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Let's Talk about Dex: When do the Benefits of Dexamethasone for Prevention of Bronchopulmonary Dysplasia Outweigh the Risks?

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Abstract

Bronchopulmonary dysplasia (BPD) is the most common complication of extreme prematurity and carries increased respiratory morbidity into childhood and adulthood. Systemic administration of dexamethasone during the preterm period has been shown to decrease the incidence of BPD in this population. However, enthusiasm about its use has been tempered by early evidence that suggested potential adverse neurodevelopmental outcomes. More recent studies suggest that the timing, dosing, and duration of therapy may have a significant impact on the safety and efficacy of dexamethasone administration and that side effects and harms may be minimized if its use is appropriately targeted. Focusing on studies published since the 2010s American Academy of Pediatrics (AAP) statement on dexamethasone, this review seeks to examine the evidence from recent clinical trials to present the current state of knowledge regarding the systemic dexamethasone administration to prevent BPD in extremely premature infants and how dose, duration, and timing might impact its safety and efficacy in this vulnerable population.

Keywords

Bronchopulmonary dysplasia; Corticosteroids; Dexamethasone; Prematurity

Introduction

Bronchopulmonary dysplasia (BPD) is the most common complication of extreme prematurity and carries increased respiratory morbidity into childhood and adulthood, including increased risk of chronic obstructive pulmonary disease (COPD) in later

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adulthood.[1–4] As has been shown for caffeine[5] and vitamin A,[6] systemic administration of corticosteroids (primarily dexamethasone) decreases the incidence of BPD in extremely premature infants.[7] The precise mechanism by which postnatally administered dexamethasone confers its protection against BPD is not fully known. It has been postulated that the benefits of dexamethasone are mediated by its potent anti-inflammatory effects.[8] Alternatively, the benefit may derive from the fact that short-term improvement in lung function[9] includes increased compliance[10] and functional residual capacity[11] facilitating earlier extubation to noninvasive ventilation. However, balancing the potential benefits of systemic corticosteroid therapy to decrease the incidence of BPD with its potential harms has been an evolving challenge in neonatology. The clear short-term beneficial physiologic effects on lung function that facilitates extubation and reduces BPD in the most at-risk infants must be balanced against concerns for adverse events including intestinal perforation and hypertrophic cardiomyopathy[12] as well as adverse long-term neurodevelopmental outcomes such as cerebral palsy (CP).[13,14]

Interpretation of data on the long-term neurodevelopmental outcomes after systemic dexamethasone therapy is complicated by the fact that clinical trials have employed different dosing regimens, with different timing of administration, and different durations of treatment. Some studies have suggested that adverse neurodevelopmental outcomes (e.g., CP) occur more commonly with higher dosing and longer courses of dexamethasone. For example, while one early study did find a benefit in long-duration/high-dose dexamethasone (cumulative dose 7.98 mg/kg) in reducing BPD, follow-up studies of these patients raised concerns about possible impairment of motor development.[14] These concerns led to the American Academy of Pediatrics (AAP) and Canadian Pediatric Society (CPS) jointly to release a statement in 2002 recommending dexamethasone therapy be limited in its use. Subsequently, a 2005 meta-regression analysis of published dexamethasone studies showed that for infants with >50% risk of BPD, the risk/benefit ratio favors the use of dexamethasone, an early indication that the harm/benefit ratio is favorable for at least some at-risk infants.[15] Even so, in the most recent update of this statement released in 2010, the AAP revised its statement, concluding the data were still insufficient to recommend routine use of glucocorticoid therapy in ventilator-dependent neonates, but that “the clinician must use clinical judgment when attempting to balance the potential adverse effects of glucocorticoid treatment with those of BPD.”[16] Importantly, the resulting relative decrease in dexamethasone use at this time, stemming from concerns about its side effects and caveats from the AAP and CPS, is temporally related to a relative increase in BPD rates over the same time period.[17] This tension between the benefits and harms of dexamethasone therapy continues to complicate clinical decision-making at the bedside in neonatal intensive care units (NICUs) around the world. To address this ongoing knowledge gap, we have reviewed the relevant studies (Table 1) published in the decade since the last AAP statement to assess what is currently known regarding dose, duration, and timing of systemic dexamethasone administration to prevent BPD in extremely premature infants.

