

# EFFICACY AND SAFETY OF PHARMACOLOGICAL TREATMENTS FOR PATENT DUCTUS ARTERIOSUS CLOSURE: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF CLINICAL TRIALS AND OBSERVATIONAL STUDIES INVOLVING 15,725 SUBJECTS

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**Introduction:** Importance: Efficacy and safety profiles of different pharmacological interventions used to treat patent ductus arteriosus (PDA) are relatively unexplored. Integrating the findings of randomized clinical trials (RCTs) with those from observational studies may provide key evidence on this important issue. Objectives: To estimate the relative likelihood of PDA closure, need for surgical closure, and occurrence of adverse events among preterm infants treated with different pharmacotherapies.

**Methods:** Data Sources: We searched PubMed, Embase, and the Register of Controlled Trials from inception to October 30, 2018. Study Selection: We considered RCTs and observational studies conducted on newborns with clinically or echocardiographically diagnosed hemodynamically-significant PDA treated with indomethacin, ibuprofen, or acetaminophen, placebo, or no treatment. Data Extraction and Synthesis: We summarized results at the end of treatment reported in the papers, regardless of number of administration(s), dose, route and type of administration, and study design and quality. We also summarized separately first, second and third cycles of treatment. We compared active drugs with each other and with placebo through Bayesian random-effects network meta-analysis and reported results as Odds Ratios (ORs) and 95% Credible Interval (CrI) for mixed comparisons, ORs and 95% Confidence Interval (CI) for direct comparison. Main Outcomes and Measures: Primary: hemodynamically-significant PDA closure; secondary: need for surgical closure, selected adverse events.

**Results:** We included 67 RCTs and 24 observational studies. At end of treatment, compared to control, we found inverse associations between all active drugs and failure to close PDA (for indomethacin OR was 0.18[0.12-0.25], ibuprofen 0.20 [0.13-0.29], and acetaminophen 0.16[0.09-0.28]), without differences among active drugs. We showed inverse associations between effective drugs and need for surgical closure, as compared to control (for indomethacin OR was 0.39[0.26-0.57], ibuprofen 0.42[0.26-0.63], and acetaminophen 0.26[0.11-0.61]), without differences among drugs. Indomethacin was directly associated with intraventricular hemorrhage (IVH) (1.26; 1.01, 1.57) compared to ibuprofen, and to oliguria as compared to ibuprofen (3.91; 1.69, 9.76) or acetaminophen (10.8; 1.87, 92.5).

**Conclusion:** Active pharmacological treatment with indomethacin, ibuprofen, or acetaminophen, effectively promotes PDA closure compared to non-treatment. Ibuprofen should be the best choice to avoid occurrence of intraventricular hemorrhage or acute renal failure, acetaminophen to avoid acute renal failure.

Neonatologists' prescription choices should be based more on the potentially different safety profiles of these medications rather than on efficacy concerns, tailoring treatment to the newborn's specific clinical conditions.