Systematic review and meta-analysis of early postnatal dexamethasone for prevention of chronic lung disease

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Abstract

***Aim*—To review systematically the evidence to determine whether dexamethasone treatment of very low birthweight infants begun within 14 days of age prevents chronic lung disease (CLD) without clinically significant side effects.**

***Methods*—Randomised controlled trials of dexamethasone started within this time frame were identified through a search of electronic databases, proceedings of scientific meetings, and personal files. Meta-analyses using event rate ratio (ERR), event rate difference (ERD), and if significant, numbers needed to treat (NNT) for benefits and numbers needed to harm (NNH) for adverse effects were calculated. Weighted mean difference were used for continuous variables. Three prespecified subgroup analyses were performed for; (i) dexamethasone begun within 36 hours (hours) of birth; (ii) dexamethasone initiated between 7–14 days of age; or (iii) if surfactant treatment was used.**

***Results*—Ten studies were included in the review; six where dexamethasone was initiated within 36 hours of age, four studies for dexamethasone started between 7 and 14 days and six studies using surfactant. Mortality ERR and NNT with 95% confidence intervals for dexamethasone initiated at 7–14 days of age were 0.35 (0.16, 0.74) and 8 (4, 30). ERRs and NNTs for CLD at 28 days and 36 weeks of postmenstrual age were 0.71 (0.61, 0.84), 8 (5, 17), and 0.57 (0.44, 0.76), 10 (6, 23) in the overall analyses. When dexamethasone was started at 7 to 14 days of age ERR and NNT for CLD at 36 weeks were 0.63 (0.47, 0.85) and 3 (2, 9). Clinically significant side effects included increased risk of hypertension, hyperglycaemia, and increased time to regain birthweight.**

***Conclusions*—These meta-analyses show a significant reduction in risk of CLD at 28 days and 36 weeks of postmenstrual age. In the subgroup where dexamethasone was started between 7 and 14 days of age mortality was significantly reduced. Caution is warranted in the routine use of dexamethasone because of lack of data on long term neurodevelopmental outcomes.**

(*Arch Dis Child Fetal Neonatal Ed* 1998;**79**:F26–F33)

Keywords: dexamethasone; chronic lung disease; prevention; meta-analysis; randomised controlled trials

Abstract presented at the Perinatal Society of Australia and New Zealand, 1st Annual Congress, Fremantle, Western Australia (16–20 March 1997) and at the Canadian Paediatric Society Meeting, Halifax, Nova Scotia, Canada (24–26 June 1997)

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Accepted 26 January 1998

Routine use of surfactant replacement for respiratory distress syndrome (RDS) has reduced the incidence of pneumothoraces in premature infants.[1–3] However, multicentre trials have failed to show a reduction in the incidence of chronic lung disease (CLD).[4–6] The combined use of antenatal steroids and postnatal surfactant replacement significantly decreased the overall morbidity and mortality caused by RDS relative to either treatment alone.[7]

Steroids have been used in several controlled trials to treat established CLD and have shown significant short term improvements in lung function.[8–12] Postulated mechanisms by which steroids might improve lung function include increased surfactant synthesis, inhibition of prostaglandins and leucotriene synthesis, enhancement of β adrenergic activity and reduced pulmonary oedema.[13] Cellular and biochemical studies have shown inflammatory changes in the lungs of ventilated infants[14–16] as early as the first few days of life and dexamethasone has been shown to reduce this inflammation.[17 18] But there is still concern over the potential side effects of dexamethasone in preterm neonates.[19–25]

In view of the conflicting results of the effectiveness of early postnatal dexamethasone for the prevention of CLD and the small number of patients in some of these trials, we undertook a systematic review and meta-analyses of the results of these trials.

Methods

A search was undertaken with the use of three databases: MEDLINE (National Library of Medicine) for the years 1980–97, EMBASE for the years 1989–96, and the Oxford Database of Perinatal Trials (ODPT). The Proceedings of American Pediatric Society/Society of Pediatric Research meeting abstract books from the years 1991–6 were searched manually. Further studies were identified from reference lists of publications noted above. To be included in the review, trials had to meet each of the following criteria:

(1) randomised controlled trial
(2) the study infants were newborns with a birthweight of 2000 g or less
(3) the intervention was dexamethasone
(4) dexamethasone was started within 14 days of birth
(5) dexamethasone was electively started for prevention of CLD
(6) the study included some measure of some of the following outcomes

