Effects of prophylactic indomethacin on morbidity and mortality in infants < 25 weeks gestation: a protocol driven intention to treat analysis

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Background:

- Clinical trials have not shown a benefit for early PDA treatment; however, several studies using large retrospective databases have reported improved neonatal mortality and morbidity in nurseries that use early PDA screening and/or treatment.
- Meta-analysis of 11,000 very preterm infants found prophylactic indomethacin (PINDO) was associated a significant, albeit small reduction in neonatal death
  - PINDO may act in a gestational age dependent manner with beneficial effects in sickest, most immature (<750g <25 weeks)

Questions:

- Does prophylactic indomethacin (PINDO) decrease death or BPD grade 2 and 3 in newborns < 25 weeks?

Study Design:

- Single center, cohort-controlled study using data from an ongoing QI project examining neonatal outcomes associated with a protocol-driven treatment approach
- Two groups: Infants admitted during an epoch where all were eligible for PINDO, and those admitted during an epoch where all received expectant management, and none received PINDO
- Inclusion: Delivery before 25 wks gestation and admission to NICU within 24 hours and survival beyond 24 hours.
- Not many <25 wks; 17 years to enroll study's 106 infants (2005-2022). Attempted to minimize differences by bracketing expectant management 2011-2017 with two PINDO epochs before 2005-2011 and after 2017-2022
- PINDO (n=68) : all infants started within 24 hours providing no contraindications. Five potential doses Q24h (0.2 mg/kg load then 0.1 mg x2-4). Doses 3 and 4 only given if evidence of PDA on echocardiogram after 2nd dose (routinely performed on day 7 or 8)
- Expectant Management (n=38) t: no PINDO, no infant treated with indomethacin during the first 7 days to allow for spontaneous PDA closure.
- Primary outcome: Death before 36 weeks or BPD grades 2 or 3 (modified room air challenge at 36 wks and using Jensen et al criteria)
- Secondary outcomes: Death during hospitalizations, BPD grades 2 or 3, Severe IVH, pulmonary hemorrhage, NEC, or SIP

Results:

- 111 infants < 25 weeks GA admitted during study period and 106 survived beyond 24 hours
- Demographics – preeclampsia, chorioamnionitis and outborn birth were significantly associated with birth year
- Clinical Practice changes – increased use of indomethacin for tocolysis, increased use of rescue betamethasone for mothers > 10 days beyond first dose, increased use of delayed cord clamping, increased NIV/avoidance of tracheal intubation/ventilation at delivery. [No changes in initiation/duration of caffeine, feeding advances. Probiotics and vit A not used]
- 91% of infants born in the PINDO epochs received indomethacin treatment in the first 24 hours. Only 24% moderate/large PDA shunt at the end of the week.
- In contrast, 85% of expectant management epoch infants had a moderate/large shunt at the end of the first week. 45% received indomethacin or acetaminophen as rescue PDA treatment after 7 days.
- Statistically significant PDA mod/large PDA at 7 days, 14 days, days exposed to mod/large ~23 EM and 0 PINDO
- No significant differences in the incidences of primary outcomes or secondary outcomes in unadjusted comparisons. Also created multivariable models to adjust for confounding effects also found no significant relationships between outcomes.

Limitations:

- Small, single center over 17 years. Incidence of PDA/other morbidities varies by center therefore not generalizable
- Confounding variables adjusted for however there may have been unmeasured changes that could have affected morbidity rates

Strengths

- Protocol-driven approach – minimally confounded by indication or selection bias
- Standardized, time-limited room air challenge to define BPD and reduce outcome bias

Conclusion:

- No significant differences in the incidences of BPD (grades 2 or 3) or death or secondary outcomes in unadjusted comparisons. Also created multivariable models to adjust for confounding effects also found no significant relationships between outcomes when prophylactic indomethacin was used routinely in infants < 25 weeks