Dexamethasone Treatment after the First Week of Life for Bronchopulmonary Dysplasia in Preterm Infants: A Systematic Review

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Key Words

Dexamethasone • Bronchopulmonary dysplasia • BPD, preterm infants • Mortality rate • Cerebral palsy

Abstract

Background: Dexamethasone has powerful anti-inflammatory effects and has been used to treat established bronchopulmonary dysplasia (BPD), but it is uncertain whether the benefits outweigh the risks of treatment. **Objectives:** To determine the effect of late (>7 days) postnatal dexamethasone treatment compared with control (placebo or nothing) to prevent or treat BPD in the preterm infant. **Methods:** Randomised controlled trials (RCTs) of late postnatal dexamethasone therapy to treat or prevent BPD were sought using methods of the Cochrane Collaboration. Data regarding clinical outcomes including mortality, BPD, death or BPD, complications during the primary hospitalisation, and long-term outcome were abstracted and analysed using RevMan 5. **Results:** 19 RCTs enrolling 1,345 participants were eligible for this review. Late dexamethasone treatment reduced neonatal mortality, but not later mortality. Benefits of late dexamethasone included reductions in failure to extubate, BPD and the combined outcome of death or BPD. There were clear short-term complications, including hyperglycaemia and hypertension, but not intestinal perforation. Trends of

an increase in cerebral palsy or abnormal neurological examination were partly offset by a trend in the opposite direction in death before late follow-up. **Conclusions:** The benefits of late dexamethasone may not outweigh actual or potential adverse effects. Given the evidence of both benefits and harms of treatment, and the limitations of the evidence at present, it appears prudent to reserve the use of late dexamethasone to infants who cannot be weaned from mechanical ventilation, and to minimise the dose and duration of any course of treatment.

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Background

Bronchopulmonary dysplasia (BPD) is a major problem for newborn babies in neonatal intensive care units, and is associated with both a higher death rate and worse long-term outcomes in survivors [1]. Persistent inflammation of the lungs is a major contributor to BPD, and hence corticosteroids, because of their strong anti-inflammatory effects, appeal as a drug to either prevent or

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treat BPD, particularly in babies who cannot be weaned from assisted ventilation. Postnatal corticosteroids have some acute effects on lung function in infants with established BPD, especially those who are ventilator-dependent [2, 3]. However, there is concern that the benefits of corticosteroids might not outweigh the adverse effects [4], and animal studies have also raised concerns about adverse effects of corticosteroids [5, 6].

Of the corticosteroids available, dexamethasone is the one that has been most extensively evaluated in clinical trials. Broadly speaking, investigators have aimed either to prevent BPD by starting treatment during the first week of life, or they have treated evolving or established BPD, with treatment started after the first week of life. The risks of dexamethasone started in the first week of life outweigh the benefits, as reviewed elsewhere [7, 8]. The aim of this study was to review systematically the data from randomised controlled trials (RCTs) in newborn infants where dexamethasone was compared with placebo, to establish the balance between risks and benefits of such treatment in newborn infants in the prevention or treatment of BPD when treatment was started after the first 7 days of age. This report is a synthesis of the more clinically important outcomes, all of which are detailed in the recently updated Cochrane Review [9].

Methods

Data were sought on all RCTs of postnatal dexamethasone treatment started after the first week of life for preterm infants with or developing BPD defined as oxygen dependence and/or ventilator dependence, with or without radiographic changes of BPD, that reported clinically important outcomes. The intervention compared dexamethasone, either orally or parenterally, with either placebo or nothing. The outcomes included mortality, BPD defined usually as needing oxygen at either at 28 days or 36 weeks, death or BPD, late rescue with corticosteroids, survivors discharged home on oxygen, failure to extubate, complications during the primary hospitalisation (including infection, hyperglycaemia, glycosuria, hypertension, hypertrophic cardiomyopathy, necrotising enterocolitis (NEC), gastrointestinal (GI) bleeding, GI perforation, and severe retinopathy of prematurity (ROP), and long-term outcomes (including blindness, deafness, cerebral palsy and major neurosensory disability).

