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Authors' Reply to Dr. Davies

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Dear Editor,

We thank Dr. Davies for his thoughtful comments (1) on our study on inhaled Nitric Oxide (iNO) treatment in children with Pediatric Acute Respiratory Distress Syndrome (PARDS). (2) We wholeheartedly agree with Dr. Davies' comment that iNO treatment as a rescue therapy deserves more investigation. However, our study also demonstrates that iNO treatment (in 2 large United States Pediatric Intensive Care Units) is still frequently used in children with initial oxygenation indexes that are in the mild to moderate PARDS severity range. As such, we felt it important to consider all PARDS patients in the analysis, and oxygenation index was a variable used in the propensity matching.

Although our study is one of the largest of iNO treatment in PARDS, we did not perform subgroup analyses by mild, moderate, and severe PARDS due to the small number of children within each category and the need to control for multiple confounding variables. Acknowledging the importance of PARDS severity, as Dr. Davies highlights, we did a sensitivity analysis in our study restricted to children with moderate to severe PARDS (n=130), which also showed no benefit for iNO treatment (OR 0.98 (95% CI 0.37–2.64; p=0.97)). However, based on the request of Dr. Davies we have re-analyzed our data by initial PARDS severity. We were unable to control for use of extracorporeal membrane oxygenation (ECMO) in this analysis due to the small number of children treated with ECMO in each group. In 54 children with severe PARDS matched on their propensity for iNO treatment, iNO treatment was not associated with mortality (OR 1.6 (95% CI 0.42–5.5),

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p=0.65) after controlling for use of non-conventional ventilation. In the 72 matched children with moderate PARDS, iNO treatment was not associated with mortality (OR 0.5 (95% CI 0.07–3.7), p=0.5) after controlling for use of non-conventional ventilation. In the 26 matched children with mild PARDS, iNO treatment was not associated with mortality (OR 2.4 (95% CI 0.18–31.3), p=0.51) after controlling for use of non-conventional ventilation. In these subgroups, the 95% confidence intervals are wide given the small number of children in each subgroup. As such, changes in the “direction” of the odds ratios should be interpreted with caution. Nonetheless, our data do not show evidence for a trend in the association between iNO treatment with mortality according to PARDS severity.

Although our data suggests no relationship between iNO treatment and mortality amongst PARDS patients, it remains possible that in a subset of children with PARDS, which remains to be identified, there is a clinically meaningful effect of iNO treatment. We hope the results of our study will lead to more clinical equipoise for a properly designed prospective study to assess the impact of iNO treatment in children with PARDS.

References

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