

Postnatal hydrocortisone treatment for chronic lung disease in the preterm newborn and long-term neurodevelopmental follow-up

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ABSTRACT

The benefits versus the risks of postnatal administration of steroids in preterm-born infants are still debatable. This review examines the literature on postnatal hydrocortisone treatment for chronic lung disease (CLD) in preterm-born infants with a particular focus on the effects of such treatment on long-term neurodevelopmental outcomes. Quantitative published evidence does not point to a clear advantage of treatment with hydrocortisone over dexamethasone with regard to the impact on long-term neurological outcomes. However, in the absence of a randomised comparison, a consensus may soon have to be reached on the basis of the best available evidence whether hydrocortisone should replace dexamethasone in the treatment of CLD.

In contrast with the consensus about the benefits of maternal steroid treatment to accelerate fetal lung maturation,¹ there is an ongoing debate about the pros and cons of postnatal corticosteroid administration to preterm-born infants.²⁻⁶ After initial reports in the 1980s suggested short-term benefits of steroids in ventilator-dependent children, dexamethasone became the widely and almost exclusively used drug for preventing or treating chronic lung disease (CLD).⁷ One retrospective study examining the outcome of neonates with a birth weight between 500 g and 749 g, showed that 43% of infants born between 1990 and 1992 received dexamethasone compared with as many as 84% of those born between 1993 and 1995.⁸ The almost routine use of dexamethasone continued until 1998, when Yeh *et al* published the results of a large multicentre follow-up study that showed a marked increase in neurodevelopmental dysfunction in neonates treated with dexamethasone compared with controls.⁹ More alarming publications on the long-term negative effects of dexamethasone appeared^{10 11} and as a result there was a gradual decrease in postnatal steroid prescription.¹² The American Academy of Pediatrics stated in 2002 that, outside clinical trials, postnatal steroid use should be reserved only for "exceptional clinical circumstances".¹³ However, a recent prospective evaluation of postnatal steroid administration in California, from April 2002 to March 2003, showed that 19.3% of children ≤ 1500 g were still receiving steroids.¹⁴

Over the past years, there have been more reports of long-term negative neurodevelopmental sequelae following neonatal dexamethasone treatment,^{9-11 15 16} and recently an MRI study at term

equivalent age showed reduced brain volumes in infants treated with a moderately low dose of dexamethasone after 28 days of life.¹⁷

Hydrocortisone may be an alternative to dexamethasone if it has fewer negative long-term side effects, but there have been scarcely any studies on long-term outcome after postnatal use of hydrocortisone in preterm infants. Hydrocortisone is also being increasingly used for treatment or prevention of vasopressor-resistant hypotension in neonatal medicine.¹⁸⁻²⁰ However, besides one abstract presented at the Society for Pediatric Research meeting in 2007,²¹ there are no long-term developmental outcome data for infants treated with hydrocortisone for this indication.

The aim of this review was to summarise the literature on postnatal hydrocortisone treatment for CLD in preterm-born infants with a special focus on long-term neurodevelopmental outcome following this treatment. We will not discuss hydrocortisone treatment for refractory hypotension, as it is beyond the scope of this review.

HYDROCORTISONE AND CHRONIC LUNG DISEASE

Six reports have been published on postnatal hydrocortisone administration for prevention ($n = 5$) or treatment ($n = 1$) of CLD (summarised in table 1). The first randomised placebo controlled trial of hydrocortisone treatment was published as early as in 1972.²² This trial evaluated the ability of postnatally administered hydrocortisone to alter the course of outcome in infants with hyaline membrane disease. In all, 44 infants (mean gestational age 32.5 weeks) were treated with hydrocortisone or a lactose placebo within 24 h after birth. There was no remarkable effect on PaO₂, PaCO₂, need for assisted mechanical ventilation or survival.