RCTs of postnatal corticosteroid therapy were sought from the Cochrane Controlled Trials Register, MEDLINE, hand-searching paediatric and perinatal journals, examining previous review articles and information received from practising neonatologists. MEDLINE was searched from 1966 through March 2009 using the terms adrenal cortex hormones or dexamethasone or steroids or corticosteroids and limits RCTs, human, all infant: birth – 23 months. Meta-analysis of data from the included trials was per-

formed using RevMan 5. For some statistically and clinically significant outcomes the number needed to treat for additional beneficial (NNTB) or harmful (NNTH) outcomes and 95% confidence intervals (CIs) were calculated from the typical relative risks according to methods of the Cochrane Handbook for Systematic Reviews of Interventions [10], assuming the control group event rate as the baseline rate. Significant heterogeneity was present if the I^2 statistic was >50%, suggesting caution when interpreting the results of meta-analysis.

Results

Nineteen RCTs qualified for inclusion in this review [3, 11–28]. These trials enrolled preterm infants who were oxygen- and/or ventilator-dependent beyond 7 days of age. All trials used dexamethasone; there were no trials of other corticosteroids. The starting dose of dexamethasone was typically as high as 0.5–1.0 mg/kg/day, with the duration of therapy varying between 3 days and up to 6 weeks. Details of the subjects included in the studies and the dexamethasone regimens are listed in table 1.

Details of individual trial methods are listed in table 2. All were randomised trials, but the method of random allocation was not always described. Treatment allocation was mostly concealed from the study investigators. Blinding of intervention from the investigators was by use of placebos in most studies, and blinding of outcome measures and complete reporting of in-hospital outcomes for infants randomised applied to most studies. Not all trials had follow-up components; those that did had reasonable to excellent (>90%) follow-up rates. However, ages of assessment were often only into early childhood and not to school-age in the majority of studies reporting outcomes after discharge home.

Results of Meta-Analysis

The results of the meta-analysis of these 19 studies of late dexamethasone treatment, including the NNTB and NNTH where results were statistically significant, are shown in table 3 and figures 1 and 2.

Mortality and Acute Lung Morbidity. Late steroid treatment was associated with reduced mortality at 28 days, but had no significant effect on mortality at the latest reported age (table 3). BPD was significantly decreased at both 28 days of postnatal age and at 36 weeks of PMA. The combined outcome of mortality or BPD was decreased at both 28 days' postnatal age and 36 weeks' PMA. In addition to these major benefits, dexamethasone had other respiratory advantages – it reduced the need for late corticosteroids, the need for

