Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants (Review)

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Overview

- Chronic lung disease: a major problem in neonatal intensive care units
- Persistent inflammation in the lungs is the most likely underlying pathogenesis
- Corticosteroids: used to either prevent or treat chronic lung disease because of their potent antiinflammatory effects but there are major adverse effects of the drugs

Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants?

Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants (Review)

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Objectives

To examine the relative benefits and adverse effects of postnatal corticosteroids commenced within the first seven days of life to preterm infants at risk of developing chronic lung disease

Results:

- 29 RCTs
- 3750 participants: Preterm infants at risk of developing chronic lung disease, including those who are ventilator-dependent
- Types of interventions: Intravenous or oral corticosteroids versus control (placebo or no treatment).

Data collection and analysis

1. Mortality,
2. Chronic lung disease,
3. Death or chronic lung disease,
4. Failure to extubate,
5. Complications during the primary hospitalisation,
6. Long-term health outcomes.

1. Mortality:

Comparison 1. Mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal mortality (up to 28 days)	19	2950	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.88, 1.19]
1.1 Dexamethasone	16	2603	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.90, 1.24]
1.2 Hydrocortisone	3	347	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.50, 1.23]
2 Mortality to hospital discharge	28	3730	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.88, 1.12]
2.1 Dexamethasone	19	2840	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.90, 1.18]
2.2 Hydrocortisone	9	890	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.66, 1.14]
3 Mortality at latest reported age	28	3730	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.88, 1.11]
3.1 Dexamethasone	19	2840	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.90, 1.17]
3.2 Hydrocortisone	9	890	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.67, 1.14]

→ no evidence that early postnatal corticosteroid treatment reduced mortality either at 28 days, discharge, latest age possible to determine the outcome

2. Chronic lung disease:

Comparison 2. Chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CLD (28 days)	17	2874	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.93]
1.1 Dexamethasone	16	2621	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.79, 0.92]
1.2 Hydrocortisone	1	253	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.85, 1.18]
2 CLD (36 weeks)	21	3286	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.71, 0.88]
2.1 Dexamethasone	15	2484	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.61, 0.81]
2.2 Hydrocortisone	6	802	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.12]
3 CLD at 36 weeks in survivors	18	2462	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.74, 0.90]
3.1 Dexamethasone	13	1841	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.64, 0.84]
3.2 Hydrocortisone	5	621	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.85, 1.12]
4 Late rescue with corticosteroids	14	2483	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.68, 0.82]
4.1 Dexamethasone	10	1974	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.65, 0.80]
4.2 Hydrocortisone	4	509	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.73, 1.40]
5 Survivors who had late rescue with corticosteroids	7	895	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.67, 0.89]
5.1 Dexamethasone	6	853	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.68, 0.91]
5.2 Hydrocortisone	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.24, 0.98]
6 Survivors discharged home on oxygen	6	691	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.51, 1.03]
6.1 Dexamethasone	3	406	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.48, 1.26]
6.2 Hydrocortisone	3	285	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.40, 1.11]

→ reduce: the incidence of chronic lung disease at 28 day or 36 weeks, later corticosteroid treatment overal

3. Death or chronic lung disease

Comparison 3. Death or chronic lung disease (CLD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or CLD at 28 days	15	2546	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.88, 0.96]
1.1 Dexamethasone	14	2293	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.86, 0.96]
1.2 Hydrocortisone	1	253	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.90, 1.12]
2 Death or CLD at 36 weeks	22	3317	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.84, 0.95]
2.1 Dexamethasone	15	2481	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.80, 0.94]
2.2 Hydrocortisone	7	836	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.86, 1.06]

→ reduce the incidence of death or chronic lung disease

4. Failure to extubate:

Outcome: 1 Failure to extubate by 3rd day

Study or subgroup	Steroid n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rastogi 1996	20/36	27/34		21.0 %	0.70 [0.50, 0.98]
Shinwell 1996	54/132	71/116		57.0 %	0.67 [0.52, 0.86]
Wang 1996	29/34	27/29		22.0 %	0.92 [0.77, 1.09]
Total (95% CI)	**202**	**179**		**100.0 %**	**0.73 [0.62, 0.86]**

→ reduced the rates of failure to extubate at 3 days

4. Failure to extubate:

Outcome: 2 Failure to extubate by 7th day

Study or subgroup	Steroid n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Biswas 2003	49/125	59/128		24.4 %	0.85 [0.64, 1.13]
Rastogi 1996	11/36	22/34		9.5 %	0.47 [0.27, 0.82]
Sanders 1994	15/19	14/21		5.6 %	1.18 [0.81, 1.73]
Shinwell 1996	27/132	34/116		15.2 %	0.70 [0.45, 1.08]
Vento 2004	3/10	8/10		3.3 %	0.38 [0.14, 1.02]
Wang 1996	22/34	23/29		10.4 %	0.82 [0.60, 1.11]
Yeh 1997	54/132	75/130		31.6 %	0.71 [0.55, 0.91]
Total (95% CI)	**488**	**468**		**100.0 %**	**0.75 [0.65, 0.86]**

→ reduced the rates of failure to extubate at 7 days

4. Failure to extubate:

Outcome: 3 Failure to extubate by 14th day

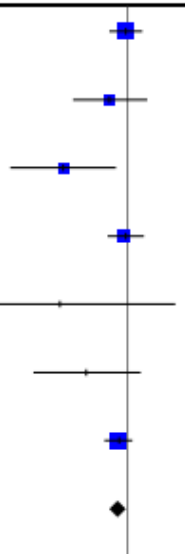
Study or subgroup	Steroid n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Biswas 2003	40/125	40/128		39.0 %	1.02 [0.71, 1.47]
Rastogi 1996	10/36	20/34		20.3 %	0.47 [0.26, 0.86]
Wang 1996	17/34	19/29		20.3 %	0.76 [0.50, 1.17]
Yeh 1990	12/28	21/29		20.4 %	0.59 [0.37, 0.96]
Total (95% CI)	**223**	**220**		**100.0 %**	**0.77 [0.62, 0.97]**

