

A breath of fresh air: Does spontaneous breathing and early repair in neonates with very mild congenital diaphragmatic hernia lead to earlier discharge?

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Dear Editor:

We read with great interest the article by Kipfmüller et al. that investigated the feasibility and outcomes of a spontaneous breathing approach (SBA) versus immediate intubation in neonates with prenatally diagnosed very mild CDH and found that it appears to be feasible and beneficial¹. The authors present an approach that is quite novel - spontaneous breathing and enteral feeding in the pre-surgical repair phase. We compliment the authors for their attempt to address an issue very relevant to the acute management of CDH. Nonetheless, we feel compelled to highlight some aspects that should be considered for adequate interpretation of their findings.

The study's sample size is quite small (n=24), but the fact that the investigators found statistical significance for numerous associations despite such a small sample size demonstrates the strength of the relationships. It is a common misconception that statistical significance due to chance (i.e., Type I error) is more likely when the sample size is small, although low power due to the small sample size is actually difficult to overcome². However, when evaluating Table 1, after matching on observed-to-expected lung-to-head-ratio (o/e LHR), liver position, gestational age at delivery, birth weight, and defect size, we note that prerepair characteristics such as early feeding, Oxygenation Index (OI) and FiO₂, and Apgar at 10min are still significantly imbalanced between the SBA and standard treatment groups, which raises concerns about potential confounding. For this reason, we recommend the authors complement the unadjusted analyses they report with multivariable regression analyses that compare SBA versus standard treatment after controlling for Apgar 10, OI and FiO₂, although the study sample size of n=24 would typically be considered too small for this kind of multivariable regression analysis. Per the authors, 39 patients met their prenatal eligibility criteria. A better and more meaningful comparison of outcomes would be to compare the 8 patients that underwent SBA versus the remaining 31 patient that met their predetermined 'eligibility criteria' and did not undergo planned SBA. Using this approach would diminish the potential differences in cohort caused by severity of hernia defect, given the fact that some patients in the standard treatment group required patch repair. In the study, the authors incorporated the post natively determined CDH defect size into the matching process; we would advise against using defect size for matching as it cannot be replicated prospectively.

The authors utilized the Mann-Whitney U test and Fisher's exact test to compare the SBA versus standard treatment groups in terms of quantitative and categorical variables, respectively. These methods ignore the dependence structure in the data resulting from matching. Although this type of oversight is common, we would recommend analyzing the data differently. Utilizing mixed-effects linear models and generalized estimating equations for quantitative and categorical outcomes, respectively, would appropriately accommodate

the clustering of study patients due to matching.

We were impressed by the decision to initiate enteral feeding prior to surgery and wonder if this approach could be a gut priming strategy favoring outcomes beyond the need for parenteral nutrition³. However, while novel and potentially beneficial, this strategy carries with it risks and will need to be investigated further before others will choose to adopt such a practice.

Overall, the authors tackle an important subject and their findings raise questions on whether routine intubation is beneficial for infants with mild CDH. As SBA infants were compared to those with more severe hernias, the observed differences noted between groups are likely a reflection of the severity of lung hypoplasia and not a result of the intervention. We encourage the authors to further explore this strategy with a larger multicenter study to draw meaningful conclusions from the study results.

Clinicians should be cautious of implementing guideline changes based on retrospective studies, as prospective studies do not always validate inferences derived from retrospective studies, such as permissive hypercapnia to prevent bronchopulmonary dysplasia in extremely low birth weight infants (ELBW)⁴. Centers that perform early repair could consider an SBA approach for a well-defined cohort of infants with mild CDH, as it appears this can decrease the duration of ventilation and length of hospital stay. However, this precision-based medicine approach would be best evaluated by a prospective study to assess the benefits and risks of implementing this strategy.

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