Table 1. Types of subjects and dexamethasone regimens

First author, year [reference]	Subjects	Dexamethasone regimen	Total dose mg/kg	Duration days
Avery 1985 [11]	n = 16; BW <1,500 g; inability to be weaned from the ventilator after 2 weeks and radiological evidence of stage II or III Northway BPD [33]	0.5 mg/kg/day for 3 days; 0.3 mg/kg/day for 3 days; then decreased by 10% every 3 days until 0.1 mg/kg/day; 0.1 mg/kg/day alternate days for 1 week	8.0	42
Ariagno 1987 [12]	n = 34; BW <1,501 g; 3 weeks of age; ventilator-dependent	(a) 1.0 mg/kg/day for 4 days; 0.5 mg/kg/day for 6 days (b) 1.0 mg/kg/day for 4 days; 0.5 mg/kg/day for 4 days	7.0 5.0	10 7
Cummings 1989 [13]	n = 36; BW <1,251 g; GA <31 weeks; oxygen-dependent (>29%); mechanical ventilation (rate >14 per min); no weaning during the previous 72 h; 2 weeks of age	(a) 0.5 mg/kg/day for 3 days; 0.3 mg/kg/day for 3 days; then decreased by 10% every 3 days until 0.1 mg/kg/day; 0.1 mg/kg/day alternate days for 1 week (b) 0.5 mg/kg/day for 3 days; reduced by 50% every 3 days until 0.06 mg/kg on days 10, 11 and 12; 0.06 mg/kg/day on alternate days for 1 week	8.0 2.98	42 18
Noble-Jamieson 1989 [14]	n = 18; >4 weeks; >30% oxygen	0.5 mg/kg for 7 days 0.25 mg/kg for 7 days; 0.1 mg/kg for 7 days	5.95	21
Harkavy 1989 [15]	n = 21 ventilator-dependent; 30 days of age	0.5 mg/kg/day for minimum of 14 days	7	14 mini- minimum
Kazzi 1990 [16]	n = 23; <1,500 g BW; BPD on X-ray; 3–4 weeks of age; ventilator-dependent; >34% oxygen; rate >14 breaths/min; inspiratory pressure >17 cm H ₂ O; no weaning 5 days	0.50 mg/kg/day for 3 days; 0.40 mg/kg/day for 2 days; 0.25 mg/kg/day for 2 days; then hydrocortisone 8 mg/kg/day for 2 days; 4 mg/kg/day for 2 days; 2 mg/kg/day for 2 days; 1 mg/kg/day for 2 days; 0.5 mg/kg/day for 2 days	2.8; 31 mg HC	17
Collaborative Dexamethasone Trial Group 1991 [3]	n = 287 infants oxygen-dependent; static or deteriorating over the preceding week; from around 3 weeks of age. Not all mechanically ventilated	0.6 mg/kg/day for 1 week. Option of a second tapering 9-day course; 0.6, 0.4, and 0.2 mg/kg/day for 3 days each	3.5	7 mini- minimum
Ohlsson 1992 [17]	n = 25; <1,501 g BW; 21–35 days of age; X-ray of BPD; >29% oxygen; ventilator-dependent	1 mg/kg for 3 days; 0.5 mg/kg/day for 3 days; 0.25 mg/kg/day for 3 days; 0.125 mg/kg/daily for 3 days	5.62	12
Kari 1993 [18]	n = 41; <1,501 g BW; >23 weeks' GA; ventilator-dependent; 10 days of age	0.5 mg/kg/day for 7 days	3.5	7
Brozanski 1995 [19]	n = 78; BW <1,501 g; 7 days of age	0.5 mg/kg/day 12 hourly for 3 days at 10-day intervals until no longer required supplemental oxygen or assisted ventilation, or reached 36 weeks' PMA	1.5	3 mini- minimum
Durand 1995 [20]	n = 43; 600–1,500 g BW; 24–32 weeks' GA; ventilator-dependent at 14 days; not weaning	0.5 mg/kg/day 3 days; 0.25 mg/kg/day 3 days; 0.1 mg/kg/day 1 day	2.35	7
Kovacs 1998 [21]	n = 60; <1,501 g BW; <30 weeks GA; ventilator-dependent; 7 days	0.5 mg/kg/day for 3 days; budesonide 500 µg/day for 18 days	1.5	3
Papile 1998 [22]	n = 371; <1,501 g BW; ventilator-dependent; respiratory index >2.4; 14 days of age	0.5 mg/kg/day for 5 days; then 0.3 mg/kg/day for 3 days, then 0.14 mg/kg/day for 3 days, then 0.06 mg/kg/day for 3 days	4	14
Romagnoli 1998 [23]	n = 30; 10 days of age; ventilator-dependent; >90% chance of BPD	0.5 mg/kg/day for 6 days; 0.25 mg/kg/day for 6 days; 0.125 mg/kg/day for 3 days	4.87	15
Vincer 1998 [24]	n = 20; ventilator-dependent; 30 days of age	0.5 mg/kg/day for 3 days; 0.3 mg/kg/day for 3 days	2.4	6
Kothadia 1999 [25]	n = 118; <1,501 g BW; 15–25 days of age; ventilator-dependent	0.5 mg/kg/day for 3 days; 0.3 mg/kg/day for 3 days; then decreased by 10% every 3 days until 0.1 mg/kg/day; 0.1 mg/kg/day alternate days for 1 week	8.0	42
Walther 2003 [26]	24–32 weeks GA; >599 g BW; ventilator-dependent; >29% oxygen; 7–14 days of age	0.2 mg/kg/day for 4 days; 0.15 mg/kg/day for 4 days; 0.1 mg/kg/day for 4 days, and 0.05 mg/kg/day for 2 days	1.9	14
Vento 2004 [27]	n = 20; <1,251 g BW; <33 weeks GA; ventilator-dependent; 10 days	0.5 mg/kg/day for 3 days, 0.25 mg/kg/day for 3 days and 0.125 mg/kg/day for 1 day	2.35	7
Doyle 2006 [28]	n = 70; BW <1,000 g or GA <28 weeks; ≥7 days of age; ventilator-dependent	0.15 mg/kg/day for 3 days; 0.10 mg/kg/day for 3 days; 0.05 mg/kg/day for 2 days; 0.02 mg/kg/day for 2 days	0.89	10