Mortality
CLD at 28 days
CLD at 36 weeks of postmenstrual age
Days in supplemental oxygen
Days in hospital
Days on mechanical ventilation
Days to regain birthweight
Hypertension defined as systolic or diastolic blood pressure > 2 SD above mean values[26]
Sepsis
Intraventricular haemorrhage (IVH) any grade
Intraventricular haemorrhage (grades 3 or 4)
Necrotising enterocolitis (NEC)
Retinopathy of prematurity (ROP) any stage
Hyperglycaemia defined as greater than 8.3 mmol/l
Insulin for hyperglycaemia
Air leak syndromes
Long term pulmonary and neurodevelopmental follow up

This review used the guidelines of the Cochrane Collaboration as outlined in the Cochrane Library[27] and the *Effective Care of the Newborn Infant.*[28] The data were extracted separately by each author and then compared. A third data extraction and discussion resolved discrepancies. Additional information was sought from the authors when required. The data taken from abstracts were compared with data taken from the full manuscripts by the same author(s) where possible to try and avoid inclusion of duplicate data. Meta-analyses of dichotomous outcomes were expressed in three ways. The event rate ratio (ERR), event rate difference (ERD), and if significant, numbers needed to treat (NNT) for benefits and numbers needed to harm (NNH) for adverse effects were calculated (95% confidence intervals were used for all the analyses). Continuous data were expressed as a mean difference and weighted mean difference in the meta-analyses. Heterogeneity between the trial results was assessed for significant outcomes. The data were synthesised using Meta-Analyser, version 1.2 (Update software Ltd).

Key messages
- Early postnatal dexamethasone begun within 14 days of age significantly reduces the risk of CLD at 28 days and 36 weeks of postmenstrual age
- When started between 7 and 14 days of age there is also a significant reduction in mortality.
- Significant side effects include increased risk of hypertension, hyperglycaemia, and increased time to regain birthweight
- There are no data on long term neurodevelopmental outcomes

For these analyses the authors chose to base validity assessment on four methodological criteria that can be associated with significant bias in trials assessing treatment effect,[29] and these were evaluated separately by each author. These included concealment at randomisation, blinding of treatment, blinding of outcome assessment and completeness of follow up. No scoring system is incorporated in this particular method of evaluation. The final assessment of the validity of the studies included is therefore left to the individual reader.

Three subgroup analyses were determined a priori. Two subgroups were based on the time

Table 1 Characteristics of trials included in the review: trials where dexamethasone has begun <36 hours of age

Author	*Year*	*Double blinded*	*Dose (mg/kg/day)*	*Course (days)*	*Start age*	*No of patients*	*Characteristics*
Rastogi *et al*[30]	1996	Yes	0.5(3),0.3(3),*0.2(3),0.1(3)	12	<12h	64	700–1500 g; stratified 700–999 g, 1000–1249 g, 1250–1500g; surfactant, MV, 13% in dex and 47% in control received steroids
Shinwell *et al*[31]	1996	Yes	0.5(3)	3	<12h	248	500–2000 g; stratified 500–1000 g,1001–2000 g surfactant, MV, 27% in dex and 26% in control received steroids
Sander *et al*[32]	1994	Yes	1 (1)	1	12–18h	40	<30 w GA; MV at 12–18 h; surfactant 10% in dex and 14% in control received steroids
Yeh *et al*[33]	1990	Yes	1 (3),0.5(3),0.25(3),0.1(3)	12	<12h	60	700–1999 g; stratified <1000 g; 1001–1500 g; 3 excluded; MV
Tapia *et al*[39]	1996	Yes	0.5(3),0.3(3),0.2(3),0.1(3)	12	<36h	109	700–1600 g, MV; surfactant
Yeh *et al*[38]	1994	Yes	0.5(7),0.25(7),0.1(7),0.05(7)	28	<12h	142	<2000 g; MV

*Figures in parentheses indicate number of days. MV = mechanically ventilated; dex= dexamethasone.

Table 2 Characteristics of trials included in the review: trials where dexamethasone has begun 7–14 days of age

Author	*Year*	*Double blinded*	*Dose (mg/kg/day)*	*Course length (day)*	*Start age*	*No of patients*	*Characteristics*
Durand *et al*[34]	1995	No	0.5 (3), 0.25 (3), 0.1 (3)	7	7–14 d	43	501–1500 g; 24–32 w; MV at 7–14 d; surfactant 26% in dex and 65% in control received steroids
Brozanski *et al*[35]	1995	Yes	0.5 (3) every 10 days, until *36 w PMA or no O_2 therapy	Until 36 w PMA	7 d	78	<1500 g; stratified <1000, >1001; surfactant; MV No crossover
Kari *et al*[36]	1993	Yes	0.5 (7)	7	10 d	41	<1500 g; >24 w; MV at 10 days; only 3 patients in in dex group and 1 control received surfactant 33% of controls received steroids
Cummings *et al*[37]	1989	Yes	0.5 (3), 0.3 (3), then ↓ by 10% every 3 days until 0.1 and then on alternate days for 1 week	42 18	14 d	36	<1250 g; <30 w; MV at 14 days; randomised to three groups, 42 d, 18 d, and control

Figures in parentheses indicate days. PMA = post menstrual age; dex = dexamethasone.