→ reduced the rates of failure to extubate at 14 days

4. Failure to extubate:

Outcome: 4 Failure to extubate by 28th day

Study or subgroup	Steroid n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Garland 1999	50/118	53/123		26.2 %	0.98 [0.73, 1.32]
Lin 1999	8/20	11/20		5.6 %	0.73 [0.37, 1.42]
Romagnoli 1999	4/25	13/25		6.6 %	0.31 [0.12, 0.81]
Stark 2001	43/111	44/109		22.5 %	0.96 [0.69, 1.33]
Suske 1996	1/14	3/12		1.6 %	0.29 [0.03, 2.40]
Wang 1996	5/34	9/29		4.9 %	0.47 [0.18, 1.26]
Yeh 1997	55/132	64/130		32.6 %	0.85 [0.65, 1.11]
Total (95% CI)	**454**	**448**		**100.0 %**	**0.84 [0.72, 0.98]**



→ reduced the rates of failure to extubate at 28 days

5. Complications during the primary hospitalisation

- *Early corticosteroids reduced the risk of*:

1. Patent ductus arteriosus (typical RR 0.79, 95% CI 0.72 to 0.85; typical RD -0.09, 95% CI -0.12 to -0.06; 23 studies and 3492 infants).

2. Any retinopathy of prematurity (typical RR 0.88, 95% CI 0.80 to 0.97; 10 studies and 1345 infants)

3. Severe retinopathy of prematurity (typical RR 0.79, 95% CI 0.65 to 0.97; RD -0.04, 95% CI -0.07 to -0.01; 13 studies and 2056 infants)

5. Complications during the primary hospitalisation

- *There were no significant effects on*:

1.Infection (typical RR 1.02, 95% CI 0.93 to 1.13; 23 studies and 3558 infants)

2. Pulmonary air leaks (typical RR 0.93, 95% CI 0.75 to 1.15; 14 studies and 2604 infants)

3. Severe intraventricular haemorrhage (typical RR 0.95, 95% CI 0.82 to 1.10; 25 studies and 3582 infants)

5. Complications during the primary hospitalisation

4. Periventricular leukomalacia (typical RR 1.18, 95% CI 0.84 to 1.65; 13 studies and 2186 infants)

5. Pulmonary haemorrhage (typical RR 1.16, 95% CI 0.85 to 1.59; nine studies and 1299 infants)

6. Necrotising enterocolitis (RR 0.87, 95%CI 0.87 to 1.08)

5. Complications during the primary hospitalisation

Adverse effects:

7. Hyperglycaemia RR 1.33,95%CI [1.20, 1.47]
8. Hypertention RR 1.85,95%CI [1.54,2.22]
9. Hypertrophic cardiomyopathy RR 4.33,95%CI [1,40, 13.37]
10. Growth failure RR 6.67,95%CI[2.27. 19.62]
11. Gastrointestinal bleeding RR 1.86,95%CI [1.35, 2.55]
12. Gastrointestinal perforation RR 1.81,95%CI [1.233, 3.48]

6. Long-term health outcomes

- 12 trials:
- There were non-significant effects on major neurosensory disability
- Developmental delay: increased with corticosteroids in one study with the criteria for the diagnosis not explicit
- Cerebral palsy: increased with corticosteroids

- Moreover the rates of the combined outcomes of death or cerebral palsy, or of death or major neurosensory disability: not significantly increased
- There were no significant effects on other long-term outcomes of blindness, deafness, formal psychometric testing, abnormal electroencephalogram (EEG), behaviour problems or rehospitalisation in infancy

Subgroup analysis by type of corticosteroid used:

→ Dexamethasone:used in most studies (n = 20); only 9 studies used hydrocortisone → the beneficial and harmful effects were attributable to dexamethasone

→ Hydrocortisone: little effect on any outcomes except for an increase in intestinal perforation and a borderline reduction in patent ductus arteriosus

CONCLUSIONS:

❖ *There were significant benefits*:

- Lower rates of failure to extubate
- Decreased risks of chronic lung disease at both 28 days and 36 weeks' postmenstrual
- Death or chronic lung disease at 28 days and 36 weeks' postmenstrual age
- Patent ductus arteriosus
- ROP, including severe ROP.

CONCLUSIONS:

❖ *There were no significant differences in:*

- Mortality,
- Infection,
- Severe intraventricular haemorrhage,
- Periventricular leukomalacia,
- Necrotising enterocolitis,
- Pulmonary haemorrhage.

❖ *Adverse effects:*

- Hyperglycaemia,
- Hypertension,
- Hypertrophic cardiomyopathy,
- Growth failure,
- Gastrointestinal bleeding,
- Intestinal perforation,

- Long-term follow-up studies report an increased risk of abnormal neurological examination and cerebral palsy. However, the methodological quality of the studies determining long-term outcomes is limited in some cases
- No study has been sufficiently powered to detect important adverse long-term neurosensory outcomes
- Hydrocortisone: has few beneficial or harmful effects → cannot be recommended for the prevention of chronic lung disease

- Need future studies → identify accurately those infants most at risk of developing chronic lung disease.
- Any future placebo-controlled trials of postnatal corticosteroids in preterm infants should include long-term neurological follow-up.
- Studies comparing different types, doses and durations of corticosteroid treatment, and examining the effects of inhaledcorticosteroids are urgently needed.

Thank You!