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Letter to the Editor: Effect on splanchnic oxygenation of breast milk, fortified breast milk and formula milk in preterm infants

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We read with interest the paper by Dani et al.[1] "Effect on splanchnic oxygenation of breast milk, fortified breast milk (FBM) and formula milk in preterm infants". Necrotising enterocolitis (NEC) remains an important morbidity in neonatal units, yet considerable uncertainties remain about the interaction between milk feeding regimes, use of human milk and milk fortifiers, gut microbiota and disturbances to gut blood flow in the pathogenesis. The difficulty of studying these factors in preterm infants contributes to this ongoing uncertainty. Near-infrared spectroscopy (NIRS) may provide a non-invasive technique to study gut blood flow and holds potential for point-of-care testing.

We congratulate Dani et al. for contributing data to this debate, but wish to raise a number of important issues. While there was no statistically significant difference in baseline demographic data between the three feeding groups, variables of potential clinical significance appear different. Infants in the preterm formula (PTF) fed group were 2 weeks more immature and over 300 g lighter at birth and were studied at a postnatal age that was 3 weeks later than the infants in the mother's own milk (MOM) group. Organ function and physiological responses change with advancing age and differences in the postnatal day at which measurements are obtained introduce potential confounding.[2] Importantly, infants in all three groups were studied at 35–38 weeks postmenstrual age when the incidence of NEC is low. Finally, for both the FBM and PTF groups there were a higher proportion of infants with bronchopulmonary dysplasia, patent ductus arteriosus and retinopathy of prematurity suggesting a difference in overall illness severity, which was not adjusted for in the analyses. Another clinical variable that would be important to include is the infant's haematocrit. It has been shown that anaemia may result in lower splanchnic regional oxygenation (rSO_2S) with feedings.[3] This is especially relevant if a difference in overall illness severity exists between the groups as suggested by the differences in the proportion of co-morbidities.

We also note that a feeding regime that promoted trophic feeds of 20–40 ml/kg per day for up to 5 days, followed by increments of 20 ml/kg per day might have been expected to achieve full feeds (150 ml/kg per day) by around 12–14 days of age, whereas full feeds were not achieved until 25 days of age, despite <5% developing NEC, and with no cases occurring in those solely fed on MOM. The feeding regime recommended the introduction of fortifier to MOM when feed volumes of 120 ml/kg per day were tolerated, yet infants in the MOM-only group were studied at around 6 weeks of age and none had been given fortifier.

NIRS provides continuous data, and 12 data points per minute over a 5-min period were used for analysis. When there were artefacts, a different time period was used, meaning the same time periods may not have been compared in all cases. The most significant changes in rSO_2S and fractional oxygen extraction ratio (FOES) occurred at time point 2 (T2) in the group fed PTF; however, the standard deviation (SD) of the rSO_2S (%) at this stage was around four times greater in the PTF (SD = 17.8) group compared to the MOM (SD = 3.7) group. Figure 2 shows that the distribution in the PTF group at T2 was heavily skewed with a median FOES of >0.6, compared to the mean value of 0.5 provided in Table 2. The mean FOES differences in the PTF group between T1 and T2 are very small (0.03), despite a highly significant p value <0.001. The mean values of FOES at T1 (0.47) and T2 (0.50) differed by only 6% in absolute terms (0.03/0.50), whereas the reported SD is six times greater (0.18), suggesting that the dataset includes some extreme values.

One of the many differences between using cerebral and splanchnic NIRS are the tissues and structures that may scatter light.[4] When used to assess cerebral oxygenation, differences over short time periods are presumed to only reflect changes in blood oxygen extraction (since no other aspects of cerebral contents can change), but when placed on the abdomen, many other tissues and fluids (including liver, bile and gut contents) may be involved. While there are few data on splanchnic NIRS in preterm infants, we think readers would value the authors' opinion on the potentially confounding role of the milk substrate in the gastrointestinal tract. Preterm formula contains much higher concentrations of several nutrients, including fat, minerals, and metals compared to MOM. Calcium and casein complexes, along with fat, are what make milk white, and we would be keen to understand whether the authors consider that milk components may alter NIRS absorptive capacity, or whether readers should consider that differences can solely be ascribed to changes in blood oxygen levels.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing, intellectual content and approved the final version for publication.

ADDITIONAL INFORMATION

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REFERENCES

1. Dani, C. et al. Effect on splanchnic oxygenation of breast milk, fortified breast milk, and formula milk in preterm infants. *Pediatr. Res*. https://doi.org/10.1038/s41390-020-0935-1, (2020).
2. Ortigoza, E. B. et al. Electrogastrography, near-infrared spectroscopy, and acoustics to measure gastrointestinal development in preterm babies. *J. Pediatr. Gastroenterol. Nutr.* **66**, e146–e152 (2018).
3. Braski, K. et al. Splanchnic-cerebral oxygenation ratio decreases during enteral feedings in anemic preterm infants: observations under near-infrared spectroscopy. *Neonatology* **113**, 75–80 (2017).
4. Thompson, A., Benni, P., Seyhan, S. & Ehrenkranz, R. in *Oxygen Transport to Tissue XXXIV, Advances in Experimental Medicine and Biology* (ed. Welch, W. J.) 287–292 (Springer, 2013).