Table 3 Validity of trials included in the review

Author	*Year*	*Method of randomisation*	*Blinding of intervention*	*>90% Follow up*	*Blinding of outcomes*
Rastogi *et al*[30]	1996	Phone/coded drugs	Yes	Yes	Yes
Shinwell *et al*[31]	1996	Phone/coded drugs	Yes	Yes	Yes
Sander *et al*[32]	1994	Sealed envelopes/coded drugs	Yes	Yes	Yes
Yeh *et al*[33]	1990	Assigned list by pharmacy	Yes	Yes	Yes
Tapia *et al*[39]	1996	Not described	Yes	Yes	Yes
Yeh *et al*[38]	1994	Not described	Yes	Yes	?
Durand *et al*[34]	1995	Sealed envelopes	No	Yes	Yes
Brozanski *et al*[35]	1995	Sealed envelopes	Yes	Yes	Yes
Kari *et al*[36]	1993	Not described	Yes	Yes	?
Cummings *et al*[37]	1989	Assigned list/coded drugs	Yes	Yes	Yes

of postnatal initiation of dexamethasone. In the first subgroup all the studies in which dexamethasone was started within 36 hours of postnatal age were included and in the second subgroup were those studies which started dexamethasone between 7 and 14 days of postnatal age. The third subgroup consisted of all studies where surfactant replacement was used in addition to dexamethasone.

Sensitivity analyses were done to look at the effectiveness of different doses and duration of dexamethasone treatment.

Results

Ten studies were selected for inclusion in the review, eight of which were full publications[30–37]; two were abstracts at the time of the review.[38 39] One of the abstracts was in the process of being submitted for publication. Additional information was sought from the authors of these abstracts and also of the published studies as required. The characteristics of the trials, as reported, are summarised in tables 1 and 2.

Most of the trials allowed for open treatment with dexamethasone at the discretion of the clinician after the treatment period. Only ventilator dependent patients were randomised in all trials.

The study design of each trial is shown in table 3. Of the 10 trials reviewed in this systematic review, in nine the intervention was blinded and in eight the outcomes were blinded; all the trials having more than 90% follow up.

MORTALITY

There was no significant difference (table 4) in mortality in the neonates randomised to dexamethasone in the overall analyses, the subgroups where dexamethasone was started within 36 hours of age (table 5), and the subgroup where surfactant was administered[30 37–39] [ERR 0.98 (0.70, 1.36)]. However, in the subgroup analyses where dexamethasone was started within 7 to 14 days of postnatal age (table 5) there was a significant reduction in mortality [ERR 0.35 (0.16, 0.74), NNT 8 (4, 30)]. This suggests that on average eight infants would need to be treated with dexamethasone between 7 to 14 days of postnatal age to prevent one death. There was no significant heterogeneity between the results of the trials.

CHRONIC LUNG DISEASE AT 28 DAYS

In the overall[31 33–36 38 39] (table 6) and all three subgroup analyses there was a significant reduction in CLD in the neonates given

Table 4 Effect of dexamethasone on mortality: all trials

Trials	*Year*	*Expected observed*	*Expected total*	*Controls observed*	*Controls total*	*ERR (95% CI)*	*ERD (95% CI)*	*NNT (95% CI)*
Durand *et al*[34]	1995	2	23	4	20	0.43 (0.08,2.37)	−11.30 (−32.28,9.67)	
Brozanski *et al*[35]	1995	2	39	9	39	0.22 (0.05,1.03)	−17.95 (−32.87,−3.02)	
Yeh *et al*[38]	1994	28	75	20	67	1.25 (0.70,2.22)	7.40 (−8.01,22.97)	
Cummings *et al*[37]	1989	3	12	6	11	0.46 (0.11,1.83)	−29.55 (−67.84,8.74)	
Kari *et al*[36]	1993	1	17	3	24	0.24 (0.01,4.70)	−6.62 (−23.94,10.71)	
Shinwell *et al*[31]	1996	31	132	22	116	1.24 (0.72,2.14)	4.52 (−5.64,14.68)	
Rastogi *et al*[30]	1996	4	36	2	34	1.89 (0.35,10.31)	5.23 (−7.73,18.19)	
Sander *et al*[32]	1994	2	19	7	21	0.32 (0.07,1.52)	−22.81 (−47.24,1.63)	
Tapia *et al*[39]	1996	17	55	18	54	0.93 (0.48,1.80)	−2.42 (−19.95,15.10)	
Yeh *et al*[33]	1990	3	28	8	29	0.39 (0.10,1.46)	−16.87 (−36.77,3.02)	
Pooled [χ^2 14.00 (df=9)]		93	436	98	415	0.88 (0.69,1.13)	−3.44 (−8.57,1.68)	