Table 2. Assessment of bias in reported studies

First author, year [reference]	Adequate method for randomisation	Blinding of randomisation	Blinding of intervention	Complete FU reporting ^a	Blinding of outcome assessment	Age latest FU	FU rate %
Avery, 1985 [11]	yes	yes	unsure	yes	uncertain	NA	NA
Ariagno, 1987 [12]	yes	yes	yes	yes	yes	36 months	96
Cummings, 1989 [13, 34]	yes	yes	yes	yes	yes	(a) 15 months (b) 4 years (c) 15 years	(a) 100 (b) 100 (c) 100
Noble-Jamieson, 1989 [14]	unclear	unclear	yes	yes	yes	NA	NA
Harkavy, 1989 [15]	yes	yes	yes	yes	21/22	6–24 months	32
Kazzi, 1990 [16]	yes	yes	yes	yes	yes	NA	NA
CDTG, 1991 [3, 35–37]	yes	yes	yes	yes	yes	(a) 3 years (b) 13–17 years	(a) 94 (b) 77
Ohlsson, 1992 [17]	yes	yes	yes	yes	attempted	18 months	96
Kari, 1993 [18, 38]	unclear	yes	yes	yes	yes	2–9 years	80
Brozanski, 1995 [19, 39]	yes	yes	yes	no (78/88)	yes	12 months	68
Durand, 1995 [20]	yes	yes	yes	yes	43/44	NA	NA
Kovacs, 1998 [21]	yes	yes	yes	yes	yes	up to 90 months	70
Papile, 1998 [22]	yes	yes	yes	yes	yes	NA	NA
Romagnoli, 1998 [23, 40]	yes	yes	no	yes	unclear	36–42 months	100
Vincer, 1998 [24]	unclear	unclear	unclear	yes	yes	24 months	100
Kothadia, 1999 [25, 41, 42]	unclear	unclear	yes	yes	yes	(a) 12 months (b) 4–11 years	(a) 98 (b) 88
Walther, 2003 [26]	yes	yes	yes	yes	yes	NA	NA
Vento, 2004 [27]	unclear	unclear	no	yes	unclear	NA	NA
Doyle, 2006 [28, 43]	yes	yes	yes	yes	yes	2 years	98

NA = Not applicable.

^a For outcomes during primary hospitalisation.

home oxygen, and the rate of failure to extubate by 7 days.

Complications during the Primary Hospitalisation. Dexamethasone after the first week of life was associated with many short-term complications, such as higher rates of hyperglycaemia and glycosuria, high blood pressure, severe ROP, and hypertrophic cardiomyopathy. There were no significant increases in rates of infection, or in GI problems, such as NEC, GI bleeding or GI perforation.