No other studies on hydrocortisone and respiratory disease were published hereafter until 1999, when Watterberg *et al* enrolled 40 preterm infants into a randomised pilot study to test whether early treatment with low-dose hydrocortisone for 12 days, started within 48 h after birth would increase the likelihood of survival without CLD.²³ The rationale for this study was that many extremely low birthweight infants show biochemical evidence of adrenal insufficiency in the first week of life, correlating with subsequent development of CLD.²⁴ Adrenal insufficiency is also associated with amplified inflammatory responses, because cortisol is essential for resolution of inflammation. Infants who develop CLD have

Table 1a Hydrocortisone and chronic lung disease

Study no.	Study	Type of study	No of patients	Treatment allocation	Mean GA	Mean BW	HC indication
1	Baden <i>et al.</i> , ²² 1972	Randomised, placebo controlled	44	22 HC 22 placebo	32.5 31.8	1730 1767	Prophylaxis
2	Watterberg <i>et al.</i> , ²³ 1999	Randomised, double-masked, placebo controlled pilot	40	20 HC 20 placebo	25.2 25.4	732 770	Prophylaxis
3	Heide-Jalving <i>et al.</i> , ²⁶ 2003	Retrospective non-randomised	50	25 HC 25 control	28.3 28.4	1040 1090	Treatment of CLD
4	Watterberg <i>et al.</i> , ²⁷ 2004	Randomised, double-masked, placebo controlled	Enrolment stopped at 360*	180 HC 180 placebo	25.2 25.3	731 734	Prophylaxis
5	Peltoniemi <i>et al.</i> , ²⁸ 2005	Randomised, placebo controlled	Enrolment stopped at 51*	25 HC 26 placebo	26.7 26.5	888 903	Prophylaxis
6	Bonsante <i>et al.</i> , ²⁹ 2007	Randomised, placebo controlled	Enrolment stopped at 50† 25 placebo	25 HC 26.5	26.2 900	840	Prophylaxis

Table 1b Hydrocortisone and chronic lung disease

Study no.	Dose	Duration	Cumulative dose	Postnatal age at start	Effects on pulmonary function	Open label systemic steroids (dexamethasone)
1	15 mg/kg twice	1 day	30 mg/kg	<24 h	No remarkable effect on PaO ₂ , PacO ₂ , oxygen need, need for assisted ventilation and survival	No
2	1 mg/kg 9 days	12 days	10.5 mg/kg	<48 h	HC treatment decreased days on >40% and >25% oxygen, days on ventilator and oxygen at discharge	Yes
3	0.5 mg/kg 3 days 5 mg/kg 7 days	22 days	72.5 mg/kg	2.1 weeks (SD 1.5)	From day 7 no significant difference in amount of extra oxygen needed between HC-treated infants and controls	No
4	3.75 mg/kg 5 days 2.5 mg/kg 5 days 1.25 mg/kg 5 days 1 mg/kg 12 days 0.5 mg/kg 3 days	15 days	13.5 mg/kg	12–48 h	No difference in survival without CLD and mortality For patients exposed to histological chorioamnionitis (n = 149), HC treatment markedly decreased mortality and increased survival without CLD compared with placebo	HC: 18% during treatment; 38% during/after treatment Placebo: 28% during treatment; 41% during/after treatment
5	2.0 mg/kg 2 days 1.5 mg/kg 2 days 0.75 mg/kg 6 days	10 days	11.5 mg/kg	<36 h	Incidence of BPD tended to be lower and PDA was lower in the HC group	HC: 28% after treatment Placebo: 46% after treatment
6	1.0 mg/kg 9 days 0.5 mg/kg 3 days	12 days	10.5 mg/kg	<48 h	HC prophylaxis improved oxygen-free survival and early cardiocirculatory function	HC: 30% Placebo: 63% p<0.05

been shown to have raised levels of indicators of both prenatal and postnatal inflammation.²⁵ Among the infants treated with hydrocortisone, 60% survived without supplemental oxygen at 36 weeks' postmenstrual age in contrast with 35% in the placebo group. Treatment with hydrocortisone decreased the number of days on >40% oxygen, days on >25% oxygen, days on ventilator and oxygen at discharge. Although fewer children in the hydrocortisone group were subsequently treated with dexamethasone, there was no difference in median days of dexamethasone administration between the two groups. Adverse short-term neonatal complications were similar for the two groups.

