Postnatal steroids for chronic lung disease

Chronic lung disease (CLD) remains a major problem in neonatal intensive care units. Steroids given either soon after birth to prevent CLD, or later to reduce its severity, are effective, but there are acute and long-term adverse effects. When steroids are given early (first 4 days) there is an increased risk of cerebral palsy in surviving infants which precludes their use at this time. Dexamethasone may be effective in far lower doses than used in most of the randomised trials to date. There are probably situations where its use is associated with more benefit than harm. There is no convincing evidence that inhaled steroids alter the course of CLD. More research is needed into ways of preventing or reducing CLD in at risk preterm infants.

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Key points

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1. Chronic lung disease is associated with long-term neurodevelopmental problems.
2. Postnatal corticosteroids reduce the incidence and severity of chronic lung disease, but early (<4 days of age) treatment increases the risk of neurodevelopmental problems such as cerebral palsy.
3. Inhaled steroids have little effect on the course of chronic lung disease.
4. There may still be a need to use low dose, short duration corticosteroids for infants with significant chronic lung disease or at high risk of developing it.

Chronic lung disease

Since the widespread introduction of surfactant therapy for management of respiratory distress syndrome (RDS) in the 1990s, survival rates of preterm babies have significantly improved[1]. However, surfactant treatment has had a more modest effect on reducing the incidence of chronic lung disease (CLD)[2,3] and this translates into an increased overall number of surviving infants with CLD[4]. Although the terms CLD and bronchopulmonary dysplasia (BPD) are used interchangeably, until recently there has been no consistent definition of these conditions[5]. The best definition of both CLD and BPD is probably one of oxygen dependency at a corrected age of 36 weeks after efforts have been made to ensure that oxygen is indeed needed to prevent desaturation to below 88%; the so called 'physiologic definition'[6]. The prevalence of CLD varies by birth weight and gestational age, with rates of less than 5% in infants weighing more than 1500 grams, increasing to 85% in those of less than 700 grams[7]. Overall at least 20% of babies needing mechanical ventilation will go on to develop CLD[2].

Bronchopulmonary dysplasia was first described by Bill Northway and colleagues in 1967 as a severe sequela of mechanical ventilation – the so called ventilator lung disease[8] (**FIGURE 1**). Pathologically in classic BPD there is severe alveolar fibrosis and squamous metaplasia of the airways as a result of volutrauma. With advances in neonatal care, including use of gentler strategies of mechanical ventilation, the typical 'Northway BPD' has become uncommon and is largely replaced by a picture of lung maldevelopment[9] or arrested development, also known as 'the new BPD'[10]. Inflammation and oxidative stress have been particularly associated with the development of new BPD[11,12] and knowledge of this relationship provided some rationale for the postnatal use of corticosteroids in an attempt to modify this inflammatory response.

Children with CLD have long-term neurodevelopmental and respiratory problems. They have low average IQ, academic difficulties, delayed speech and language development, visual-motor integration impairments and behaviour problems[13]. The pulmonary problems from CLD persist into adolescence with reduced airflow, although lung volumes are not significantly different from very preterm infants who do not have CLD[14]. As these sequelae are important it is not surprising that attempts have been made to modify the course of CLD with various postnatal interventions including systemic and inhaled steroids. If CLD could be prevented or its severity reduced, then improved long term neurological and respiratory outcomes would be expected.

History of postnatal steroids

There is a long history of use of postnatal steroids in neonatal medicine. Cortisone was first reported in 1956 in the US as a potential treatment for respiratory distress in infants of diabetic mothers[15]. Later in South Africa, steroids were described as part of the conservative management of RDS[16], but the first randomised controlled trial was not reported until 1972[17]. This trial using hydrocortisone and another

Outcome	Timing	Studies	Subjects	RR (95%CI)	NNT (95%CI)
Extubation	Early	6	963	1.32 (1.14 to 1.51)	8 (6 to 17)
(by 7 days)	Mod	2	84	1.61 (1.19 to 2.17)	3 (2 to 7)
	Late	5	288	1.45 (1.22 to 1.72)	4 (3 to 7)
CLD	Early	15	2415	0.69 (0.60 to 0.80)	11 (8 to 20)
(36 weeks)	Mod	5	247	0.62 (0.47 to 0.82)	4 (3 to 8)
	Late	1	118	0.76 (0.58 to 1.00)	6 (3 to 100)
Mortality	Early	18	2900	1.05 (0.90 to 1.22)	–
(28 days)	Mod	6	599	0.44 (0.24 to 0.80)	17 (10 to 50)
	Late	–	–	–	–
PDA	Early	17	2881	0.75 (0.68 to 0.83)	10 (7 to 14)

RR=relative risk, CI=confidence interval, NNT=number needed to treat, CLD=chronic lung disease, PDA=persistent ductus arteriosus. Data derived from Cochrane systematic reviews[26-28].