What’s New? Updated Evidence from Clinical Trials

Two closely related meta-analyses published in the Cochrane Database describe the benefits of corticosteroids (primarily dexamethasone) in extremely premature infants. The first,

summarizing dexamethasone administration initiated within the first week after birth, showed a decrease in BPD [relative risk (RR) 0.7 (0.61, 0.81)] as well as a decrease in the composite outcome of BPD or death [RR 0.87 (0.80, 0.94)]. Additionally, this study showed a decrease in extubation failure and in need for repeated administration of dexamethasone later in an infant's course. However, these benefits were accompanied by significant harms including an increased incidence of gastrointestinal bleeding [RR 1.87 (1.35, 2.58)], intestinal perforation [RR 1.73 (1.20, 2.51)], hypertrophic cardiomyopathy [RR 4.33 (1.4, 13.4)], and CP [RR 1.75 (1.20, 2.55)] as well as increased incidence of hypertension, hyperglycemia, and growth failure. The authors conclude that although there are clear benefits to the early administration of dexamethasone, these benefits "may not outweigh the adverse effects of this treatment."[12]

In a second meta-analysis of dexamethasone administered after 7 days of age, dexamethasone was shown to decrease BPD [RR 0.77 (0.67, 0.88)], composite of BPD or death [RR 0.77 (0.70, 0.86)], and the need for oxygen at discharge [RR 0.71 (0.54, 0.94)]. Importantly, these benefits were accompanied by far fewer adverse events than in those with early exposure to dexamethasone. Of note, there was no increase in CP [RR 1.16 (0.82, 1.64)] or a composite outcome of death or CP [RR 0.95 (0.78, 1.15)] in this analysis of >900 infants.[7] Further, these studies have shown no increase in short-term risk such as necrotizing enterocolitis (NEC) [RR 1.03 (0.61, 1.74)] or spontaneous intestinal perforation [RR 1.60 (0.28, 9.31)] when dexamethasone is given after the first week of life. This meta-analysis concludes that the use of dexamethasone should be limited to infants who cannot be weaned from the ventilator after 7 days of age and that both dose and duration should be limited as much as possible. Taken together, these studies show the clear benefits of dexamethasone on rates of BPD, and they suggest that harms might be minimized by delaying administration until after the first week after birth. However, given the considerable heterogeneity in dose and duration, even these important meta-analyses leave critical questions incompletely answered.

Optimal Dosing of Dexamethasone

In light of the data from this meta-analysis and the conclusion that the dose and duration should be limited, especially in the context of the cautionary statements from the AAP, the relatively low-dose regimen described in the DART trial[18] has become one of the most commonly used. The DART trial aimed to determine whether low-dose dexamethasone (0.89 mg/kg over 10 days) would lead to a reduction in BPD by facilitating extubation. This study found a 34.3% extubation rate by day 3, 51.4% by day 7, and 60% by day 10 [p <0.01; number needed to treat (NNT) = 2 by day 10]. However, there was no difference in either oxygen dependence at 36 weeks of postmenstrual age (PMA) [85 vs 91%; odds ratio (OR) 0.58 (0.13, 2.66)] or in mortality rate [11 vs 20%; OR 0.52 (0.14, 1.95)]. No cases of intestinal bleeding or intestinal perforation were reported. In a follow-up study, no difference in CP was noted at 2 years of age.[19] Importantly, though the target sample size was intended to be 814 infants to ensure sufficient power to detect the primary outcome, difficulty in recruitment caused enrollment of the DART trial to be prematurely halted after only 70 participants were enrolled. Thus, this study may be significantly underpowered to detect true differences in either benefits or harms.