A retrospective matched-cohort study compared 25 preterm infants who were treated for CLD with a much higher dose of

hydrocortisone, with 25 controls from the same centre. It showed equal reduction in the need for extra oxygen and successful weaning from the ventilator, similar to the results of another study conducted at a different centre that compared 23 infants receiving dexamethasone with 23 controls.²⁶ The hydrocortisone and non-steroid groups did not differ with regard to mean arterial blood pressure, blood glucose, weight gain or spontaneous gastrointestinal perforation.

The multicentre trial following the 1999 pilot study²³ enrolled mechanically ventilated infants with a birth weight of 500–999 g between 12 h and 48 h of life.²⁷ Enrolment stopped at 360 infants because of an increase in spontaneous gastrointestinal perforation in the hydrocortisone-treated group. For the total population, prophylactic treatment of early adrenal insufficiency

did not improve survival without CLD or mortality at 36 weeks. However, for the patients exposed to histologically confirmed chorioamnionitis, hydrocortisone did markedly decrease mortality and increase survival without CLD. The study suggested an interactive effect between hydrocortisone and indometacin administered simultaneously, as a much higher percentage of these children had spontaneous gastrointestinal perforation.

Peltoniemi *et al* investigated the effect of early hydrocortisone treatment on survival without CLD in infants ≤ 30 weeks and noticed a tendency towards lower CLD in the hydrocortisone-treated group.²⁸ This study was also discontinued early after inclusion of 51 infants due to a higher incidence of gastrointestinal perforation in the hydrocortisone group. Three of the four children in the hydrocortisone group who had this complication had been treated simultaneously with indometacin/ibuprofen. The infants treated with hydrocortisone who had serum cortisol concentrations above the median had a high risk of gastrointestinal perforation. Infants treated with hydrocortisone but with cortisol values below the median showed increased survival without bronchopulmonary dysplasia.

Finally, Bonsante *et al* conducted a double-blind, randomised, placebo controlled trial in 50 mechanically ventilated infants (birth weight 500–1249 g) (see table 1 for details).²⁹ Oxygen-free survival was higher in the hydrocortisone-treated group, especially in infants without antenatal steroids. Hypotension after recruitment was reduced by hydrocortisone. There was no difference in gastrointestinal perforation between the groups, however as many as 82% of all recruited infants received ibuprofen. This study showed more positive effects of hydrocortisone prophylaxis than the large trial by Watterberg *et al* and the trial by Peltoniemi *et al*. The authors explained the difference in outcome on the basis of the lower antenatal steroid used, the earlier start of hydrocortisone treatment and not allowing open-label use of steroids during the treatment period.

Five of the six studies reviewed above aimed to prevent CLD by early administration of hydrocortisone, whereas in the only retrospective study, hydrocortisone was prescribed to treat CLD. Dose and duration of hydrocortisone treatment varied considerably between the prevention and treatment studies, and four of the six studies were contaminated by open-label steroids prescription (dexamethasone) during and after hydrocortisone treatment (table 1).

LONG-TERM FOLLOW-UP

There have been two follow-up reports based on the initial 1972 hydrocortisone trial to alter the course or outcome in infants with respiratory distress syndrome. In 14 of the 16 children who died within 2 months of birth (seven in the hydrocortisone and seven in the placebo group) an autopsy revealed no differences in lung, liver, adrenal, thymus, heart and spleen pathology, attributable to steroid treatment. However, a significant association ($p < 0.05$; χ^2 with Yates correction) was found between the occurrence of intraventricular haemorrhage and hydrocortisone treatment.³⁰ At the age of 1 year, 24 survivors (12 in both groups) were examined. There was a tendency to slightly increased incidence of gross neurological and electroencephalographic abnormalities among the infants who received hydrocortisone, but the Griffiths Developmental Scale showed a normal developmental quotient in both groups. However, analysis of the subtests revealed a substantial difference in the results for the gross motor development with a lower mean score for the hydrocortisone group.³¹