Follow-Up Data. The increase in ROP did not translate into a significant increase in blindness. There were no significant differences in the rates of deafness, cerebral palsy at the latest reported age, or the combined rate of either death or cerebral palsy at the latest reported age. Major neurosensory disability was not significantly increased, but the number of studies where this outcome could be determined ($n = 7$) was smaller than the number of studies reporting cerebral palsy outcomes ($n = 12$). The combined rate of either death or major neurosensory disability was not significantly affected. There was an in-

creased rate of abnormal neurological examination overall, but there were only four studies reporting this outcome, and the clinical importance of this finding is unclear in the absence of important increases in either cerebral palsy or major neurosensory disability.

Pooled rates of selected outcomes for both treated and control groups, and the relative risks and 95% CIs for benefit are shown in figure 1 and for harm are shown in figure 2.

Discussion

In this systematic review, infants who were mostly ventilator-dependent after the first week of life were transiently improved by a course of dexamethasone initiated after the first 7 days of life. Dexamethasone facilitated extubation from the ventilator and reduced the rate of BPD, the need for a later course of corticosteroids and the need for home oxygen therapy. Survival to 28 days was

Table 3. Meta-analysis of selected outcomes, and NNTB or NNTH where differences were statistically significant

Outcome	Studies	Infants	Typical relative risk (95% CI)	p value	NNTB or NNTH (95% CI)
Mortality and acute lung morbidity					
Mortality at 28 days	8	656	0.49 (0.28–0.85)	0.01	19 (14–63)
Mortality at latest reported age	16	936	0.87 (0.67–1.13)	0.29	
BPD at 28 days	6	623	0.87 (0.81–0.94) ^a	<0.001	9 (6–20)
Death or BPD at 28 days	5	563	0.84 (0.78–0.89)	<0.001	7 (5–10)
BPD at 36 weeks	8	471	0.72 (0.61–0.85) ^a	<0.001	6 (4–11)
Death or BPD at 36 weeks	8	471	0.72 (0.63–0.82) ^a	<0.001	5 (4–8)
Failure to extubate by 7 days	10	497	0.64 (0.56–0.74)	<0.001	4 (3–5)
Late rescue with corticosteroids	12	1,032	0.46 (0.36–0.58)	<0.001	6 (5–8)
Discharge home on oxygen	7	611	0.71 (0.54–0.94)	0.02	13 (8–62)
Other early complications					
Infection	14	1,225	1.17 (0.98–1.39)	0.08	
Hyperglycaemia	14	1,192	1.52 (1.25–1.84)	<0.001	10 (7–21)
Glycosuria	2	48	8.03 (2.43, 26.52)	<0.001	2 (1–9)
Hypertension	12	1,096	2.66 (1.58–4.49)	<0.001	21 (10–59)
Hypertrophic cardiomyopathy	4	238	2.76 (1.33–5.74) ^a	0.006	9 (4–45)
NEC	8	952	0.98 (0.56–1.73)	0.95	
Intestinal perforation	2	95	0.36 (0.02–8.05)	0.52	
Gastrointestinal bleeding	7	992	1.38 (0.99–1.93)	0.06	
Severe ROP	12	558	1.38 (1.07–1.79)	0.01	12 (6–60)
Long-term follow-up					
Blindness	9	621	0.81 (0.32–2.04)	0.66	
Deafness	6	458	0.56 (0.22–1.44)	0.23	
Abnormal neurological exam	4	200	1.81 (1.05–3.11)	0.03	8 (3–122)
Cerebral palsy at latest age assessed	12	756	1.22 (0.84–1.77)	0.30	
Death or cerebral palsy	12	756	0.98 (0.80–1.21)	0.87	
Major neurosensory disability	7	612	1.19 (0.86–1.66)	0.30	
Death or major neurosensory disability	7	612	1.07 (0.88–1.30)	0.51	

Typical relative risks and 95% CIs <1 indicate a significant benefit from treatment with dexamethasone and those >1 indicate harm.

