Neuromuscular Blocking Agents for ARDS: Incentive for Personalized Medicine

To the Editor:

We thank Drs Vargas and Servillo for their interest in our meta-analysis and the important points they raised regarding the use of neuromuscular blocking agents (NMBAs) in ARDS.[1] Based on the findings from the 6 trials included in our meta-analysis, we reported that early use of NMBAs in moderate-to-severe ARDS improves oxygenation, decreases ventilator-induced lung injury, and decreases 21–28-d mortality.[1] We agree that the current literature does not support a 90-d mortality benefit associated with NMBA use. NMBAs are thought to exert a benefit in ARDS by decreasing inflammatory markers, increasing recruitment, improving ventilation/perfusion matching, and reducing ventilator asynchrony and ventilator-induced lung injury.[2-4] Given the mechanism of action of NMBAs, these benefits may be transient and may only provide a short-term mortality benefit due to the progression of ARDS to a fibrotic phase.[5]

We also agree that there are limitations in concluding that NMBAs provide a short-term mortality benefit, as evidenced by the results of fragility index calculations shared by Drs Vargas and Servillo. The use of the fragility index in critical care, however, has its own limitations due to heterogeneity in critical care trials.[6,7] For example, the I^2 statistics for 21–28-d and 90-d mortality in our meta-analysis were 60% and 54%, respectively.[1] Additionally, trial sequential analysis (TSA) is a complex statistical tool, and application in meta-analyses is not universal. TSA is not routinely employed within the Cochrane Collaboration, with its standardized methods and clinical reviews, and the Cochrane Scientific Committee Expert Panel recommends against the routine use of sequential methods for updated meta-analyses.[8] Although systematic reviews can address the effect of an intervention on different outcomes and subgroups, sequential methods such as TSA cannot accommodate multiple thresholds for different outcomes. Meta-analyses are retrospective and observational by nature; therefore, we are unable to control for the trials that have already been performed and are eligible for the meta-analysis. It is difficult to create a retrospective sequential program that would maintain the prespecified assumptions of a TSA.

In addition to heterogeneity in critical care trials, there are also limitations in study recruitment and trial design. The calculated sample size of almost 19,000 subjects with moderate-to-severe ARDS needed to effectively conclude whether NMBAs impact 21–28-d and 90-d mortality is likely not feasible and is unlikely to ever be completed. We must use existing literature and carefully evaluate for limitations before applying the data to clinical practice. Based on the findings from our meta-analysis and scrutiny of the included trials, we do not believe that NMBA therapy should be applied in all patients with moderate-to-severe ARDS. The use of NMBA therapy is not without risk,[9] and use should be reserved for patients who do not experience improvements in oxygenation and ventilator synchrony despite application of first-line nonpharmacologic interventions.[10] The solution is not larger trials, but more studies evaluating the impact of pharmacologic therapies like NMBAs on ARDS phenotypes and subphenotypes. Application of therapies that specifically target ARDS phenotypes will improve patient outcomes and limit adverse effects associated with these therapies.[11,12]

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