

Evidence-Based Neonatal Drug Therapy for Prevention of Bronchopulmonary Dysplasia in Very-Low-Birth-Weight Infants

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Key Words

Very-low-birth-weight infant · Vitamin A · Corticosteroids · Cerebral palsy · Caffeine · Bronchopulmonary dysplasia

Abstract

Corticosteroids, intramuscular vitamin A and caffeine reduce the risk of bronchopulmonary dysplasia (BPD) in very-low-birth-weight infants. We compared the size of the beneficial drug effects on BPD and evaluated long-term drug safety by estimating the number needed to treat (NNT) and the number needed to harm (NNH) for the outcome of cerebral palsy (CP). When given prophylactically during the first 4 days of life, corticosteroids increase the risk of CP (NNH 22; 95% CI: 12–133). When prescribed between days 7 and 14, corticosteroids reduce the 28-day mortality rate in addition to reducing BPD. Their effect on CP remains uncertain: the limited data available are consistent with a best-case scenario (NNT 15) and a worst-case scenario (NNH 14). Although repeated intramuscular injections of vitamin A during the 1st month of life reduce BPD (NNT 12; 95% CI: 6–94), estimates for CP range from an NNT of 11 to an NNH of 33. Early use of caffeine reduces both BPD and CP. The NNT for BPD is 10 (95% CI: 7–16), while the NNT for CP is 34 (95% CI: 20–132). We conclude that caffeine is the drug of choice for the prevention of BPD in very-low-birth-weight infants. Corticosteroids

should be avoided during the first few days of life. However, when given during the 2nd week of life to infants at high risk of BPD corticosteroids may have important short- and long-term benefits. These should be urgently confirmed or refuted in well-designed controlled trials.

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What Is Bronchopulmonary Dysplasia?

Bronchopulmonary dysplasia (BPD) is a common morbidity of very preterm and very-low-birth-weight (VLBW <1,500 g) infants. It is a chronic respiratory disease that results from abnormal repair after acute lung injury and from impaired lung growth. Different definitions of BPD have been used over the past 40 years, but one of the most enduring has been oxygen dependency at 36 weeks' postmenstrual age [1, 2]. More recently, efforts have been made to distinguish three different levels of disease severity [3] and to standardize the oxygen saturation target range on which a classification of oxygen dependency is based [4]. The future application of these revised definitions should make the diagnosis of BPD more precise. However, the simple definition of oxygen dependency at 36 weeks' postmenstrual age has aged well since it was first proposed 20 years ago. Using this definition,

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Table 1. Efficacy of neonatal drugs for prevention of BPD: outcome of BPD

Drug	Treatment		Control		ARR (95% CI)	NNT (95% CI)	NNH (95% CI)
	n/N	%	n/N	%			
Caffeine [6]	350/963	36.3	447/954	46.9	10.5 (6.1–14.9) ¹	9.5 (6.7–16.4) ¹	NA
Vitamin A [5]	163/346	47.1	193/347	55.6	8.5 (1.1–15.8) ¹	11.8 (6.3–93.5) ¹	NA
Corticosteroids, <96 h [15]	241/1,216	19.8	345/1,199	28.8	8.5 (5.3–11.6) ²	11.8 (8.6–18.8) ²	NA
Corticosteroids, day 7–14 [16]	44/132	33.3	63/115	54.8	22.4 (10.8–34.0) ²	4.5 (2.9–9.3) ²	NA

ARR = Absolute risk reduction; NNT = number needed to treat; NNH = number needed to harm; NA = not applicable. BPD was defined as oxygen dependency at 36 weeks' postmenstrual age.

¹ These estimates were calculated using the Wilson score method [21] because the data were derived from single studies.

² These estimates were calculated using the Woolf method [22] because the data were pooled from multiple studies.

BPD has been validated as a modifiable outcome in large randomized controlled trials of neonatal therapies [5, 6] and as an important predictor of death and long-term neurologic and respiratory impairment after very pre-term birth [7–10].

How Common Is BPD?

Nineteen percent of 3,689 VLBW infants who were admitted to a neonatal intensive care unit between 2001 and 2004 and who received oxygen therapy or ventilatory assistance during their primary hospitalization were recorded in the Israeli National VLBW database to have received supplemental oxygen at 36 weeks' postmenstrual age [11]. Of the 1,141 infants with gestational ages below 29 weeks who were admitted to 6 neonatal intensive care units in the Northern California Kaiser Permanente Medical Care Program between 1994 and 2002, 409 babies (28%) received oxygen therapy at a postmenstrual age of 36 weeks. The overall rate of BPD in this retrospective cohort was fairly stable during this 9-year period [12].

The investigators of the National Institute of Child Health and Human Development Neonatal Research Network studied 1,598 inborn survivors to 36 weeks' postmenstrual age. Their birth weights ranged from 501 to 1,249 g and they were born between 2000 and 2002. A total of 499/1,598 (31%) received oxygen therapy or ventilatory assistance at 36 weeks. After the administration of the oxygen reduction test to standardize the oxygen saturation target range, the incidence of BPD dropped to 398/1,598 (25%) [13].