^a Significant heterogeneity ($I^2 > 50\%$).

improved, but whether this was maintained overall is unclear, partly because of the high rate of open-label use of corticosteroids in most studies, and because the results of Papile et al. [22] could not be used for survival outcomes beyond 28 days because of treatment of the majority of the delayed group with dexamethasone after that time. However, there were significant short-term side effects of dexamethasone, including hyperglycaemia, glycosuria, hypertension and cardiomyopathy, and some evidence of longer-term side effects, including severe ROP and abnormal neurological examination. The methodological quality of the studies determining the long-term outcome was limited in some cases; surviving children were assessed predominantly before school age, and no study was sufficiently powered to detect important adverse

long-term neurosensory outcomes. Given the evidence of both benefits and harms of treatment, and the limitations of the evidence at present, it appears prudent to reserve the use of late corticosteroids to infants who cannot be weaned from mechanical ventilation after the first week of life and who are at high risk of BPD [29], and to minimise the dose and duration of any course of treatment.

A subgroup analysis limited to those studies where there was no open-label corticosteroid treatment was considered, but where it was possible to determine if open-label corticosteroids were allowed, they were prescribed in most trials. Open-label corticosteroids make it harder to determine the true effects of dexamethasone alone. There were too few studies with too few subjects where it is known for certain that open-label corticoste-

Fig. 1. Forest plot of typical relative risks for favourable outcomes from late dexamethasone.

Fig. 2. Forest plot of typical relative risks for adverse outcomes from late dexamethasone.

roids were not prescribed to justify such a subgroup analysis.

More studies are needed to examine the lowest safe dose and type of corticosteroid. Hydrocortisone, and other corticosteroids such as betamethasone or methylprednisolone, should be compared with lower doses of dexamethasone in ventilator-dependent infants. Thus far, hydrocortisone is the only other systemic corticosteroid to be evaluated in RCTs; it has only been started in the first week of life in relatively low doses, where it has few effects, as reviewed elsewhere [7, 30]. Long-term follow-up studies on all children who have been enrolled in randomised trials of dexamethasone are required. These studies need to examine both major and more subtle (e.g. cognitive and behavioural) adverse neurological outcomes, in addition to long-term visual function. Any new

studies should be designed to assess the overall risks and benefits of corticosteroids and be sufficiently powered to detect important adverse long-term neurosensory sequelae.

In this review, data on long-term neurosensory follow-up were available from 12 studies comprising 800 infants randomised, but these were of varying methodological quality. The significant increase in abnormal neurological examination in those randomised is of potential concern; however, this is tempered by the findings that cerebral palsy and major neurosensory disability, both overall and in survivors, were not significantly increased, and the abnormal neurological examination findings were reported in only 4 of the 11 follow-up studies and in only 200 subjects randomised. It should be noted, however, that some studies reporting cerebral palsy as an outcome

did so early in childhood; before 5 years of age the diagnosis of cerebral palsy is not certain in all cases [31]. Moreover, no study was designed primarily to test the effect of postnatal corticosteroids on adverse long-term neurosensory outcome, except for the DART study [28], which had to cease recruitment with <10% of the projected sample size recruited, and all were underpowered to detect clinically important differences in long-term neurosensory outcome. Clearly more information on long-term outcome of infants is needed.

Clinicians must weigh the benefits of acute improvement in respiratory function and increased chances of extubation (with a possible improved survival) against the potential detrimental effects, both metabolic and

neurological. Dexamethasone may be a harmful drug to the immature brain and consideration must be given to limiting its use to situations where it is essential to achieve weaning from the ventilator. Lower doses and shorter courses should be considered for these infants; the DART study [28], with a total dose of only 0.89 mg/kg over 10 days, was able to demonstrate acute benefits of extubation and reduced respiratory support. There are limited data on the effects of inhaled corticosteroids in infants with BPD, but this potentially useful intervention should have fewer systemic side effects and warrants further study [32]. Further studies of low-dose systemic corticosteroids initiated beyond the first week of life in infants at high risk of developing BPD are also warranted.

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