In the last 5 years, there have been several new clinical trials reexamining the use of systemic dexamethasone at widely differing cumulative dosages ranging from 0.72 mg/kg over 10 days[20] to 7.98 mg/kg over 42 days[20–22] to try to maximize benefits and minimize harms. To explore the minimum effective dose in ventilator-dependent infants born at <29 weeks, Cuna et al. compared two dexamethasone regimens: 27 patients received the DART regimen (0.89 mg/kg over 10 days) and 32 patients received a reduced version of the DART regimen (0.72 mg/kg over 7 days). Similar successful extubation rates (defined as extubation within 14 days of starting therapy and remaining extubated for more than 72 hours) were reported in both groups: 56% in 7-day group and 67% in 10-day group. The average time to successful extubation was also similar: 5 days in 7-day course and 6 days in 10-day course.[20] This study suggests that relatively low doses of dexamethasone are effective in facilitating beneficial short-term outcomes including extubation. Long-term outcomes, however, were not assessed.

A significantly larger cumulative dexamethasone dosing regimen was reported from a prospective, single-center, randomized study in 59 infants ≤27 weeks of gestational age (GA) and ~14 days of postnatal age at randomization.[22] Infants were randomized to either a 42-day course (cumulative dexamethasone dose of 7.98 mg/kg), or a 9-day course (cumulative dose of 2.63 mg/kg—allowing for repeat courses if necessary). Importantly, this study was designed to evaluate the long-term impact of dexamethasone on neurodevelopment rather than focusing on the more clearly established short-term benefits such as BPD rates. As such, the primary outcome measure was intact survival, defined as survival to 7 years of age without severe neurologic, cognitive, or academic handicap [IQ >70 and with no need for Individualized Education Program (IEP)]. There were no differences between groups for height, weight, or head circumference at 7 years of age—as had been reported in prior studies of a similar dosing regimen, but started within the first week after birth.[14] Significantly, more children in the 42-day group were alive without neurodevelopmental impairment (NDI) compared to those in 9-day group (93% vs 66%, p <0.02). More children in 42-day group received regular classroom without IEP (75 vs 38%, p <0.01) with an NNT of 4. Overall intact survival with IQ >70 was significantly greater for children in 42-day course (75 vs 35%, p <0.005) with an NNT of only 3. Regarding secondary outcomes, successful extubation rates were earlier (median 23 vs 35 days of age, p <0.01) and higher (50 vs 15% after 1 week, p <0.005) in the 42-day group. Successful extubation continued to be significantly higher for infants in the 42-day group at weeks 2, 3, and 4 (p <0.005 for all time points). The need for re-intubation was lower in 42-day group (7 vs 25%, p <0.001), but there was no difference in BPD (defined as the need for supplemental oxygen at 36 weeks of PMA) between the two groups: 93% in 42-day group and 89% in 9-day group.[22] Due to significant outcome differences in the 6-month preliminary data evaluation, study enrollment was terminated early (after 59 of the intended, 72 patients were enrolled). As with any individual study, the conclusion must be interpreted with caution, especially given the surprisingly large effect sizes and resulting NNTs. However, this study supports that notion that rather than causing harms, high-dose dexamethasone for infants born at ≤27 weeks of GA may support improved neurodevelopmental outcomes at 7 years of age. Prior to the publication of this study, a 2017 meta-analysis found that compared with moderate-dose dexamethasone regimens, high-dose regimens were associated with a lower

risk of BPD and lower risk of adverse neurodevelopmental outcomes.[23] However, due to concerns about the degree of heterogeneity among the studies, the authors refrained from formally recommending any particular dosing regimen. Further study of this question is urgently needed.

Timing of Treatment: Is There an Optimal Window?

Meta-analysis of recent clinical trials suggests that timing of systemic dexamethasone administration may have a significant modifying effect on benefits and adverse outcomes,[7,12] perhaps greater than the effect of the cumulative dose. Amid the conflicting data on dosing and duration, one clear signal that has emerged is that early administration of systemic dexamethasone (within the first 7 days), though effective in reducing the incidence of BPD, confers more harm than benefit. As noted above, early administration is associated with an increased risk of intestinal perforation, gastrointestinal hemorrhage, hypertrophic cardiomyopathy, and CP; thus, it should be avoided.[12] Dexamethasone administration after the first week reduces the incidence of BPD while minimizing the harms.[7] But beyond this, what else can be gleaned from recent studies about optimal timing of dexamethasone administration? Is there a window of optimal benefit?

