

# Oral Paracetamol versus Oral Ibuprofen in the Management of Patent Ductus Arteriosus in Preterm Infants: A Randomized Controlled Trial

## BACKGROUND:

- Acetaminophen has shown success in previous studies in PDA closure and ibuprofen is associated with the adverse effects such as peripheral vasoconstriction, GI bleed and perforation, decreased platelet aggregation, hyperbilirubinemia, and renal failure
- Another therapeutic option would be beneficial for the treatment of PDA

## OBJECTIVE

- to compare the efficacy and safety of oral paracetamol and oral ibuprofen for the pharmacological closure of patent ductus arteriosus in preterm infants

## METHODS

- **Design:** one maternity teaching hospital, randomized parallel trial; Duration: 11 months
- **Inclusion criteria:** Patients were  $\leq 30$  weeks gestation, birthweight  $\leq 1250$  g, postnatal age 48-96 hours, and either 1) a duct size  $> 1.5$  mm 2) a left atrium-to-aorta ratio  $> 1.5$  3) end diastolic reversal of blood flow in the aorta 4) poor cardiac function in addition to clinical signs of PDA
- **Exclusion criteria:** 1) this presence of major congenital abnormalities 2) right-to-left ductal shunting 3) life threatening infection 4) grade III or grade IV IVH 5) urine output of less than 1ml/kg/h during the preceding 8 hours 6) Scr  $> 1.6$  mg/dl 7) plt count  $< 60,000$  mm 8) liver failure 9) hyperbilirubinemia requiring exchange transfusion 10) persistent pulmonary hypertension.
- **Primary outcome measure:** success rate, defined as a closed duct on echocardiography after the completed course and the safety of the drug in preterm infants with birth weight  $\leq 1250$ g  
**Secondary outcome measures:** 1) need for retreatment or surgical ligation of the PDA 2) mode and duration of ventilation 3) increase in BUN, Scr, bilirubin, aspartate amino transferase, or ALT levels after treatment 4) rates of ductal reopening, surfactant treatment, pneumothorax, pulmonary hemorrhage, CLD, IVH, NEC, GI bleed, ROP, definite sepsis, and death.
- 80 patients
  - 40 in the acetaminophen group
  - 40 in the ibuprofen group
- a study group of 78 patients was required to detect a difference of at least 25% between the groups, assuming 83.3% closure rate with ibuprofen, with a p value of 0.05 and a power of 80%

## RESULTS

- all patients completed the study
- **Primary outcome measure:** PDA closed in 31 (77.5%) of IBU patients and 29 (72.5%) of acetaminophen group 95% CI (0.381 -1.757), RR, 0.818, p value 0.6.
- **Secondary outcome measures:** Nine (22.5%) patients in ibuprofen group required second course of therapy compared with 11 (27.5%) of acetaminophen group p value 0.6. The reopening rate was higher in the acetaminophen group 24.1% (7 of 29) vs 16.1% (5 of 31) 95% CI (0.239- 1.871), RR 0.668, p =0 .43. Only 1 patient in acetaminophen group (2.5%) and 2 (5%) in IBU group required surgical ligation 95% CI (0.047- 5.296), RR 0.5, p= .55. Bilirubin levels and renal and liver function results were not significantly different between the groups. Secondary outcome measures were not statistically significant between groups. Safety outcomes were not statistically significant between groups.

- **Author's conclusion:** Although closure rates were similar, the broad CI does not allow conclusion that the drugs are equally effective. Closure rates in infants > 27 weeks could have been due to spontaneous closure. Data on stratified patients based on gestational age < 28 and 26 weeks gestation reveal a higher but not significant rate of closure in those who received paracetamol compared with those given IBU. It can be surmised that paracetamol administration enhances closure of PDA in even very early gestation age infants. The study was not large enough to evaluate safety.

#### STRENGTHS

- Active control was appropriate dose and schedule for specific indication
- Addressed limitations of the study and need for further research
- No patients lost to follow-up

#### LIMITATIONS

- Unblinded
- High rate of spontaneous PDA closure were observed in the study which may confound the true efficacy of the medications
- Sample size was not sufficient to achieve goal power
- Sample population age did not correspond to population of interest for disease state
- Effect size used for power calculation was larger than what would be considered clinically important

#### CONCLUSION

- The study did not evaluate a large enough sample of patients to gain the results they desired therefore the comparative efficacy of ibuprofen and acetaminophen cannot be determined and the null hypothesis cannot be rejected.
  - Inclusion criteria was for patients  $\leq 30$  weeks gestation; since research shows spontaneous closure rates increase after 27 weeks they should exclude above this age
  - They used an effect size of 25% in the power calculation which is larger than would be clinically important and therefore should have used a smaller difference between groups to detect significance
  - Treatment regimens should have been performed using the double dummy method to blind investigators in the study
- Future research:
  - Exclude patients >27 weeks gestation
  - Study a larger sample of patients
  - Use a blinded study design
  - Determine a smaller effect size of clinical importance

**Reference:** Oncel, M., Yurttutan, S., Erdeve, O., Uras, N., Atug, N., Oguz, S., Canpolat, F., Dilmen., U. Oral Paracetamol versus Oral Ibuprofen in the Management of Patent Ductus Arteriosus in Preterm Infants: A Randomized Controlled Trial. The Journal of Pediatrics. 2014; 164(3): 510-14.

Prepared by: Kayla Mitchell, Doctor of Pharmacy Candidate