Van de Heide *et al* retrospectively studied a group of 25 preterm infants treated with high-dose hydrocortisone. At the age of 5–7 years this group did not differ from a non-treated control group (matched for gestational age, birth weight, severity of infant respiratory distress syndrome, intraventricular haemorrhage and period of admission) with regard to neurological outcome, psychomotor development or school performance. Infants treated with dexamethasone required more special school education and had worse neurological outcome compared with controls.²⁶

Of 294 survivors, 252 (86%) infants who participated in Watterberg and colleagues' prophylactic hydrocortisone trial were evaluated at the age of 20.0 (SD 2.1) months by certified examiners masked to treatment assignment. The incidence of cerebral palsy was similar as was the mean Mental and Physical Developmental Index, estimated with the Bayley Scales of Infant Development II. However, a significantly smaller percentage of infants treated with hydrocortisone had a Mental Developmental Index below 70 (27% in the hydrocortisone group vs 37% in the placebo group, $p = 0.017$).³²

In a follow-up study from our own institute, 23 preterm-born children (mean (SD) gestational age 28 (2) weeks), who received hydrocortisone treatment for chronic lung disease (starting dose of 5 mg/kg/day, tapered over a minimum of 3 weeks) in the neonatal period and 35 children (mean gestational age 30.4 (1.5) weeks) not treated with hydrocortisone during the neonatal period, were evaluated with quantitative MRI and neurocognitive assessment at the age of 8 years. Hydrocortisone treatment was introduced at a median age of 18 days (range 4–43 days) and none of the children was treated with dexamethasone at a later stage, thus avoiding contamination of the outcome results. We found that the children treated with hydrocortisone and the non-treated children had similar volumes of grey matter, white matter, cerebral fluid and hippocampus. The Wechsler Intelligence Scale for Children—Revised scores were within the normal range for both groups, with no difference between the groups.³³ A subgroup of these patients underwent proton magnetic resonance spectroscopy of the hippocampus³⁴: 18 hydrocortisone-treated infants (mean gestational age 27.9 (1.7) weeks) were compared with 19 non-treated preterm infants (mean gestational age 30.6 (1.7) weeks). Although the infants treated with hydrocortisone were younger, lighter and sicker than their counterparts, who were not treated with steroids, there was no difference in the *N*-acetyl aspartate/(choline and (phospho) creatine) ratios between the two groups at a median age of 8.4 years.

An extended group of children born preterm, including the above mentioned population, was evaluated recently.³⁵ In all, 62 preterm-born children treated with hydrocortisone for CLD during the neonatal period were compared with 164 children who did not receive steroids during their admission to the neonatal intensive care unit. The hydrocortisone-treated children had a lower gestational age as well as lower birth weight, and were sicker than the non-steroid-treated children. To better deal with these group differences, adjustments were made for gestational age, birth weight, gender, need for mechanical ventilation and small for gestational age. The adjusted mean IQ, and visual-motor integration and memory test results, were similar in the hydrocortisone-treated and non-treated groups. The incidence of cerebral palsy was also similar, and there was no difference in motor function between the two groups, as assessed with the Movement Assessment Battery for Children. All children had a brain MRI, and the occurrence of brain lesions

as well as mean midsagittal corpus callosum areas were similar in the two groups of children.