In a retrospective cohort study of preterm infants treated with dexamethasone (0.72 mg to 0.89 mg/kg over 7–10 days) for BPD prevention, infants were grouped by timing of dexamethasone exposure into two cohorts: moderately late [14–28 day of life (DOL) when therapy started, $n = 25$] and delayed (29–42 DOL, $n = 30$). Baseline demographics were similar, except that there were more male patients (84 vs 57%; $p = 0.03$) and more patients on high-frequency ventilation (96 vs 47%, $p < 0.0001$) in the moderately late group. The average postnatal age and PMA were 23 days (28.2 weeks) for moderately late group compared to 53 days (30.2 weeks) in the delayed group. Despite having a greater burden of comorbidities, those in the moderately late group had fewer intubation days (46 ± 18 days vs 77.4 ± 67 days, $p = 0.02$), fewer days of supplemental O_2 (114.3 ± 40.8 vs 149.8 ± 57 days, $p = 0.005$), and fewer hospital days (125.5 ± 33 vs 157 ± 57.6 days, $p = 0.02$) that the those in the delayed group. However, rates of the composite outcomes of BPD or mortality were similar, as well as rates of tracheostomy, BPD-associated pulmonary hypertension, retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH) grade III or IV, and periventricular leukomalacia (PVL).[21] This small study suggests that dexamethasone may have beneficial effects when initiated up to 6 weeks after birth, though the benefits may be greater with earlier administration. Importantly, neurodevelopmental outcomes were not assessed in this study.

Harmon et al.[24] reported a retrospective cohort study of 863 infants born at <27 weeks of GA with steroid exposure dichotomized to either the early group (started ≤28 DOL) or the late group (started >28 DOL). Of these, 73% received dexamethasone and 27% received hydrocortisone (HC). Total doses and duration of courses were not reported. The adjusted Odds Ratio (aOR) of NDI (cognitive composite score <70, or motor composite score <70, or moderate-to-severe CP, or visual impairment, or permanent hearing loss) at 18–26 months was only statistically significant when therapy was started 36–49 DOL. The aOR for severe BPD was significantly higher in those who received therapy between DOL 50–63 and

older. Interestingly, the aOR for death or BPD is higher in those who received therapy between DOL 15–21 and DOL ≥ 64. The early group was less likely to be discharged on O_2 (55 vs 68%, p <0.001), less likely to have moderate or severe BPD (84 vs 92%, p <0.001), and statistically shorter duration of ventilation and supplemental O_2 (p <0.001 and <0.01, respectively). Though the interpretation of this study is complex, its findings suggested that postnatal steroid therapy starting between DOL 8 and 49 is associated with no greater risks of neurodevelopmental delay and may potentially minimize severe BPD risks compared to later therapy.[24] In a recent systematic review and meta-analysis involving 5,559 extremely premature infants, Ramaswamy et al. simultaneously evaluated the effects of dosing and timing of dexamethasone on the prevention of BPD.[25] This study concludes that moderate-dose dexamethasone courses (cumulative dose of 2–4 mg/kg) initiated at 8–14 days carried the greatest protection against BPD with an RR of 0.61 (0.45, 0.79). High-dose dexamethasone courses (cumulative dose of >4 mg/kg) initiated within the same time window conferred a similar but slightly smaller benefit with an RR of 0.64 (0.48, 0.82). Importantly, this study notes that none of the regimens studied was associated with an increased risk of NDI. Taken together, these data support the conclusion that there may be an optimal time frame to consider initiating dexamethasone in ventilator-dependent premature neonates between the second and third weeks after birth, and its use up to DOL 49 is less likely to result in greater risks of neurodevelopmental delay.

