scale RCTs to improve the quality of our findings.

APP seems to be a strategy that is useful and relatively easy to implement in Covid-19 patients with acute respiratory failure. The beneficial effect of APP decreasing the intubation rate could be a great help against the potential shortage of mechanical ventilators in some countries in a new pandemic wave.

Conflict of interest

The authors declare not to have any interest conflicts.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.medin.2021.11.003](https://doi.org/10.1016/j.medin.2021.11.003).

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- R. Santa Cruz^{a,b,*}, C. Irrazábal^c, L. Gonzalez^b, A. Geloso^a, C. Nuñez^b, R. Cornejo^d
- ^a *Department of Intensive Care, Hospital Ramos Mejía, Ciudad Autónoma de Buenos Aires, Argentina*
^b *Laboratory of Physiology, School of Medicine, University of Magallanes, Punta Arenas, Chile*
^c *Hospital de Clínicas José de San Martín, Buenos Aires, Argentina*
^d *Unidad de Pacientes Críticos, Departamento de Medicina, Hospital Clínico Universidad de Chile, Chile*
- * Corresponding author.
 E-mail address: resc.hrrg@gmail.com (R. Santa Cruz).
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Tribulations of conducting critically ill cancer patients research: Lessons from a failed septic shock trial and Murphy's law



Tribulaciones de la investigación en pacientes críticos con cáncer: lecciones de un ensayo clínico fallido sobre el shock Séptico y la Ley de Murphy

Dear Editor,

Clinical researchers face numerous challenges, while receiving <2% of the National Institutes of Health funding in previous years.^{1–5} A search for the terms “critically ill” and “ICU” and “randomized” in PubMed between 2010 and 2021 rendered 2,585 publications; only 3% of those included “cancer.” We conducted a single-center, randomized controlled clinical trial, and included adult cancer patients who met the Sepsis-3 septic shock definition within 12 h of ICU admission. Patients were randomized to either standard of care or Early Metabolic Resuscitation (dextrose 50%, amino acids, and micronutrients). The sample size (112 patients, 56 per group) provided 90% power to detect a 30% absolute reduction in 28-day mortality. The complete methodology is available at ClinicalTrials.gov (NCT03895853). During the available enrollment month, 56/194 cancer patients had sepsis and shock. Among them, 32 met inclusion criteria, but 94% had at least one exclusion criteria (Figs. 1A, B and 2); only two patients were enrolled/randomized to standard of care. On May 4, 2020, the study was terminated due to overwhelming obstacles (Fig. 2).

Despite significant planning, we report the failure of the trial associated with a combination of unforeseen events. Using a previously described matrix, we organized the discussion of these obstacles in six groups²:

- A) External factors. The study start was delayed for over three months because of two unexpected and consecutive institution-wide audits conducted by the *Centers for Medicare and Medicaid Services* and the *Joint Commission*. The audits distracted dozens of teams from clinical research to address the additional workload caused by the regulatory activities.
- B) Specific unit needs. The complex and intensively involved protocol demanded scrupulous re-education of the participating healthcare personnel due to the delays in starting the trial caused by the audits.
- C) Study-related factors. Previous studies have identified the difficulty of defining diseases in the intensive care environment.³ Defining sepsis and septic shock has been a critical point of discussion for the experts in the field that has evolved over time. In our study, almost half of the patients did not meet the Sepsis-3 criteria because 43% had normal lactate despite shock and vasopressors. Moreover, between the Sepsis-3 definition and the exclusion criteria, most of the screened patients (96.4%) became ineligible, thus impacting enrollment and potential generalizability of the trial.⁴
- D) Study population. Our institution is a referral comprehensive cancer center. We manage high volumes of complex cancer patients that are admitted to our unit, many of whom arrive in multi-organ failure with SOFA scores above 12 and Do-Not-Resuscitate (DNR) orders (21.9%) at the time of diagnosis. Both the SOFA and DNR