Karemaker *et al* reported a retrospective matched-cohort study on long-term effects on behaviour and motor skills in school age (7–10 years) children who received either dexamethasone or hydrocortisone for CLD. A non-treated control group and a group treated only antenatally with betamethasone were included in the analysis. All groups were matched for gestational age, birth weight, gender, grade of respiratory distress syndrome and rate of peri/intraventricular haemorrhage. The children treated with dexamethasone had more neuromotor problems than the children in the control and betamethasone groups, whereas the outcomes in children treated with hydrocortisone did not differ from these two groups.³⁶

DISCUSSION

Compared with preterm infants not treated with hydrocortisone, no differences have been found in neurocognitive or motor outcome, or in the incidence of brain abnormalities on MRI, after hydrocortisone treatment for bronchopulmonary dysplasia in long-term follow-up studies at 5–8 years of age.^{26 33–36} Importantly these children were treated exclusively with hydrocortisone and there was no contamination by later prescription of dexamethasone. However, the patient population was retrospectively enrolled and hydrocortisone administration did not commence until after the first postnatal week. In the single follow-up study of prophylactic hydrocortisone for prevention of CLD, a large percentage of children were treated with open-label dexamethasone during or after the study period.³² Open-label contamination can result in the treatment and placebo groups becoming more similar than intended, making it difficult to detect a difference in outcome among the two groups. In addition, open-label contamination will also increase the steroid dose received by babies in the index treatment arm, making interpretation even more difficult.

There may be several explanations why hydrocortisone treatment might not be associated with long-term neurological deficits, whereas dexamethasone is. Dexamethasone is a synthetic glucocorticoid with a 25–30 times higher anti-inflammatory action than hydrocortisone. The typical dose of hydrocortisone is much lower than that of dexamethasone in most studies. This is also reflected in the fewer short-term neonatal complications with the use of hydrocortisone as compared with dexamethasone.²⁶

In the brain, dexamethasone binds preferentially to the glucocorticoid receptor,³⁷ and hydrocortisone binds preferentially to the mineralocorticoid receptor. Animal studies have shown that activation of the glucocorticoid receptor leads to adverse neuronal effects.^{38 39} In a neuronal cell culture model, stimulation of the glucocorticoid receptor, such as occurs with (high-dose) dexamethasone treatment, promotes apoptosis of the granular cells in the hippocampus, whereas stimulation of the mineralocorticoid receptor, such as with (low-dose) hydrocortisone treatment, is protective against apoptosis. The opposing actions of mineralocorticoid receptor and glucocorticoid receptor on neuronal survival result from their ability to differentially influence the expression of members of the bcl-2 gene family (major regulatory components of the apoptotic pathway).⁴⁰ Yet another mechanism may have a role. The enzyme 11 β -hydroxysteroid dehydrogenase type 2, which catalyses rapid inactivation of cortisol to inert 11-keto derivatives, is abundant in the developing brain. It may protect the developing nervous system against the deleterious consequences

of glucocorticoid overexposure such as in early hydrocortisone treatment.^{41 42} This hypothesis needs further exploration.

The biologic half-life of dexamethasone is 36–72 h in contrast with that of 8–12 h for hydrocortisone.⁴³ There may be less risk of accumulation of medication with hydrocortisone. The preservative agent in dexamethasone, which is used to control microbial and oxidative degeneration, is sodium bisulphite. Exposure of a neuronal cell line (rat mesencephalic cells) to high levels of sulphite induced a time-dependent decrease in viability.⁴⁴ Sulphites have been shown to be toxic in vitro to cultures of neurons and in vivo to the brains of 3–5-day-old mouse pups.⁴⁵

A recent study showed that a lower dose of dexamethasone than generally used (0.89 mg/kg/10 days) is also effective in facilitating extubation and shortening of duration of intubation among ventilator-dependent extremely low birthweight infants at a median treatment age of 23 days.⁴⁶ There was little evidence for reduction in either the mortality rate or the rate of oxygen dependency at 36 weeks. Follow-up showed no difference in outcome in the treated and non-treated groups at 2 years of age, but doses of dexamethasone varied widely within and between the two groups. In addition, there was a high rate of contamination with open-label dexamethasone treatment in the placebo group.⁴⁷