Hydrocortisone and Methylprednisolone

Though this review is primarily focused on the use of dexamethasone to minimize the risk of BPD, it is worth noting that other steroids, namely HC and methylprednisolone (MP), have been studied for this purpose as well. In a recent retrospective, single-center, cohort study of 98 intubated preterm infants ≤34 6/7 weeks and >7 postnatal days, Nath et al. compared three steroid regimens including dexamethasone starting at 0.2 mg/kg/day, HC starting at 4–8 μg/kg/day (equivalent to dexamethasone 0.15–0.3 mg/kg/day), and methylprednisolone (MP) 2.4 mg/kg/day (equivalent to dexamethasone 0.4–0.5 mg/kg/day) over an average 10-day course.[26] In this study, the decrease in the respiratory severity scale (RSS) was different only between the dexamethasone group (58.6% decrease) and HC group (19.4% decrease, p <0.002). The rates of extubation at day 3 and at day 7 were higher for dexamethasone (44 and 59%), than for either HC (40 and 44%) or MP (23 and 41%). Given concerns about potential undesirable neurodevelopmental side effects of dexamethasone, a multicenter randomized controlled trial (RCT) of 800 premature infants at <30 weeks of GA to investigate the efficacy of HC in facilitating extubation and increasing survival without BPD was recently completed. In this as-yet-unpublished study, although HC was found to increase the rate of extubation in this population, no difference in survival without BPD or survival without NDI was found.[27] These recent studies underscore the notion that a superior alternative to dexamethasone has yet to be identified.

Additional Potential Risks

As mentioned in recent individual studies above, NEC, culture-proven sepsis, ROP, IVH, and PVL have been consistently similar and in dexamethasone-treated neonates regardless of dosing regimen, exposure duration, and timing of therapy. These rates have not been found

to be increasing compared to previous studies. Though no causal link has been shown, ROP has been associated with systemic steroids used during the first 96 hours of life[28] and after 3 weeks.[29] However, a more recent study specifically looking at the association between dexamethasone and betamethasone administration (via insulin growth factor-1 and vascular endothelial growth factor expression) and ROP showed that his apparent association became insignificant after regression model was applied.[30] Importantly, retrospective studies such as these latter two cannot demonstrate causation and may simply identify late dexamethasone administration as a marker of greater illness severity, a known risk factor for ROP.

Conclusion and Remaining Knowledge Gaps

Despite almost 50 years of study regarding systemic dexamethasone therapy to treat or prevent BPD, significant questions remain unanswered. Meta-analyses of clinical trials have demonstrated clear short-term benefits of dexamethasone in reducing the incidence of BPD in extremely premature infants, especially those who have difficulty being weaned from mechanical ventilation. But studies show conflicting data on the simple but critical question of whether its effects on neurodevelopmental outcomes are beneficial or deleterious.[7,12,22,31] A potential explanation for these disparate findings could be that the timing of administration of dexamethasone may modify the harm/benefit ratio. If there is a clear signal that emerged from repeated analyses, it is that the harms outweigh the benefits when dexamethasone is administered during the first week after birth. Beyond that, there is no definitive consensus on optimal dosing or duration of systemic dexamethasone that maximizes benefits while limiting harms. Could there be an optimal window of timing for administration in the second or third week as some research has suggested? More RCTs examining the relationship between timing, dosing, and duration with primary endpoints involving long-term outcomes like survival without NDI are urgently needed.

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Abbreviations

BPD	Bronchopulmonary dysplasia
COPD	Chronic obstructive pulmonary disease
CP	Cerebral palsy
DOL	Day of life
GA	Gestational age
IVH	Intraventricular hemorrhage
NDI	Neurodevelopmental impairment
NICU	Neonatal intensive care unit

NNT	Number needed to treat
PMA	Postmenstrual age
PVL	Periventricular leukomalacia
ROP	Retinopathy of prematurity
RR	Relative risk
OR	Odds ratio
aOR	adjusted odds ratio

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Table 1:

