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JOURNAL CLUB

Does inhaled budesonide for bronchopulmonary dysplasia affect the neurodevelopmental outcomes?

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Type of investigation

Prognosis; exploratory secondary analysis of an interventional randomized controlled trial: "Early Inhaled Budesonide for the Prevention of Bronchopulmonary Dysplasia".

Question

In extremely preterm infants (<28 weeks) does treatment with early inhaled budesonide, compared to placebo, affect neurodevelopmental outcomes at 2 years of age?

Patients: The study population consists of 629 surviving infants with complete follow-up data, among 863 extremely preterm infants who required positive pressure respiratory support at birth (born between April 2010 and August 2013). Subjects were stratified based on gestational age (GA) at birth: 23 weeks 0 days to 25 weeks 6 days and 26 weeks 0 days to 27 weeks 6 days. In all, 438 infants received budesonide, of which 82 died, between birth and follow-up, and 308 with adequate data were included in the analysis. In all, 422 infants received placebo, of which 58 died and 321 were included in the analysis.

Intervention: A total of 863 infants were randomly assigned to receive either inhaled budesonide or placebo within 24 h after birth. Inhaled budesonide or placebo was given two puffs (200 µg/puff) every 12 h for 14 days, then one puff every 12 h until supplemental oxygen and/or positive pressure respiratory support was no longer required, or the infant was 32 weeks 0 days postmenstural age (PMA).

Outcome: Neurodevelopmental impairment (NDI) among survivors.

NDI was defined as cerebral palsy, cognitive delay (defined as mental developmental score < 85 Bayley's II), deafness, or blindness at a corrected age of 18–22 months.

Allocation: Concealed, blinded medication box.

Randomization and masking of treatment assignments: Blocked randomization (fixed block sizes of 8) with allocation ratio of 1:1.

Blinding: Group allocation was blinded to everyone involved in care of the patients except the pharmacist.

Follow-up period: Infants were followed up at 18–22 months' corrected age.

Setting: Forty centers (Neonatal Intensive Care Units taking care of extremely preterm infants) of nine countries.

Analysis and sample size: In this effectiveness trial, 863 infants were recruited to demonstrate a 20% relative risk reduction in death or bronchopulmonary dysplasia (BPD). This provided a power of 80% and type I error rate of 5%. Intention-to-treat principle was used to analyze the outcomes. Of note, this article reports long-term, secondary outcomes for which the study was not adequately powered.

Patient follow-up: Adequate data were available for 629 (72.8%) of 863 infants recruited in the study.

Main results

Two hundred and thirty (59%) infants in the budesonide group and 223 (58.8%) in placebo group had combined outcome of death or NDI (relative risk (RR): 1.00, 95% confidence interval (CI): 0.89–1.13, $p = 0.97$). One hundred and forty-eight (48.1%) infants assigned to budesonide and 165 (51.4%) infants assigned to placebo had NDI (RR

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[adjusted for gestational age]: 0.93, 95% CI: 0.80–1.09, $p = 0.40$). There were no significant differences between the groups in cerebral palsy, blindness, hearing loss, and cognitive delay. Infants in budesonide group, compared to placebo, had higher mortality rate (19.9% vs. 14.5%, RR 1.37; 95% CI: 1.01–1.86; $p = 0.04$).

Study conclusion

The composite outcome of death or NDI was not different between infants that received inhaled budesonide and those that received placebo. NDI at 2 years did not differ between the two groups, but the mortality rate was higher among those who received budesonide.

Commentary

As the primary outcome of this trial, the authors assessed the effect of inhaled corticosteroids on the combined outcome of BPD or death. The authors used the NICHD definition of BPD, which is the requirement of positive pressure respiratory support at 36 weeks postmenstrual age or inability to wean off oxygen and keep pulse oximetry saturation more than 90% [1]. BPD is a multifactorial disease with both prenatal and postnatal factors playing roles in the pathogenesis of the disease. Infections and inflammation, including oxygen and ventilator-mediated lung injury are believed to impair the growth and development of airways, lung parenchyma, and blood vessels [2, 3]. Systemic steroids, dexamethasone being the most frequently studied, are used both to prevent and treat BPD due to their potent anti-inflammatory properties. Prophylactic use of systemic steroids facilitates early extubation and reduces the incidence of BPD [4, 5], but increases the risk of infections, gastrointestinal bleeding, and cerebral palsy. The baseline risk of an infant to develop BPD may modify the risk-benefit ratio of postnatal steroid use. Postnatal steroids may decrease the death or cerebral palsy among infants with higher risk (>65%) while increase death or cerebral palsy among infants with lower risk (<35%) to develop BPD [6]. Inhaled steroids are used to get the benefits of systemic corticosteroids without the adverse effects.

Inhaled aerosolized steroids have topical anti-inflammatory properties in the airway and the lungs with minimal systemic side effects [7]. The authors chose to use inhaled budesonide at <24 h of life to prevent BPD by suppressing the ongoing inflammatory processes. The primary outcome of the "Early Inhaled Budesonide for the Prevention of Bronchopulmonary Dysplasia" randomized controlled trial was reported in 2015. There was a marginally significant improvement in composite outcome of death or BPD following treatment with budesonide (40% vs. 46.3%) (RR: 0.86, 95% CI: 0.75- 1.00), with no difference in death before 36 weeks (RR: 1.24, 95% CI: 0.91–1.69, $p = 0.17$) but a lower rate of BPD (RR: 0.74, 95% CI: 0.6–0.91, $p = 0.004$) [8].

