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Association between prophylactic indomethacin and death or bronchopulmonary dysplasia: A systematic review and meta-analysis of observational studies

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ABSTRACT

The use of prophylactic indomethacin in very preterm infants is controversial. The last randomized controlled trial (RCT) to study this therapy enrolled infants over 20 years ago. More recently, observational studies have investigated the association between exposure to prophylactic indomethacin and neonatal morbidities and mortality. We performed a systematic review and meta-analysis of these studies for the outcomes of death and bronchopulmonary dysplasia (BPD). Two observational studies involving a total of 11,289 very preterm infants were suitable for meta-analysis. The pooled data showed that prophylactic indomethacin was not associated with higher or lower risk-adjusted odds of death or BPD (0.93, 95% CI: 0.76–1.13) and of BPD among survivors (0.94, 95% CI: 0.78–1.12). However, there was a weak association between indomethacin prophylaxis and decreased risk-adjusted odds of mortality (0.81, 95% CI: 0.66–0.98). It is unknown whether this finding resulted from unmeasured confounding, chance, or represents a true benefit. To confirm the hypothesis that prophylactic indomethacin has a small effect on mortality in the current era, a contemporary RCT would need to enroll over 3500 very immature infants at high risk of death.

Introduction

Since the earliest descriptions of ductal closure following administration of indomethacin, nearly 3000 very preterm infants have been enrolled in 19 randomized controlled trials (RCT) of prophylactic indomethacin.[1–4] The trials have shown that administration of indomethacin soon after birth reduces the incidence of severe peri- and intraventicular hemorrhage and symptomatic patent ductus arteriosus (PDA).[4] Despite these benefits, no difference was observed in the rates of mortality, bronchopulmonary dysplasia (BPD), or adverse long-term neurodevelopment.[4] The lack of evidence for a treatment effect on BPD is noteworthy, because of the strong association between the presence of a PDA and the subsequent development of BPD.[5–7] However, a key limitation of the RCTs is that most defined BPD as the use of supplemental oxygen at 28

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days of life.[4] Only the Trial of Indomethacin Prophylaxis in Preterms (TIPP) assessed supplemental oxygen use at 36 weeks post-menstrual age (PMA).[4,8]

Importantly, the last participants in the published RCTs were enrolled over 20 years ago.[4,8] Although by most estimates, rates of BPD have not improved during that time span, survival among the most extremely preterm infants has increased.[9,10] Moreover, modern obstetrical and neonatal care includes greater use of antenatal corticosteroids and exogenous surfactant, and less use of early invasive mechanical ventilation.[9] Whether the safety and efficacy of prophylactic indomethacin differ in the current era is unknown. Over the past 2 decades, several observational studies were conducted with varying methodologies and rigor and have produced conflicting results.[11–19] In the absence of contemporary trial data, clinicians may increasingly be tempted to use data from these observational studies to assess the risks and benefits of prophylactic indomethacin and inform their practice.[20] We undertook the present systematic review and meta-analysis to synthesize data from these observational studies and evaluate the association between exposure to prophylactic indomethacin and the outcomes of death and BPD. We compare these results to the existing pooled data from randomized clinical trials.

Review methods

Two authors (E.A.J. and E.E.F.) independently conducted a systematic search of PubMed according to the strategy summarized in Box 1). Studies selected for inclusion compared the risk of developing BPD, defined as the use of supplemental oxygen at 36 weeks PMA, between infants who received prophylactic indomethacin (treatment on the day of birth or day after birth) and contemporary untreated controls. The meta-analysis was limited to studies reporting risk-adjusted estimates of effect to reduce the influence of unmeasured confounding. Separate meta-analyses were performed for the composite outcome of death or BPD and the individual outcomes of BPD among survivors and mortality. To pool data from multiple observational studies, we obtained adjusted log[odds ratio] and log[standard error] values from the respective corresponding authors. Each meta-analysis was conducted using a random effects models and the generic inverse variance method in RevMan version 5.3 (The Cochrane Collaborative, Copenhagen, Denmark).

To compare the observational and RCT data, we recreated the forest plots for the outcomes of BPD and mortality that were included in the most recent Cochrane review on the use of prophylactic indomethacin.[4] The composite outcome of death or BPD was not reported in this review.[4] In addition, we conducted an exploratory meta-analysis of all 10 trials reporting BPD as an outcome (defined as supplemental oxygen use at 28 days or 36 weeks PMA). Finally, we performed cumulative meta-analyses to assess whether the measured effect of prophylactic indomethacin on BPD and mortality changed over time. The cumulative plots were generated using Stata/SE version 13.1 (StataCorp LP, College Station, TX).

BOX 1–Observational study systematic review and meta-analysis search strategy.

Search terms:

PubMed queried on 01/01/2018 for human studies identified using the following search phrase: (indomethacin) AND (infant OR neonate) AND (preterm or premature).

Inclusion criteria:

- Original, observational research studies comparing preterm infants (gestational age < 32 weeks and/or birth weight < 1500 g) treated with prophylactic indomethacin (treatment initiated on the day of birth or day after birth) to concurrent, untreated controls.
- Report bronchopulmonary dysplasia diagnosed at 36 weeks PMA as an outcome
- Abstract available in English
- For inclusion in the meta-analysis—studies must report risk-adjusted estimates of the association between prophylactic indomethacin and the study outcomes.

Exclusion criteria:

- Randomized trials
- Studies using historical (non-concurrent) controls
- Studies using only select infants as control (e.g., those with echocardiography diagnosed PDA)
- Studies likely to have a high degree of bias or non-generalizability (e.g., studies evaluating primarily outborn infants)

Literature search results

The PubMed search identified 1101 potential articles for inclusion, of which 4 fulfilled the pre-specified inclusion/exclusion criteria and 2 were suitable for inclusion in the meta-analysis (Fig. 1).[11,12,14,15] The studies by Laughon et al. and Cordero et al. were excluded from the meta-analysis because neither reported adjusted estimates of effect for the association between treatment with prophylactic indomethacin and the risk for developing BPD.[14,15] Laughon et al. performed adjusted analyses for their comparison of infants treated with indomethacin after the first day of life and those who did not undergo treatment for a PDA.[15] However, infants treated with prophylactic indomethacin were not included owing to differences in the demographic characteristics of these infants relative to the other evaluated babies.[15] Cordero et al. compared 167 infants born <1000 g who were treated with prophylactic indomethacin to 167 untreated infants matched by year of birth, birth weight, gestational age, and gender.[14] The unadjusted rates of BPD were similar between the groups, however the authors did not report adjustment for potential confounding variables.[14]

The methods and results of the 2 studies included in the meta-analysis are summarized in Table 1. In total, the studies included 11,289 very preterm infants cared for in hospitals participating in the Canadian Neonatal Network (CNN) and the US National Institute of Child Health and Human Development Neonatal Research Network (NRN), respectively.[11,12] Among the study infants, 2856 (25.3%)