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Prone positioning and NMBAs are part of the standard of care in severe ARDS patients: con

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The concept of ‘standard of care’ has different definitions and implications according to its contextual use.[1] In this commentary we will focus on whether prone positioning and neuromuscular blockade should be considered ‘standard of care’ in the sense of what is ‘best’ practice for these patients as this has relevance for both patient care and future research.[1, 2]

Prone ventilation has been studied for over three decades with consistent findings of improved oxygenation and, with one exception, no change in mortality. However, meta-analyses suggest benefit with a longer daily duration of proning when applied to the subset with more severe ARDS.[3, 4] Based on this background, Guerin and colleagues studied longer duration prone ventilation (17 hours per day) and limited enrollment to patients with more severe ARDS. They demonstrated improved oxygenation (likely indicating recruitment) and a substantial mortality benefit (likely reflecting lung protection) in comparison to a low tidal volume and lower PEEP approach in the semirecumbent position.[5] Based on this trial and prior work, should prone ventilation now be standard of care for patients with severe ARDS? We think not.

First, consider the results of an individual patient-level meta-analysis of randomized trials of higher PEEP. Higher PEEP approaches improved mortality in the moderate and severe ARDS subsets (PaO_2/FiO_2 (P/F) ≤ 200) in comparison to the lower PEEP approach used by the PROSEVA investigators.[6] Furthermore, a post-hoc analysis of the LOV study revealed

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that when P/F increases after PEEP is increased, mortality is reduced (adjusted odds ratio, 0.80 [95% confidence interval, 0.72–0.89] per 25–mm Hg increase in P/F).[7] This was particularly evident in patients with more severe disease (P/F </=150mmHg), the threshold for enrollment used by the PROSEVA investigators. Thus it remains unclear if prone ventilation is superior to higher PEEP strategies particularly in patients with severe ARDS who respond to an increase in PEEP with a substantial increase in P/F (so called responders). Finally, the safety of prone ventilation in inexperienced centers is also unclear.

Until the results of much needed studies comparing higher PEEP in responders with prone ventilation are complete, we recommend a lower tidal volume/higher PEEP strategy as the initial approach for patients with severe ARDS. Patients with a favorable response to higher PEEP could continue to be treated in the semirecumbent position, though we acknowledge it is unclear if this approach is superior to going directly to prone ventilation. Patients with severe ARDS who fail to respond to higher PEEP with improved P/F should be managed in the prone position with a return to a lower PEEP strategy, as tested in the PROSEVA study. Inexperienced centers should train their staff on safe prone practices before adopting this approach.

A similar situation exists regarding the use of early routine neuromuscular blockade in patients with ARDS. The potential benefits of neuromuscular blockade may be mediated by improved patient-ventilator interactions. Spontaneously breathing patients with ARDS can have a very high drive to breathe. This can lead to patients drawing larger-than-targeted tidal volumes on each breath with frequent and potentially erratic triggering of the ventilator and ultimately volutrauma and biotrauma. Small RCTs examining mechanistic effects of neuromuscular blockers have shown improved oxygenation along with reductions in inflammatory cytokines in both broncho-alveolar lavage fluid and serum in those patients receiving neuromuscular blockade.[8, 9]

In 2010 French investigators reported that the neuromuscular blocker cisatracurium saved lives in patients with moderate-severe ARDS. The ACURASYS trial compared early cisatracurium infusion for 48 hours to placebo in 340 patients from 20 French ICUs and showed an improved adjusted survival for patients in the neuromuscular blocker group (hazard ratio 0.68; 95% CI 0.48-0.98).[10] However, this approach has not been widely adopted, potentially due to several study limitations. First, the mortality benefit was noted only after statistical adjustment for baseline differences and the authors themselves acknowledge that the trial was underpowered, a fact that can lead to false positive results. [11] Second, assessment of potential adverse effects of the intervention, including muscle paresis in survivors, lacked sensitivity, potentially leading to their underestimation. Third, both groups in this trial received high doses of sedatives that may impair long-term functional and cognitive outcomes and the control ventilation strategy used a lower PEEP approach that may not have been optimal given the severity of the ARDS, as noted above. Thus it is possible that ventilation with higher PEEP and less sedation, an approach increasingly used in usual care, could be superior to cisatracurium if adverse effects of sedation and paralysis outweigh the potential benefits of reducing ventilator-induced lung injury through paralysis. As a result of these concerns, the critical care community has

collectively recommended a confirmatory clinical trial to definitively test the safety and efficacy of neuromuscular blockade in patients with ARDS.[12]