Table 5 Effect of dexamethasone on death

Trials	*Year*	*Expected observed*	*Expected total*	*Controls observed*	*Controls total*	*ERR (95% CI)*	*ERD (95% CI)*	*NNT (95% CI)*
When begun at <36 h of age:								
Yeh *et al*[38]	1994	28	75	20	67	1.25 (0.70,2.22)	7.48 (−8.01,22.97)	
Shinwell *et al*[31]	1996	31	132	22	116	1.24 (0.72,2.14)	4.52 (−5.64,14.68)	
Rastogi *et al*[30]	1996	4	36	2	34	1.89 (0.35,10.31)	5.23 (−7.73,18.19)	
Sander *et al*[32]	1994	2	19	7	21	0.32 (0.07,1.52)	−22.81 (−47.24,1.63)	
Tapia *et al*[39]	1996	17	55	18	54	0.93 (0.48,1.80)	−2.42 (−19.95,15.10)	
Yeh *et al*[33]	1990	3	28	8	29	0.39 (0.10,1.46)	−16.87 (−36.77,3.02)	
Pooled χ^2=6.92 (df=5)		83	345	77	321	1.03 (0.78,1.34)	0.64 (−5.42,6.69)	
Subgroup when begun between 7–14 days of age:								
Durand *et al*[34]	1995	2	23	4	20	0.43 (0.08,2.37)	−11.30 (−32.28,9.67)	
Brozanski *et al*[35]	1995	2	39	9	39	0.22 (0.05,1.03)	−17.95 (−32.87,−3.02)	
Cummings *et al*[37]	1989	3	12	6	11	0.46 (0.11,1.83)	−29.55 (−67.84,8.74)	
Kari *et al*[36]	1993	1	17	3	24	0.24 (0.01,4.70)	−6.62 (−23.94,10.71)	
Pooled [χ^2=0.94 (df=3)]		8	91	21	94	0.35 (0.16,0.74)	−12.13 (−20.97,−3.29)	8 (4,30)

Table 6 Effect of dexamethasone on CLD at 28 days: all trials

Trials	*Year*	*Expected observed*	*Expected total*	*Controls observed*	*Controls total*	*ERR (95% CI)*	*ERD (95% CI)*	*NNT (95% CI)*
Durand *et al*[34]	1995	7	22	13	19	0.47 (0.19,1.17)	−36.60 (−65.16,−8.04)	
Brozanski *et al*[35]	1995	33	37	31	32	0.92 (0.56,1.50)	−7.69 (−19.37,4.00)	
Yeh *et al*[38]	1994	11	47	24	47	0.46 (0.22,0.94)	−27.66 (−46.39,−8.93)	
Kari *et al*[36]	1993	15	17	21	22	0.92 (0.48,1.79)	−7.22 (−24.84,10.40)	
Shinwell *et al*[31]	1996	32	132	24	116	1.17 (0.69,1.99)	3.55 (−6.83,13.94)	
Rastogi *et al*[30]	1996	5	32	21	32	0.24 (0.09,0.63)	−50.00 (−70.71,−29.29)	
Tapia *et al*[39]	1996	11	55	16	54	0.68 (0.31,1.45)	−9.63 (−25.76,6.50)	
Yeh *et al*[33]	1990	8	26	12	20	0.51 (0.21,1.25)	−29.23 (−57.08,−1.38)	
Pooled [χ^2=37.94 (df=7)]		122	368	62	342	0.71 (0.61,0.84)	−11.53 (−17.17,−5.88)	8 (5,17)

Table 7 Effect of dexamethasone on CLD at 36 weeks postmenstrual age: all trials

Trials	*Year*	*Expected observed*	*Expected total*	*Controls observed*	*Controls total*	*ERR (95% CI)*	*ERD (95% CI)*	*NNT(95% CI)*
Durand *et al*[34]	1995	2	21	8	17	0.20 (0.04,0.95)	−37.54 (−64.38,−10.69)	
Brozanski *et al*[35]	1995	24	40	30	37	0.74 (0.43,1.27)	−21.08 (−40.83,−1.34)	
Yeh *et al*[38]	1994	3	47	11	47	0.27 (0.08,0.98)	−17.02 (−31.00,−3.04)	
Shinwell *et al*[31]	1996	15	132	11	116	1.20 (0.55,2.61)	1.88 (−5.72,9.48)	
Rastogi *et al*[30]	1996	0	32	6	32	0.08 (0.00,1.49)	−17.19 (−31.38,−3.00)	
Sander *et al*[32]	1994	4	17	5	14	0.66 (0.18,2.45)	−12.18 (−44.38,20.01)	
Tapia *et al*[39]	1996	3	55	12	54	0.25 (0.07,0.87)	−16.77 (−29.38,−4.16)	
Pooled [χ^2=11.05 (df=6)]		51	344	83	317	0.57 (0.44,0.76)	− 9.41 (−14.50, −4.32)	10 (6,23)