Compilation of recent studies of dexamethasone in premature infants

Study and location	Method	Inclusion criteria	Dexamethasone regimen	# of participants	GA at birth (weeks)	BW(g)	Age @ treatment (days)	Findings
Doyle et al. (2006) International	RCT; 11 centers	GA <28 weeks BW <1000 g Ventilator dependent after 1 week of life	0.89 mg/kg over 10 days	70	24 IQR 24–26	680 IQR 605–785	13–34	Extubation by day 3: 34.3%, p <0.01 Extubation by day 7: 51.4%, p <0.01 Extubation by day 10: 60%, p <0.01 No difference in BPD and mortality Less weight gain −76 g, p = 0.006
Cuna et al. (2017) Kansas, MO	Retrospective Single center Two closing regimens	GA <29 weeks Mechanical ventilated	• 0.89 mg/kg over 10 days • 0.72 mg/kg over 7 days	27 32	24.9 ± 1.0 25.4 ± 1.3	762 ± 141 740 ± 148	33 ± 9 36 ± 13	Extubation within 14 days of treatment: 67% in 10-day and 56% in 7-day groups No difference between two groups in rates of severe BPD, tracheostomy, days on O_2, and days on mechanical ventilation
Cuna et al. (2018) Kansas, MO (same cohort from Cuna et al., 2017)	Retrospective Single center Late (DOL 14–28) vs Delayed (DOL 29–42) therapy	GA <29 weeks Mechanical ventilated	• 0.89 mg/kg over 10 days • 0.72 mg/kg over 7 days	55	Late: 24.9 ± 1.4 Delayed 25.2 ± 1.2	Late 728.5 ± 190.4 Delayed 750 ± 135.4	Late 22.8 ± 4.1 Delayed 35.1 ± 3.9	Delayed treatment group had significantly longer LOS, intubation days, days on oxygen. No difference between two groups in rates of severe BPD, mortality, IVH grade III or IV
Marr et al. (2019) Syracuse, NY	RCT Single center Two closing regimens	GA <28 weeks DOL 10–21	• 7.98 mg/kg over 42 days • 2.625 mg/kg over 9 days	30 29	25 ± 1.2 25.2 ± 1.1	769 ± 149 785 ± 167	14 ± 4 13 ± 3	9-day course: 17% received two courses, 17% received three courses (mean 4.04 mg ± 0.07 mg/kg) Extubation rates were higher in 42-day group at weeks 1, 2, 3, and 4 (p <0.005) 42-day group had earlier extubation (median 23 vs 35 days), less frequent needs for re-intubation (7 vs 25%), and shorter ventilation duration (25 vs 37 days) No difference in rates of BPD, NEC, and LOS 7-year outcomes: • No difference in height, weight, head circumference, re-hospitalization rate • 42-day group had higher survival rate without neurodevelopmental impairment (93 vs 66%, p <0.05), more attended school without IEP (75 vs 38%, p <0.01), higher intact survival rate (75 vs 35%, p <0.005)

Study and location	Method	Inclusion criteria	Dexamethasone regimen	# of participants	GA at birth (weeks)	BW(g)	Age @ treatment (days)	Findings
Harmon et al. (2020) NICHD Multicenter	Retrospective cohort 25 centers Early (by DOL 28) vs Late (after DOL 28)	GA <27 weeks	Various regimens Two main agents Dexamethasone: 73% Hydrocortisone: 27%	951 total Early: 420 Late: 951	24.9 ± 1.0 24.9 ± 1.0	669 ± 132 687 ± 136* *$p = 0.04$	21 (16–25) 43 (35–54)	Early group had shorter ventilation days (47.9 ± 23.4 vs 53.8 ± 23.5, $p < 0.001$), shorter supplemental oxygen days (99.4 ± 22.8 vs 103.8 ± 21.6, $p < 0.01$), fewer patients on oxygen upon discharge (55.4 vs 68%, $p < 0.001$) Higher aOR for severe BPD in patients started therapy DOL ≥ 50 (week 8) Higher aOR for death or BPD in patients started therapy DOL 15–21, and DOL ≥ 64 Higher aOR for NDI at 18–26 months in patients started therapy DOL 8–14 and DOL 36–49

BPD, bronchopulmonary dysplasia; DOL, day of life; GA, gestational age; IEP, Individualized Education Program; IVH, intraventricular hemorrhage; LOS, length of stay; NDI, neurodevelopmental impairment; NEC, necrotizing enterocolitis