TABLE 1 Beneficial effects of systemic postnatal steroids.

using prednisolone[18] showed no clinical benefits and indeed at follow-up corticosteroid-treated infants had an increased risk of severe intraventricular haemorrhage[18,19] and neurodevelopmental problems[20]. As a result of these concerns about serious long term adverse effects of corticosteroids their use was largely discontinued until the early 1980s, when high dose dexamethasone was used to treat ventilator-dependent infants with CLD [21,22]. Both studies showed that dexamethasone improved respiratory function allowing earlier extubation, but neither found significant long term benfits. Few adverse effects were reported in these early studies and this led to some false reassurance about the safety of postnatal steroids and their gradual introduction into neonatal medicine as a means of treating or preventing CLD[23]. Indeed between 1990-2 and 1993-5 the use of dexamethasone in babies weighing less than 750 grams increased from 43% to 84%[24].

Complacency about the use of postnatal steroids was first shaken in 1998 with the publication of a large multicentre follow-up study from Taiwan[25]. This study showed an increase in neurodevelopmental problems and a doubling of the risk of cerebral palsy at two years in infants who had been treated with a 4 week course of dexamethasone, started within 12 hours of birth. This study and others that followed in 1999 and 2000 led to a reappraisal of the use of postnatal corticosteroids to prevent CLD.

Systematic reviews of systemic corticosteroids

Three systematic reviews of systemic postnatal steroids were first published in the Cochrane Library in 1999 and have been subsequently updated[26-28]. These reviews are classified according to postnatal age at the start of treatment: early (<96 hours), moderately early (7-14 days) and delayed (>3 weeks). Postnatal steroids, whether started early, moderately early or late, facilitate earlier extubation and reduce the risk of developing CLD at 36 weeks' corrected age (**TABLE 1**). Neonatal mortality is reduced in infants treated moderately early, but not in those treated either early or late. Another benefit of steroid treatment is a reduced risk of persistent ductus arteriosus, but this is seen only in early treated infants (**TABLE 1**).

However, there are also significant adverse effects of systemic postnatal steroids (**TABLE 2**). In the short term these include hyperglycaemia, hypertension, hypertrophic cardiomyopathy, growth failure and gastrointestinal haemorrhage and perforation. Some of these are potentially reversible after corticosteroid treatment has been discontinued. However, the long term adverse neurodevelopmental outcomes are the most worrying. There is about a 70% increased risk of cerebral palsy after early treatment with postnatal steroids (**TABLE 2**). It appears that this increased risk in early treated infants is due to their lower risk of developing CLD and thus the effect of steroids is weighted towards harm rather than benefit. With risks of CLD below 35% corticosteroid treatment significantly increases the chance of death or cerebral palsy, whereas with risks for CLD above 65%, it reduces the chance of these adverse outcomes[29].

Most of the randomised controlled trials used dexamethasone but the dose and duration varied considerably[23]. The most frequently used starting dose of dexamethasone was 0.5 mg/kg/day with a reducing course over two to six weeks. Another problem with interpreting the results of these systematic reviews is the cross over effect of the use of open label corticosteroids in the control groups. Many neonatologists were reluctant to withhold steroids from very ill preterm babies and this had the effect of reducing the observed difference in outcomes between treated and control groups. In a systematic review that included only studies with less than 30% cross over (or

FIGURE 1 Ventilator-dependent baby with chronic lung disease.

contamination) the increased risk of cerebral palsy was as high as one for every four treated infants[30]. It seems likely that early dexamethasone has adverse effects that outweigh its benefits. Its initial choice to treat CLD[21,22] seems to have been empirical and based on it being the most potent anti-inflammatory steroid. Dexamethasone has a very long plasma half-life, compared to cortisol, and has been used at about 10 times the physiological secretion rate of cortisol in the newborn. Other systemic corticosteroids have been used infrequently in the management of CLD, although they have their advocates.

Other systemic corticosteroids

Methylprednisolone has been compared with dexamethasone in a non-randomised trial aimed at preventing CLD in very preterm infants at risk[31]. Although there were no differences in oxygen requirements or in the rate of weaning from ventilation, the methylprednisolone-treated infants had better weight gain, less hyperglycaemia and cystic periventricular leucomalacia than those treated with dexamethasone. However, there have been no randomised trials with methylprednisolone, nor with betamethasone, a drug commonly used antenatally to mature the fetal lungs.

Hydrocortisone, prescribed in a relatively low dose as prophylaxis against adrenal insufficiency, appeared to reduce the risk of CLD in a small pilot randomised trial[32]. However, two larger randomised trials had to be terminated early because of an excess of gastrointestinal perforations in the hydrocortisone-treated groups[33,34]. The cause of these perforations may have been an interaction between early hydrocortisone treatment and prophylactic indomethacin. Hydrocortisone has also been compared with dexamethasone for treatment of CLD in non-randomised trials[35], which suggest that long term outcome may be better with hydrocortisone. These findings need to be confirmed in randomised comparative trials before alternative steroids can be recommended to replace low dose dexamethasone.

