

Title:

Paracetamol versus Indomethacin for management of Patent Ductus Arteriosus in Premature Infants- A Systematic Review and Meta-Analysis

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Background:

Premature infants with hemodynamically significant patent ductus arteriosus (HsPDA) have high rates of morbidity and mortality in neonatal units. Indomethacin has been the most common agent used for pharmacological closure of the PDA. Recently, paracetamol has gained interest in the neonatal community for its use for management of HsPDA. We conducted a systematic review of randomized controlled trials (RCTs) comparing the efficacy and safety of paracetamol with indomethacin for HsPDA management in preterm infants.

Methods:

We searched PROSPERO, OVID Medline, OVID EMBASE, Wiley Cochrane Library (CDSR and Central), EBSCO CINAHL, and SCOPUS using controlled vocabulary and key words representing the concepts "preterm neonates" and "acetaminophen" and "indomethacin". Databases were searched from inception to June 15, 2021. Bibliographies of identified studies were searched for additional references. Studies were included if they enrolled preterm infants with HsPDA (diagnosed on echocardiogram), and randomised them for treatment with paracetamol or indomethacin for the primary outcome of HsPDA closure. Discrepancies among reviewers for study selection, RoB assessments, and data extraction were resolved by consensus. Data were analyzed with the help of Review Manager (RevMan) Version 5.3.

Results:

Four RCTs were identified, enrolling a total of 380 subjects. There was no difference between the two interventions for the rates of PDA closure either after one course (4 studies; RR 1.04 [95% CIs: 0.84, 1.29], p-value 0.70) or after two courses of treatment (2 studies; RR 1.01 [95% CIs: 0.92, 1.12], p-value 0.77), and for PDA ligation (3 studies; RR 1.56 [95% CIs: 0.48, 5.12], p-value 0.46). However, the patients who received paracetamol had lower rates of necrotizing enterocolitis (NEC) (3 studies; RR 0.37 [95% CIs: 0.14, 0.95], p-value 0.04). There were no significant differences noted in the other important secondary outcomes, i.e., Intraventricular hemorrhage, bronchopulmonary dysplasia, retinopathy of prematurity requiring treatment, and death. Two studies reported baseline and post-treatment serum markers for renal and hepatic injury; there was significant post-treatment elevation of serum creatinine and blood urea noted with the indomethacin use in each of these studies, as compared to no change noted with paracetamol use.

Conclusion:

The efficacy of paracetamol is comparable to indomethacin for the outcome of PDA closure, with lesser rate of NEC and post-treatment azotemia noted with the paracetamol use. Paracetamol should be preferred over indomethacin for HsPDA management in premature infants.