Expectant Management in the BeNeDuctusTrial

We would like to thank the editors for discussing our recently published results of the BeNeDuctus trial in the journal [1,2]. We would like to comment on some concerns about open label treatment, paracetamol exposure and daily fluid intake, which were raised in the neonatologist's viewpoint [1].

Regarding the open label treatment, the data is actually presented in the article [2]. Only one patient (0.7%) in the expectant management group received open label ibuprofen for three courses in total [2]. Additionally, no patient in the expectant management group underwent surgical or endovascular patent ductus arteriosus (PDA) closure prior to discharge home. As stated, we deliberately did not design a placebo-controlled trial. In fact, we randomized treatment intention, which might have contributed to this low open label treatment percentage.

As per study protocol, no co-interventions were allowed with the intention to close the PDA. If paracetamol was given, it was given in an analgesic dosage (20 to 40 mg/kg/day), rather than the advised higher dose of 60 mg/kg/day generally used to induce PDA closure [3]. In fact, we think that the absolute risk difference of -13.0% (95% CI -23.9 to -2.0) in paracetamol exposure might be driven by our treatment intention randomization strategy and our endeavor to refrain from (co-)interventions in the expectant management group. This might have led to a higher threshold to start paracetamol in these patients, even in the analgesic dosage. Apart from the early ibuprofen treatment, the higher (co-) administration of paracetamol in the early pharmacological treatment group might have additional injurious effects on the developing lung, as has been suggested recently [4].

Regarding the daily fluid intake, we presented the intake on postnatal day 7 in the supplementary material. This did not differ significantly i.e., 162 (IQR 157-181) mL/kg/24 hour in the expectant management group vs 160 [IQR 150-184] mL/kg/24 hour in the early pharmacological treatment group [2]. Fluid restriction; although, commonly used as supportive care in infants with PDA, should, in our opinion, be avoided, since it has been association with reduced growth and probably worsened systemic hypoperfusion [5].

We are currently collecting neurodevelopmental outcome data assessed at two years corrected age. Furthermore, we are reassessing echocardiograms to further stratify those patients with a high transductal shunt volume at enrollment and analyze whether our primary hypothesis of non-inferiority holds within this group. Although, many neonatologists, including ourselves, feel there might be a subgroup that would benefit from early pharmacological treatment, to date this has not been proven.

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REFERENCES

1. Gupta N. Is expectant management noninferior to early ibuprofen for patent ductus arteriosus?: neonatologist's view-point. Indian Pediatr.2023;60:489-90.
2. Hundscheid T, Onland W, Kooi EMW, et al. Expectant management or early ibuprofen for patent ductus arteriosus. N Engl J Med.2023;388:980-90.
3. Jasani B, Mitra S, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev.2022; 12:CD010061.
4. Wright CJ. Acetaminophen and the developing lung: could there be lifelong consequences? J Pediatr.2021;235:264-76.
5. De Buyst J, Rakza T, Pennaforte T, Johansson AB, Storme L. Hemodynamic effects of fluid restriction in preterm infants with significant patent ductus arteriosus. J Pediatr.2012; 161:404-8.