In this pre-specified secondary analysis, the authors reported no differences between groups in neurodevelopmental outcomes at 18–22 months. However, they did find a statistically significant increase risk of death in the budesonide group (RR: 1.37, 95% CI: 1.01–1.86, $p = 0.04$) when they analyzed all deaths prior to follow-up period, including death prior to 36 weeks' GA. Specific cause of death, to account for higher mortality in budesonide group, was not found but the study was not powered to detect those differences.

A meta-analysis of inhaled corticosteroid for prevention or treatment for BPD, reviewed 16 studies conducted between 1993 and 2015, including this trial [9]. It is worth noting that the meta-analysis included trials that used different types and doses of inhaled corticosteroids which were administered at variable time after birth. Similar to this trial, the meta-analysis reported a marginal reduction in the composite outcome of death or BPD at 36 weeks' postmenstrual age (RR: 0.86, 95% CI: 0.75–0.99) and a reduction in BPD (RR: 0.77, 95% CI: 0.65–0.91). The meta-analysis also reported no effect on death (RR: 0.97, 95% CI: 0.42–2.2) and a reduction in the use of systemic steroids in the inhaled corticosteroids group (RR: 0.87, 95% CI: 0.76–0.98) but did not report neurodevelopmental outcomes. The use of systemic steroids remained quite high both in this trial (about 30% both groups) and the meta-analysis (32% in inhaled corticosteroids and 37% in control group). Use of postnatal dexamethasone is believed to have dose-dependent adverse effects. Each gram increase in dose of dexamethasone is associated with a two-point decrease in mental developmental index and 40% increase in risk for cerebral palsy [10]. The interaction of inhaled and systemic steroids with neurodevelopmental outcomes deserves more studies.

This rigorous and well-conducted multicenter trial adds very important findings in the pursuit of safe and effective pharmacological options for prevention and treatment of BPD.

EBM lesson

Post hoc sensitivity analysis

Several assumptions are made during study design, implementation, and analysis. Sensitivity analysis (SA) is used to identify what happens to the result when those assumptions are changed. The aim of SA is to evaluate and confirm the

credibility of the findings and the robustness of the analysis. Results that remain consistent despite changing the assumptions are robust and more reliable while the results that change after altering the assumptions are weak and less certain.

Missing data is a common problem in clinical trials. While data missing at random can be ignored, data that are missing in a nonrandom fashion should not be ignored. A decision as how to manage missing data should be made a priori. A critical question about missing data is: "Will the results of the study change if missing data are taken into account differently?" SA can be performed for missing data to clarify this issue.

The authors performed a pre-specified post hoc SA for NDI. In this analysis, missing values for the outcome were analyzed in two ways. When all infants with missing data were treated as if they were survivors with NDI in budesonide group but were survivors without NDI in placebo group, there was a nonsignificant increased risk of NDI (RR: 1.07, 95% CI: 0.92–1.25, $p = 0.38$) in budesonide group. When the analysis was repeated with assumption that all infants with missing data were survivors without NDI in budesonide group but were survivors with NDI in placebo group, the authors found survivors in budesonide group had significantly lower rate of NDI (RR: 0.82, 95% CI: 0.70–0.96, $p = 0.01$). In contrast to SA, main result, where the missing values were unaccounted for the analysis, reported no significant difference in NDI among infants in two groups (48.1% on budesonide and 51.4% on placebo (adjusted RR: 0.93, 95% CI: 0.80–1.09, $p = 0.40$). This inconsistent result between primary and SA weakens the robustness of the findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Walsh M. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. J Perinatol. 2003;23:451.
2. Jensen EA, Schmidt B. Epidemiology of bronchopulmonary dysplasia. Birth Defects Res A Clin Mol Teratol. 2014;100:145–57.
3. Wright CJ, Kirpalani H. Targeting inflammation to prevent bronchopulmonary dysplasia: can new insights be translated into therapies? Pediatrics. 2011;128:111–26.
4. Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Early (<8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev. 2017;10:CD001146.
5. Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Late (>7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev. 2017;10:CD001145.
6. Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC. Impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk for chronic lung disease. Pediatrics. 2005;115:655–61.
7. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. Am J Respir Crit Care Med. 1998;157(3 Pt 2):S1–53.
8. Bassler D, Plavka R, Shinwell ES, Hallman M, Jarreau PH, Carnielli V, et al. Early inhaled budesonide for the prevention of bronchopulmonary dysplasia. N Engl J Med. 2015;373:1497–506.
9. Shinwell ES, Portnov I, Meerpohl JJ, Karen T, Bassler D. Inhaled corticosteroids for bronchopulmonary dysplasia: a meta-analysis. Pediatrics 2016;138:https://doi.org/10.1542/peds.2016-2511.
10. Wilson-Costello D, Walsh MC, Langer JC, Guillet R, Laptook AR, Stoll BJ, et al. Impact of postnatal corticosteroid use on neurodevelopment at 18 to 22 months' adjusted age: effects of dose, timing, and risk of bronchopulmonary dysplasia in extremely low birth weight infants. Pediatrics. 2009;123:e430–7.