Inhaled steroids

These should have direct beneficial effects on the lungs and avoid the adverse systemic effects of dexamethasone. Inhaled steroids have been used early to try to prevent CLD and later to treat babies with CLD. A systematic review of inhaled steroids in the first two weeks of life included five randomised controlled trials but did not show any reduction in CLD[36]. There was an absence of adverse effects such as hypertension, hyperglycaemia, sepsis and gastrointestinal problems suggesting that either the doses used were safe, or alternatively were ineffective. A second systematic review also included five trials of infants with CLD who were ventilator-dependent[37]. Treated infants were extubated earlier (RR 0.35, 95%CI 0.20 to 0.72; NNT 2, 95%CI 1 to 4) and again no adverse effects were noted. Two further systematic reviews have compared inhaled and systemic corticosteroids, again both early (<2 weeks)[38] and late (>2 weeks)[39]. Neither review showed any significant difference in mortality or incidence of CLD. Use of early inhaled steroids compared to dexamethasone was associated with increased time on the ventilator and in oxygen, but a reduced risk of hyperglycaemia. In summary, there is no evidence that inhaled steroids are effective for prevention and treatment of CLD. They seem to be less effective than dexamethasone in reducing ventilation and oxygen requirements and may have fewer adverse effects, but long term follow-up data are not yet available.

Outcome	Timing	Studies	Subjects	RR (95%CI)	NNH (95%CI)
Hyperglycaemia	Early	11	2016	1.36 (1.23 to 1.51)	9 (7 to 13)
	Mod	7	659	1.51 (1.20 to 1.90)	8 (6 to 20)
	Late	6	497	1.42 (0.97 to 2.07)	–
Hypertension	Early	10	1446	1.84 (1.54 to 2.21)	10 (8 to 14)
	Mod	6	599	2.73 (1.25 to 5.95)	20 (13 to 100)
	Late	6	497	2.61 (1.29 to 5.26)	17 (10 to 50)
HCM	Early	1	50	4.33 (1.40 to 13.4)	3 (2 to 6)
	Mod	3	168	3.29 (1.50 to 7.20)	5 (3 to 11)
	Late	–	–	–	–
GI haemorrhage	Early	9	1440	1.90 (1.35 to 2.66)	17 (11 to 33)
	Mod	3	485	1.74 (1.02 to 2.98)	17 (9 to 100)
	Late	3	437	1.13 (0.74 to 1.73)	–
Infection	Early	18	2752	1.01 (0.90 to 1.14)	–
	Mod	7	659	1.35 (1.06 to 1.71)	11 (7 to 50)
	Late	6	497	1.03 (0.77 to 1.40)	–
Growth failure	Early	1	50	6.67 (2.27 to 19.6)	2 (1 to 2)
Cerebral palsy	Early	9	991	1.69 (1.20 to 2.38)	17 (9 to 50)
	Mod	4	130	0.83 (0.39 to 1.74)	–
	Late	6	503	1.20 (0.77 to 1.85)	–
Death or CP	Early	6	991	1.16 (1.00 to 1.34)	17 (8 to 200)
	Mod	4	204	0.83 (0.55 to 1.23)	–
	Late	6	503	1.05 (0.82 to 1.34)	–

RR = relative risk, CI = confidence interval, NNH = number needed to harm. HCM = hypertrophic cardiomyopathy, GI = gastrointestinal, CP = cerebral palsy. Data derived from Cochrane systematic reviews[26-28].

TABLE 2 Adverse effects of systemic postnatal steroids.

Overall conclusions

Following the publication of guidelines for postnatal steroid treatment in Europe[40] and North America[41], there has been a marked reduction in its usage. For example in Israel steroid use in very low birthweight infants fell from 23% in 1997-8 to 11% in 2003-4[42]. However, this was associated with increased oxygen dependency at 28 days and 36 weeks' corrected age, together with improved survival rates. Although postnatal steroids should be avoided if at all possible there are still occasions when their use may provide benefits in excess of harm[29]. Their use should be reserved for ventilator-dependent infants with significant CLD or at high risk of developing it.

There is also evidence that lower doses of steroids may be effective. Doyle and colleagues showed beneficial effects on respiratory function with a starting dose of dexamethasone of 0.15 mg/kg/day[43] and there is also anecdotal evidence that doses as low as 0.05 mg/kg/day can facilitate extubation in chronically ventilator-dependent infants[44]. More research is needed to determine the best corticosteroid drug, its optimal dose and duration and the precise indications for its use to improve the outlook for very preterm infants with or at high risk of developing CLD.

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