dexamethasone. The results suggest that eight infants would need to be treated with dexamethasone to prevent one infant developing CLD at 28 days in the overall analyses. In the subgroup where dexamethasone was started within 36 hours,[30 31 33 38 39] the ERR and NNT were 0.64 (0.49, 0.83) and 8 (5–16), respectively. The ERR and NNT of the subgroup where dexamethasone was started between 7 and 14 days[34–36] were 0.83 (0.72, 0.95) and 6 (4, 20), respectively. The findings in the surfactant subgroup[30 31 34 35 39] did not differ from the overall analysis [ERR 0.73 (0.60-0.90)]. There was significant heterogeneity in the results of the trials.

CLD AT 36 WEEKS OF POSTMENSTRUAL AGE

In the neonates given dexamethasone, the overall analysis[30–32 34 35 39] showed a significant reduction in CLD (table 7). Similar results were obtained in the subgroup where surfactant[30–32 34 35 38 39] was used [ERR 0.57 (0.43, 0.75)]. In the subgroup analyses[34 35] where dexamethasone was started between 7 and 14 days of age, the ERR was 0.63 (0.47, 0.85) and only three infants would need to be treated with dexamethasone to prevent one infant developing CLD. In the subgroup[30–33 38 39] where dexamethasone was started within 36 hours of age the ERR was 0.53 (0.33, 0.83) and 13 infants would need to be treated to prevent one infant developing CLD. There was no heterogeneity in the results of the trials.

DEATH OR CLD AT 28 DAYS

There was a significant reduction in risk of death or CLD in the overall and in all three subgroup analyses in the dexamethasone group. In the overall analyses the ERR was 0.83 (0.74, 0.93) and the NNT was 8 (5, 17). The ERRs and NNTs of the subgroups where dexamethasone was begun within 36 hours and between 7 and 14 days of postnatal age were 0.83 (0.71, 0.97), 9 (5, 36), and 0.83 (0.73, 0.93), 9 (5,60), respectively. The ERR and NNT of the surfactant subgroup were 0.89 (0.73, 0.97) and 11 (5, 31), respectively.

DEATH OR CLD AT 36 WEEKS OF POSTMENSTRUAL AGE

The risk of death or CLD at 36 weeks postmenstrual age was significantly reduced in the overall analyses, ERR 0.78 (0.66, 0.93), NNT 9 (5, 25) and in the subgroup where dexamethasone was started between 7 and 14 days of postnatal age, ERR 0.60 (0.44, 0.81), NNT 3 (2, 7). Thus to reduce the incidence of death or CLD by one on an average, only three infants would need to be treated with dexamethasone, starting between 7 and 14 days of postnatal age. Results of the surfactant subgroup were similar to those of the overall analysis.

DAYS ON MECHANICAL VENTILATION

Table 8 shows that there is a decrease in days on mechanical ventilation in the overall as well as the subgroup analyses. Overall weighted mean difference with 95% CI,−2.05 (−2.33, −1.78). Only five studies[30–32 35 39] in the overall analyses, four studies[30–32 39] in the subgroup where dexamethasone was started within 36 hours of age, and one study[35] in the subgroup where dexamethasone was started between 7 and 14 days of age assessed this outcome. Four studies assessed this outcome in the surfactant subgroup.[30 32 35 39]

DAYS ON OXYGEN

There was no significant decrease in the number of days on supplemental oxygen, (table 8) with the overall weighted mean difference being 0.66 (−0.08, 1.40). However, in the subgroup[35] where dexamethasone was started between 7 and 14 days there was a significant decrease in the days in supplemental oxygen, with the weighted mean difference being −59 (−72, −46), but only one trial assessed this outcome in the subgroup.