One could argue that the infants in the hydrocortisone follow-up studies were at a more advanced gestational age when receiving the medication than in most dexamethasone studies. The first report on the negative long-term effects of postnatal dexamethasone use by Yeh *et al*⁹ was on children with a mean gestational age of 29.8 (2.3) weeks, and Shinwell and coworkers also studied infants with a mean gestational age of 29.2 (2.6) weeks when receiving dexamethasone.¹⁰ A possible factor is that in the late treatment hydrocortisone follow-up studies, the infants were already 2 weeks postnatal, whereas in these dexamethasone studies the infants received the medication shortly after birth. Still in one study, there were considerably more cases of cerebral palsy and abnormal neurological examinations at 1 year of age after a 42-day course of dexamethasone started after 2 weeks of age.¹¹ Another study included 22 infants (birth weight <1250 g and gestational age <30 weeks) who survived to 15 years and were ventilator-dependent at 2 weeks of age. Nine received a 42-day course of dexamethasone, eight received an 18 day-course of dexamethasone and five infants did not receive steroids. The authors concluded that the 42-day course was associated with improved long-term neurodevelopmental outcome, however, the number of patients in each subgroup was very small.⁴⁸

In two early treatment (prophylactic) hydrocortisone studies, enrolment stopped because of an increased incidence of spontaneous gastrointestinal perforation with combined hydrocortisone–indometacin treatment.^{27 28} A cohort study of adult patients who were treated with corticosteroids combined with non-steroidal anti-inflammatory drugs reported a more than twofold increased risk of gastrointestinal bleeding when compared with the use of corticosteroid alone.⁴⁹ In very low birthweight infants, low-dose hydrocortisone alone (in the absence of co-treatment with prophylactic indometacin) did not lead to gastrointestinal perforation.⁵⁰ Peltoniemi *et al* found that pretreatment serum cortisol levels were associated with treatment effects and with the risk of intestinal perforations.²⁸ Hallman *et al* advocated the need to modify the dosage, limit the drug–drug interactions and perhaps above all scrutinise patient selection in corticosteroid trials on very high-risk infants in early life by incorporating pretreatment cortisol

measurements in the decision making—although this suggestion was based on only four patients in the Peltoniemi study.⁵¹ Treatment with hydrocortisone beyond 2 weeks of postnatal age will avoid the interactive effect of hydrocortisone with indometacin, therefore reducing the risk of gastrointestinal perforation considerably. Although two publications reported an increased risk of disseminated *Candida* infections in infants treated with hydrocortisone,^{52, 53} this was not confirmed by other studies.^{18, 27}

CONCLUSIONS

We should aim for the lowest dose and shortest course of the least toxic steroid that facilitates weaning off the ventilator and protects against CLD. Currently, the clinical choice of steroids, dexamethasone or hydrocortisone is largely based on local culture and training, rather than on sufficient evidence from direct comparisons. In terms of quantitative published evidence there is equipoise. Claims for either of the steroids that randomised comparison would expose children to excess (avoidable) risks or would withhold the presumably best treatment to some children are not founded on direct evidence. However, neonatology as a discipline should decide whether it is necessary to make this randomised direct comparison between dexamethasone and hydrocortisone, or whether the available publications on long-term neurodevelopmental outcome provide sufficient evidence to justify a shift from dexamethasone towards hydrocortisone prescription for the treatment of CLD in the near future.

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The Committee on Publication Ethics (COPE) has established a Grant Scheme to fund research in the field of publication ethics. The Scheme is designed to provide financial support to any member of COPE for a defined research project that is in the broad area of the organisation's interests, and specifically in the area of ethical standards and practice in biomedical publishing. The project should have a specific goal and be intended to form the kernel of a future publication.

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The terms and conditions of the Grant are as follows:

- ▶ At least one of the applicants must be a member of COPE.
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An application form can be obtained by contacting Linda Gough, COPE administrator, at LGough@bmj.com or 020 7383 6602. For more information on COPE, see <http://www.publicationethics.org.uk/>

The closing date for receipt of applications is 1 December 2007 or 1 June 2008.