In the past, neuromuscular blockade was commonly used for ventilated patients with acute respiratory failure.[13] However, with its increased utilization, neuromuscular blockade was implicated in the development of ICU-acquired weakness,[14] though this association has been recently challenged,[15] and we agree that data supporting this link are tenuous at best. If, however, the association does exist, the alleged early benefits of neuromuscular blockade may be offset by ICU-acquired weakness, a syndrome that may limit the ability of patients to be liberated from mechanical ventilation and to recover their autonomy. Neuromuscular blockade is also associated with a risk of paralyzed wakefulness since paralytics have no intrinsic sedative properties and it is very difficult to assess the depth of sedation in patients who are paralyzed. Thus, neuromuscular blocker use necessitates concomitant deep sedation. In turn, too much sedation can increase the duration of mechanical ventilation.

For all the reasons outlined above, we believe that while both prone positioning and neuromuscular blockade are promising therapies that *may* improve mortality for patients with moderate-severe ARDS, their relative place in our treatment armamentarium remains uncertain. In particular how they compare with a simpler approach of higher PEEP and less sedation is unknown. For these reasons, we believe that their use should be studied further, rather than mandated as standard care.

References

1. Miller FG, Silverman HJ. The ethical relevance of the standard of care in the design of clinical trials. American Journal of Respiratory and Critical Care Medicine. 2004; 169:562–564. [PubMed: 14701713]
2. Kim SYH, Miller FG. Varieties of Standard-of-Care Treatment Randomized Trials. JAMA. 2015 doi: 10.1001/jama.2014.18528.
3. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med. 2010; 36:585–599. doi: 10.1007/s00134-009-1748-1. [PubMed: 20130832]
4. Abroug F, Ouanes-Besbes L, Elatrous S, Brochard L. The effect of prone positioning in acute respiratory distress syndrome or acute lung injury: a meta-analysis. Areas of uncertainty and recommendations for research. Intensive Care Med. 2008; 34:1002–1011. doi: 10.1007/s00134-008-1062-3. [PubMed: 18350271]
5. Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013; 368:2159–2168. doi: 10.1056/NEJMoa1214103. [PubMed: 23688302]
6. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA. 2010; 303:865–873. doi: 10.1001/jama.2010.218. [PubMed: 20197533]
7. Goligher EC, Kavanagh BP, Rubenfeld GD, et al. Oxygenation response to positive end-expiratory pressure predicts mortality in acute respiratory distress syndrome. A secondary analysis of the LOVS and ExPress trials. American Journal of Respiratory and Critical Care Medicine. 2014; 190:70–76. doi: 10.1164/rccm.201404-0688OC. [PubMed: 24919111]
8. Gainnier M, Roch A, Forel JM, et al. Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Crit Care Med. 2004; 32:113–119. [PubMed: 14707568]

9. Forel J-M, Roch A, Marin VR, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome*. Crit Care Med. 2006; 34:2749–2757. doi: 10.1097/01.CCM.0000239435.87433.0D. [PubMed: 16932229]

10. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010; 363:1107–1116. doi: 10.1056/NEJMoa1005372. [PubMed: 20843245]

11. Christley RM. Power and Error: Increased Risk of False Positive Results in Underpowered Studies. The Open Epidemiology Journal. 2010:1–4.

12. Slutsky AS. Neuromuscular blocking agents in ARDS. N Engl J Med. 2010; 363:1176–1180. doi: 10.1056/NEJMe1007136. [PubMed: 20843254]

13. Hansen-Flaschen JH, Brazinsky S, Basile C, Lanken PN. Use of sedating drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure. A national survey. JAMA. 1991; 266:2870–2875. [PubMed: 1942456]

14. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014; 371:287–288. doi: 10.1056/NEJMc1406274. [PubMed: 25014703]

15. Puthucheary Z, Rawal J, Ratnayake G, et al. Neuromuscular blockade and skeletal muscle weakness in critically ill patients: time to rethink the evidence? American Journal of Respiratory and Critical Care Medicine. 2012; 185:911–917. doi: 10.1164/rccm.201107-1320OE. [PubMed: 22550208]