Table 8 Results: days on mechanical ventilation, in supplemental oxygen, in hospital, and days to regain birthweight

	No of patients Dex/Controls	Weighted mean difference (95% CI)		
		Dexamethasone begun 0–14 days	*Begun <36 hours of age*	*Begun 7–14 days of age*
Days on MV	277/262	−2.05 (−2.33, −1.78)[30–32 35 39]	−2.03 (−2.30, −1.76)[30–32 39]	−25 (−33.57, −16.43)[35]
Days in oxygen	303/282	0.66 (−0.08, 1.40)[30–33 35 39]	0.87 (0.12, 1.61)[30–33 39]	−59 (−71.74, −46.26)[35]
Days in hospital	204/186	−2.06 (−3.51, −1.68)[31–33 35]	−2.03 (−2.96, −1.10)[31–33]	−25 (−30.84, −19.16)[35]
Days to regain birthweight	58/52	3.86 (1.75, 5.98)[30 33]	3.86 (1.75, 5.98)[30 33]	—

DAYS IN HOSPITAL

There was a significant reduction in hospital stay in the group that received dexamethasone (table 8), which was evident in the overall as well as the subgroup analyses. Overall weighted mean difference with 95% CI was −2.06 (−3.51, −1.68). Four studies[31–33 35] in the overall analyses, three[31–33] in the subgroup where dexamethasone was started within 36 hours of age, one study [35] in the subgroup where dexamethasone was started between 7 and 14 days and two studies in the surfactant subgroup[32 35] assessed this outcome.

DAYS TO REGAIN BIRTHWEIGHT

Only two studies[30 33] have recorded this outcome. There was an increase in the number of days to regain birth weight in the group that received dexamethasone. The weighted mean difference was 3.9 days with a 95% CI of 1.8, 6.0 days.

HYPERTENSION

There was a significant increased risk of hypertension in the group that received dexamethasone in the overall (table 9) and in the subgroup analyses where dexamethasone was started between 7 and 14 days of postnatal age: ERRs 3.04 (1.34, 6.86), 3.78 (1.15, 12.38) and NNHs 42 (19, 212) 65 (16, 344), respectively. In the surfactant subgroup there were no significant differences in risk of hypertension [ERR 1.91 (0.84, 4.35)]. In all the trials that showed a significant increase, the hypertension was transient, with most patients recording normal blood pressures by day 10 of starting dexamethasone. None of the patients required continued anti-hypertensive treatment after treatment or at discharge.

HYPERGLYCAEMIA

The risk of hyperglycaemia due to dexamethasone was increased, but the risk was low and only just reached significance in the overall analyses,[30 31 34–37 39] the ERR being 1.32 (1.04, 1,69) and NNH 14 (8, 100). This was not significant in the subgroup analyses: the ERRs were 1.34 (0.94, 1.91) and 1.30 (0.93, 1.83), respectively.

INTRAVENTRICULAR HAEMORRHAGE (ANY GRADE)

The pooled results showed no significant difference in effect of dexamethasone on the incidence of IVH all grades and grades 3 or 4 in the overall[30 32 35 39] and subgroup analyses, the ERRs being 0.91(0.65, 1.29) and 1.06 (0.69, 1.61), respectively.

RETINOPATHY OF PREMATURITY (ROP) ANY STAGE

There was no significant difference in the incidence of ROP in the overall[30 32–34 36 37 39] or any subgroup analyses; the ERRs were 0.92 (0.67, 1.26), 0.86 (0.57, 1.30), 0.94 (0.41, 2.13) and 0.85 (0.55, 1.30), respectively.

NECROTISING ENTEROCOLITIS, AIR LEAK SYNDROMES, AND SEPSIS

Pooled estimates of NEC,[30–35 39] air leak syndromes,[30–32 34 35 37 39] and sepsis[30–37 39] showed no significant difference; the ERRs being 0.64 (0.37, 1.12), 0.80 (0.57, 1.12) and 0.89 (0.63, 1.25). The results were similar in all the subgroup analyses.

INSULIN TREATMENT

Insulin treatment for hyperglycaemia as an outcome was assessed in two studies[30 32]: ERR 1.68 (0.75, 3.78)

LONG TERM NEURODEVELOPMENTAL AND PULMONARY OUTCOMES

Cummings *et al*[37] assessed neurodevelopmental outcomes at 6 and 15 months. At 15 months corrected age, none (0/9) of the survivors from the 42 day course of dexamethasone had abnormalities on neurological examination, whereas more than 56% (5/9) of the survivors from the 18 day group and 40% (2/5) of the survivors from the control group had marked truncal hypotonia or cerebral palsy. Thus good neurodevelopmental outcome (normal exam and Bayley indexes > 84) were more often present in infants in the 42 day group (78%) than in 18 day group (22%) or the control group (40%). Follow up at 4 years[40] showed better results in the 42 day group on all the McCarthy subscales. The problem with long term pulmonary and neurodevelopmental outcome is that crossover was allowed in most of

