



## COMMENT

## A new gambler at the table of management of COVID-19 associated acute respiratory failure. Changing position to do it better?



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The COVID-19 pandemic has led to an increase in publications (with high percentages of retractions),<sup>1</sup> nevertheless, after three years, we still need reproducible randomised controlled trials (RCTs) on several issues, especially to evaluate strategies and tools to manage individuals with COVID-19-associated acute hypoxaemic respiratory failure such as non-invasive respiratory support (NRS), high flow nasal cannula or awake prone positioning.<sup>2–5</sup> This latter has gained attention as a potential intervention since the early phase of the pandemic, and despite the limited RCTs evidence, it has been widely used as a co-intervention even in mild hypoxaemia.<sup>6,7</sup> It has been reported that awake prone positioning has been used in one in six critically ill individuals with COVID-19, has been started early, and sessions lasted long but were often discontinued because of need for intubation.<sup>8</sup>

Prone positioning may promote more homogeneous ventilation, improving the ventilation-to-perfusion ratio by “recruiting” dorsal non-aerated but perfused lung units, reducing ventral hyperinflation, and increasing airway clearance resulting in relevant improvement in oxygenation.<sup>9</sup> Early

observational studies, with relatively small sample sizes, showed conflicting results with beneficial effects on oxygenation not sustained over time.<sup>10</sup> However, due to the limited treatment option, many clinicians have used this modality as a tool to improve oxygenation. Several predictors of its success have been proposed, including duration of intervention > 8 h/day, respiratory rate at enrollment ≤ 25 breaths/min, improvement in ROX index > 1.25 and lung ultrasound score ≥ 2 within the first 3 days.<sup>11–13</sup>

A meta-trial by Ehrmann et al.<sup>14</sup> combining six independent RCTs, with 1126 participants with PaO<sub>2</sub>/FiO<sub>2</sub> ≤ 300 mm Hg in mixed settings, showed significant improvements in the composite outcome of intubation or death rate within 28 days using awake proning as compared to standard treatment, with a number needed to treat (NNT) of 15 to avoid treatment failure. This outcome was primarily driven by a decrease in the need for tracheal intubation and awake proning did not reduce mortality as compared with usual care. However, uncertainty remains about the magnitude of a survival benefit left by the included studies that were underpowered for this outcome and heterogeneous in the severity of study population, settings, and type of NRS used.<sup>15</sup>

Another RCT failed to show a reduction in endotracheal intubation rate at 30 days using awake proning compared to usual care.<sup>16</sup> Musso et al. showed that this modality, combined with NRS strategies, reduced the intubation rate.<sup>17</sup>

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Conversely, Qian et al. showed no clinical benefit and a potential detrimental effect with progression of lung damage and worsening in oxygenation.<sup>18</sup> Li et al. showed a significant effect in reducing the need for intubation in the overall population with a 16% relative risk reduction (especially in the subgroup of individuals receiving NRS or treated in ICU settings) but not in mortality rate.<sup>19</sup> However, the interpretation of subgroup analyses in meta-analyses requires caution since estimates of treatment effect for clinically relevant subgroups of participants are observational, not accounting for the distribution of confounders and should be considered hypothesis-generating rather than confirmatory results. Weatherald et al. concluded that awake proning reduces the intubation rate with a NNT of 18 to prevent intubation without any benefit on mortality, ICU or hospital length of stay, ventilator-free days or escalation of oxygen strategies, with consistent results using both frequentist and bayesian analytical methods.<sup>20</sup> Therefore, it seems reasonable to assume that awake proning also may have little or no indirect effects on critical care beds availability, a crucial aspect to consider for the response to the pandemic. Even though a cause-effect relationship cannot be established with certainty, the current best evidence is consistent in conferring no benefit to awake proning in reducing mortality risk. However, the lack of individual data, differences in the definition and reporting of outcomes and variability in duration of intervention among studies may limit any definitive conclusion. Despite treated people's overall negative attitude towards the position, with low tolerance along the prescribed intervention time, participants would highly recommend this modality, perceiving a potential benefit.<sup>21</sup> Moreover, very recently, despite moderate quality of evidence Rapid Practice Guidelines strongly recommended a trial of awake proning under different NRS strategies, suggesting that awake proning may be considered a valid clinical strategy.<sup>22</sup>

Despite the amount of literature on the management of COVID-19-associated acute respiratory failure (also Pulmonology has contributed to, see the reference list), in the future, large international registries, multicenter cohort studies and adequately powered prospective RCTs are needed to improve our understanding of the role of awake proning as well as of other diagnostic and therapeutic options in the comprehensive management of these individuals.<sup>23,24</sup> Based on the current evidence, there is still no firm conclusion on the clinical role of awake proning in spontaneously breathing individuals with COVID-19-related acute respiratory failure, even if this tool has been shown to improve oxygenation for these individuals and appears to be safe. However, the benefits of reducing intubation rates have been only seen in moderate-to-severe individuals undergoing high-flow nasal cannula. Awake prone position should be initiated early and with a target of at least 8 h/day duration. Pillows under the body and an accurate search of individualised position are essential to enhance adherence. Oxygenation improvement and changes in the lung ultrasound findings may help to identify those individuals more likely to avoid intubation.<sup>25</sup>

So, where should we go from here? Although awake proning is challenging for healthcare workers and cared people, the growing body of literature provides several promising results to be evaluated in more depth also in non-COVID

scenarios. A more nuanced understanding regarding the type and severity of the population most likely to benefit from awake proning, its safety profile and the best daily duration and timing of its initiation, implementation, and interruption is required to avoid delayed intubation and to assess its long-term clinical efficacy. To move forward and provide definitive evidence, accurate and methodical recordings of awake proning and objective measures of adherence and compliance should be considered for the design of future research. Until then, awake proning should be a selected and tailored choice of physicians after a judicious clinical evaluation and warranted close monitoring for adherence, clinical response and need for intubation. Indeed, like any other medical intervention, awake prone positioning should not be considered a “better than nothing” strategy, even in resource-limited settings and it should be applied in locations adequate for number, and quality of trained caregivers, with dedicated structures and devices.

## Conflicts of interest

The authors declare no conflict of interests.

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