

Literature review position

Subject: The role of ibuprofen as patent ductus arteriosus treatment in the pathogenesis of bronchopulmonary dysplasia

Supervisor: Tim Hundscheid, pediatrician fellow neonatology

Co-supervisors: Willem P de Boode, pediatrician-neonatologist; Wievineke Apers, pediatric resident

Patent ductus arteriosus, in which the fetal connection between the pulmonary artery and the aorta remains patent after birth, is common in extremely preterm infants. Prolonged patency is associated with morbidity and mortality. From a pathophysiological point of view the transductal left (aorta) to right (pulmonary artery) flow might lead to a pulmonary hyperperfusion and systemic hypoperfusion. The pulmonary hyperperfusion has long been thought to be responsible for the prolonged need for respiratory support and the development of bronchopulmonary dysplasia/chronic lung disease. In an attempt to close the PDA neonatologists pharmacological treatment with ibuprofen, a cyclo-oxygenase inhibitor which lowers the exposure to prostaglandins, is often initiated. Previous trials, although successful closure was achieved in over half of the cases exposed to ibuprofen, failed to show beneficial effects on the incidence of BPD between the ibuprofen treated and placebo treated group. However, many patients in the placebo/control arm received ibuprofen during their stay at the neonatal intensive care as open label treatment.

In our recently published BeNeDuctus trial we were able to truly compare ibuprofen for PDA in one group (137 children), with no treatment (135 of 136 children randomized to this group). Although we set the trial as a non-inferiority design, in which we aimed to show that no treatment was non-inferior to treatment, we actually found that infants that received ibuprofen were more likely to develop bronchopulmonary dysplasia (Absolute risk difference 17%).

We hypothesize that ibuprofen attenuates the pulmonary angiogenesis, which is a major contributor to lung development and bronchopulmonary dysplasia. Prostaglandins are thought to play a role in the vascular endothelial growth factor pathway, and thus attenuating prostaglandin concentration by ibuprofen, might interfere in this pathway. We would like to review and interpret the available literature on the anti-angiogenic factors of ibuprofen and their role in the development of the pulmonary architecture and bronchopulmonary dysplasia.

If you are interested in this topic feel free to contact me at tim.hundscheid@radboudumc.nl

Suggested readings

[Expectant Management or Early Ibuprofen for Patent Ductus Arteriosus - PubMed \(nih.gov\)](#)

[Decreased plasma levels of PDGF-BB, VEGF-A, and HIF-2 \$\alpha\$ in preterm infants after ibuprofen treatment - PubMed \(nih.gov\)](#)

Kind regards,

Tim Hundscheid

Pediatrician, fellow neonatology

PhD Student BeNeDuctus-trial