Table 9 Effect of dexamethasone on hypertension: all trials

Trials	*Year*	*Expected observed*	*Expected total*	*Controls observed*	*Controls total*	*ERR (95% CI)*	*ERD (95% CI)*	*NNH (95% CI)*
Durand *et al*[34]	1995	2	23	1	20	1.74 (0.16,19.18)	3.70 (−11.27,18.66)	
Brozanski *et al*[35]	1995	0	39	0	39	1.00 (0.02,50.40)	0.00 (−4.99,4.99)	
Cummings *et al*[37]	1989	0	12	0	11	0.92 (0.02,46.20)	−0.38 (−17.09,16.34)	
Kari *et al*[36]	1993	7	17	1	24	9.88 (1.22,80.32)	37.01 (12.29,61.73)	
Shinwell *et al*[31]	1996	8	132	2	116	3.52 (0.75,16.55)	4.34 (−0.37,9.05)	
Rastogi *et al*[30]	1996	1	36	1	34	0.94 (0.06,15.10)	−0.16 (−7.98,7.65)	
Tapia *et al*[39]	1996	3	55	2	54	1.47 (0.25,8.81)	1.75 (−6.08,9.59)	
Pooled [χ^2 = 3.7 (df=6)]		21	314	7	298	3.04 (1.34,6.86)	2.33 (−0.47,5.13)	42 (19,212)

the trials following the study period. Recent trials have used shorter courses and smaller doses, so long term follow up from these trials would be valuable.

The sensitivity analyses were done to look at the effect of different doses and duration of dexamethasone treatment on mortality and CLD. Included in the analyses were all the trials which used dexamethasone in doses starting at 0.5 mg/kg/day for 7–14 days.[30 33 34 36 39] This was done to see if there were differences in outcomes when trials which used higher doses and longer courses were not included in the analyses. The results were similar to those of the overall analyses; the ERRs and NNTs for CLD at 28 days[30 33 34 36 39] and 36 weeks of postmenstrual age[30 34 39] were 0.57 (0.45, 0.73), 4 (3, 8), and 0.29 (0.15, 0.54), 5 (4, 10), respectively.

Discussion

This systematic review and meta-analyses of early dexamethasone to prevent CLD was based on the methods recommended by the Cochrane Collaboration.[27] This involved an extensive search of published data and rigorous methodology. Reviewer bias was minimised by independent assessment and extraction of data by two authors. Where subgroup analyses were planned the criteria were established before the search or data analyses, in keeping with the initial objectives of the review.

There were some potential sources of bias in this systematic review. No attempt was made to trace unpublished trials. The small number of patients in the few trials reporting on outcomes such as days to regain birth weight, days in supplemental oxygen, and days in hospital, may affect the pooled results if no benefit or only a small effect due to lack of statistical power, rather than the absence of true effect is shown. On the other hand, some significant results such as increased risk of hypertension, which was transient, may be of doubtful clinical importance. Another limitation was the heterogeneity of the doses and duration of dexamethasone administration among the trials. However, this was addressed by sensitivity analyses.

In the overall pooled analysis of death[30–39] there was no significant difference in risk when dexamethasone was administered. In the pooled subgroup[34–37] where dexamethasone was started between 7 and 14 days, despite the small number of patients (91 patients in the intervention group and 94 in the control group), there was a significant reduction in risk of death, NNT 8 (4, 30). This significant finding has not been reported before. This difference in mortality between the groups does not seem to be due to differences in populations, but it cannot be precluded. The differences were derived from randomised controlled trials so the potential for bias is minimal.

There was a significant reduction in the risk of CLD both at 28 days and 36 weeks of postmenstrual age in both the overall analyses and all the subgroup analyses. The risk reduction at 36 weeks was greater when dexamethasone was started between 7 to 14 days of postnatal age [NNT 3 (2, 9)]: only three infants need to be treated with dexamethasone to prevent one infant developing CLD. In this subgroup only two of the four trials assessed this outcome and in one trial steroids were administered in pulses of three days out of every 10 until 36 weeks of postmenstrual age or until supplemental oxygen was no longer required. Three out of the four trials assessed CLD at 28 days in this subgroup. The findings of risk reduction, however, were consistent in all the trials except that of Shinwell *et al*[29] where the ERR was 1.17 (0.69, 1.99), which suggested a trend towards an increase in CLD if dexamethasone was administered. This finding was not significant, but this was the largest trial with 132 patients in the intervention group and 116 in the control group. The pooled results indicate that despite the increased risk in that trial there was still a significant risk reduction in the incidence of CLD both at 28 days and 36 weeks postmenstrual age in both the overall and the subgroup analyses. The reasons for the increased risk of CLD in the trial by Shinwell *et al*[29] are unclear. They may be related to the dose, duration, or the timing of administration. The heterogeneity in the results of CLD at 28 days is due to the results of this trial. There was no significant difference in the continuous outcome such as days in supplemental oxygen, despite a significant reduction in CLD. This may be due to skewed data with wide standard deviations. It would be more appropriate to report these continuous variables with medians and ranges rather than means and standard deviations to derive more meaningful information from these continuous variables.