Why Worry about BPD?

Infants with BPD have worse long-term outcomes than those without BPD. They are more than twice as likely to be re-hospitalized in their 1st year of life than very preterm infants without BPD [14]. They are more likely to die even if they survive their primary hospitalization. The odds ratio for BPD as a predictor of post-discharge mortality among 10,602 VLBW infants in the Israeli Neonatal Network was 2.4 (95% CI: 1.4–4.2) [7]. Survivors with BPD have an increased risk of neurodevelopmental impairment [8, 9] and their respiratory function remains compromised well into school age [10].

Which Neonatal Drugs Prevent BPD and How Big Are the Treatment Effects?

Initiation of caffeine therapy during the first 10 days of life [6], repeated intramuscular injections of vitamin A during the 1st month of life [5] and early or moderately early use of postnatal corticosteroids [15, 16] have all been shown to reduce the risk of BPD in VLBW infants. Multiple trials of postnatal corticosteroids have been performed and carefully reviewed by members of the Neonatal Cochrane Review Group [15, 16]. A meta-analysis of vitamin A supplementation to prevent mortality and morbidity in VLBW infants has also been published [17]. However, this systematic review combined a trial of a month-long treatment course of intramuscular vitamin A to prevent BPD with a trial of a short 1-week course to prevent a patent ductus arteriosus [17]. We question the appropriateness of combining these 2 trials to determine

Table 2. Safety of neonatal drugs for prevention of BPD: outcome of CP

Drug	Treatment		Control		ARR (95% CI)	NNT (95% CI)	NNH (95% CI)
	n/N	%	n/N	%			
Caffeine [19]	40/909	4.4	66/901	7.3	2.9 (0.8 to 5.1) ¹	34.2 (19.5 to 131.6) ¹	NA
Vitamin A [20]	43/287	15.0	51/283	18.0	3.1 (-3.1 to 9.2) ¹	32.9 (10.9 to ∞) ¹	∞ (32.5 to ∞) ¹
Corticosteroids, <96 h [15]	81/507	16.0	45/484	9.3	-4.6 (-8.5 to -0.8) ²	NA	21.7 (11.8 to 133.3) ²
Corticosteroids, day 7-14 [16]	13/109	11.9	10/95	10.5	-0.3 (-7.4 to 6.8) ²	∞ (14.7 to ∞) ²	344.8 (13.5 to ∞) ²

¹ These estimates were calculated with the use of the Wilson score method [21] because the data were generated in single studies.

² These estimates were calculated with the use of the Woolf method [22] because the data were pooled from multiple studies.

the efficacy of vitamin A for the reduction of BPD. Finally, the Caffeine for Apnea of Prematurity Trial was the only controlled study of a methylxanthine in preterm infants that examined the outcomes of BPD and cerebral palsy (CP) [6, 18, 19].

In table 1, we have compared the published data from the two pertinent single large randomized controlled trials of caffeine and vitamin A, respectively, and from the two systematic reviews of multiple trials of early and moderately early corticosteroid therapy published by the Neonatal Cochrane Review Group. BPD was defined as oxygen dependency at 36 weeks' postmenstrual age in all trials.

We have estimated the absolute risk reductions and numbers needed to treat for each therapy, together with their 95% confidence intervals. All 4 drug regimens reduce the incidence of BPD (table 1).

Infants who die before 36 weeks' postmenstrual age cannot develop BPD as defined for this review. Therefore, any drug effects on mortality rates before 36 weeks must also be considered because death is a competing risk for the outcome of BPD. There is little evidence that caffeine, vitamin A and corticosteroids when given during the first 4 days of life have any effect on death rates [5, 6, 15]. In contrast, when initiated during the 2nd week of life, corticosteroids reduce the 28-day mortality rate in addition to preventing BPD [16].

What Is Known about the Long-Term Safety of Caffeine, Vitamin A and Corticosteroids?

Among the 4 effective neonatal drug regimens for the prevention of BPD, caffeine is the only one with known long-term benefits [15, 16, 19, 20]. Caffeine improves sur-

vival to a corrected age of 18-21 months without neurodevelopmental disability [19]. CP has been the most commonly and consistently measured longer-term impairment in trials of neonatal interventions to reduce BPD [15, 16, 19, 20]. In table 2, we have compared the effects of caffeine, vitamin A and corticosteroids on CP. Caffeine reduces the risk of CP, while corticosteroids given during the first 4 days of life increase the risk of CP. The long-term risk-benefit ratios remain uncertain for vitamin A and for corticosteroids given during the 2nd week of life. The limited available follow-up data for this moderately early initiation of corticosteroids are consistent with a best-case scenario in which the number needed to treat could be as low as 15 and a worst-case scenario in which the number needed to harm could be very similar in size (table 2).

Conclusions

Caffeine is the drug of choice for the prevention of BPD in VLBW infants.

Corticosteroids should be avoided during the first few days of life.

When given during the 2nd week of life to infants at high risk of BPD, corticosteroids may have important short- and long-term benefits that should be urgently confirmed or refuted in well-designed controlled trials.

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