The pooled estimates showed an increased risk of hypertension in the overall and in the subgroup where dexamethasone was started within 7 to 14 days of age. The increased risk was significant as the NNH was 42 (19, 212) in the overall analysis. The hypertension tended to be transient and was more apparent in the trials that used dexamethasone for longer than 14 days as well as higher doses.

There was a significant increase in risk of hyperglycaemia with NNH 14 (8, 100). This shows the wide confidence intervals, reflecting the small number of patients assessed for this outcome and the lack of strong evidence.

The sensitivity analyses showed that when dexamethasone was administered for 7 to 14 days, starting at 0.5 mg/kg/day the results were similar to those of the overall analyses except that NNT were lower for CLD at 28 days and 36 weeks of postmenstrual age [4 (3, 8), 5 (3, 9)]. Thus it seems that lower doses and shorter duration of dexamethasone treatment may be as effective as longer courses. However this needs to be further tested in randomised controlled studies. It may even be possible to use smaller doses than those used in the current studies.

There are concerns that dexamethasone may reduce cerebral DNA accretion, causing functional impairment.[20] One year follow up of 12 infants given only two doses of hydrocortisone at birth showed increased frequencies of

neurological and electroencephalographic abnormalities.[41] The shortcomings of most other trials are the subsequent treatment with dexamethasone in the control group after the study period. Thus it is difficult to get a true picture of the neurodevelopmental outcomes from these studies. Mammel *et al*[42] followed up eight ventilator dependent infants treated with a three week course of dexamethasone; at 1 year they showed a small but non-significant reduction in the Bayley mental developmental index. Ohlsson[43] found no difference in Bayley scores at 2 years of age in seven treated and nine control infants who were not crossed over. There was only one trial[37] from this review that has published long term outcomes at 6, 15 months, and 4 years. However, there were only 9/13, 9/12, and 5/11 survivors in the 42 day, 18 day, and control groups, respectively. With animal data suggesting that dexamethasone may interfere with cerebral DNA accretion, and conflicting evidence from small number of follow up patients it is still not clear whether dexamethasone adversely affects long term neurodevelopmental outcomes and whether it is related to dose or duration of treatment.

The results of this review and the meta-analyses of early postnatal dexamethasone for prevention of CLD suggest a significant reduction in risk of CLD at 28 days and 36 weeks of postmenstrual age if dexamethasone is started within 14 days of postnatal age. However, if begun between 7 to 14 days of postnatal age there is also a dramatic reduction in risk of death as well as an increase in the magnitude of risk reduction of CLD. There is the potential of substantial differences in the populations being treated early and those being treated late and thus caution is warranted in interpreting the differences between the groups. The magnitude of effect is also greater in reducing CLD at 28 days and 36 weeks of postmenstrual age when administered for 7 to 14 days at doses starting from 0.5 mg/kg/day. The only side effects found that were clinically significant were transient hypertension, hyperglycaemia, and an increase in days to regain birthweight. The clinical importance of the increased risk was low (NNH) compared with the benefits (comparing the NNT). However caution is warranted in routine administration of dexamethasone at this stage despite the above results for the following reasons:

(1) There are no significant long term studies of neurodevelopmental outcomes, in infants who received dexamethasone. There are ongoing concerns about myelination and somatic growth with dexamethasone. There are no significant long term studies of neurodevelopmental outcomes in infants who received dexamethasone. Due to the lack of the above it is difficult to assess the risk benefit ratio of the dramatic reduction in mortality *versus* the long term neurodevelopmental outcome;

(2) The above studies used different doses and duration of dexamethasone administration, therefore it is not clear which would be the minimum effective dose;

(3) There are few studies stratified according to gestational age so it is difficult to identify the group who would benefit the most with acceptable side effects. However, it can be recommended that if it is deemed necessary to give dexamethasone, it can be started between 7–14 days postnatal age in doses starting at 0.5 mg/kg/day and weaned over 7 to 14 days.

Future studies need to target infants most at risk of developing CLD. Stratification by gestational age would ensure that the most at risk group is targeted. Importantly, further studies to define the optimal dose and duration of dexamethasone are needed to reduce further the risk of side effects. Finally, long term neurodevelopmental and pulmonary outcomes of infants who received dexamethasone in optimal doses and not crossed over would need to be undertaken before dexamethasone could be recommended for routine administration to all at risk populations. Thus follow up should be inbuilt in all future primary studies.

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