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

K J Rademaker, L S de Vries, C S P M Uiterwaal, F Groenendaal, D E Grobbee, F van Bel

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, there is an ongoing debate about the pros and cons of postnatal corticosteroid administration to preterm-born infants. 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). 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. 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. More alarming publications on the long-term negative effects of dexamethasone appeared and as a result there was a gradual decrease in postnatal steroid prescription. The American Academy of Pediatrics stated in 2002 that, outside clinical trials, postnatal steroid use should be reserved only for “exceptional clinical circumstances”. 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.

Over the past years, there have been more reports of long-term negative neurodevelopmental sequelae following neonatal dexamethasone treatment 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.

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. However, besides one abstract presented at the Society for Pediatric Research meeting in 2007, 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. 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. 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. Adrenal insufficiency is also associated with amplified inflammatory responses, because cortisol is essential for resolution of inflammation. Infants who develop CLD have
been shown to have raised levels of indicators of both prenatal and postnatal inflammation. 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. 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 study enrolled mechanically ventilated infants with a birth weight of 500–999 g between 12 h and 48 h of life. Enrolment stopped at 860 infants because of an increase in spontaneous gastrointestinal perforation in the hydrocortisone-treated group. For the total population, prophylactic treatment of early adrenal insufficiency

Table 1a Hydrocortisone and chronic lung disease

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Study</th>
<th>Type of study</th>
<th>No of patients</th>
<th>Treatment allocation</th>
<th>Mean GA</th>
<th>Mean BW</th>
<th>HC indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Baden et al, 1972</td>
<td>Randomised, placebo controlled</td>
<td>44</td>
<td>22 HC</td>
<td>32.5</td>
<td>1730</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td>2</td>
<td>Watterberg et al, 1999</td>
<td>Randomised, double-masked, placebo controlled</td>
<td>40</td>
<td>20 HC</td>
<td>25.2</td>
<td>732</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td>3</td>
<td>Heide-Jalving et al, 2003</td>
<td>Retrospective non-randomised</td>
<td>50</td>
<td>20 placebo</td>
<td>25.4</td>
<td>770</td>
<td>Treatment of CLD</td>
</tr>
<tr>
<td>4</td>
<td>Watterberg et al, 2004</td>
<td>Randomised, double-masked, placebo controlled</td>
<td>Enrolment stopped at 360*</td>
<td>180 HC</td>
<td>25.2</td>
<td>731</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td>5</td>
<td>Peltoniemi et al, 2005</td>
<td>Randomised, placebo controlled</td>
<td>Enrolment stopped at 51*</td>
<td>25 HC</td>
<td>26.7</td>
<td>888</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td>6</td>
<td>Bonsante et al, 2007</td>
<td>Randomised, placebo controlled</td>
<td>Enrolment stopped at 50†</td>
<td>25 HC</td>
<td>26.2</td>
<td>840</td>
<td>Prophylaxis</td>
</tr>
</tbody>
</table>

Table 1b Hydrocortisone and chronic lung disease

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Dose</th>
<th>Duration</th>
<th>Cumulative dose</th>
<th>Postnatal age at start</th>
<th>Effects on pulmonary function</th>
<th>Open label systemic steroids (dexamethasone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15 mg/kg twice</td>
<td>1 day</td>
<td>30 mg/kg</td>
<td>&lt;24 h</td>
<td>No remarkable effect on PaO2, Paco2, oxygen need, need for assisted ventilation and survival</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>1 mg/kg 9 days</td>
<td>12 days</td>
<td>10.5 mg/kg</td>
<td>&lt;48 h</td>
<td>HC treatment decreased days on &gt;40% and &gt;25% oxygen, days on ventilator and oxygen at discharge</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>0.5 mg/kg 3 days</td>
<td>22 days</td>
<td>72.5 mg/kg</td>
<td>2.1 weeks (SD 1.5)</td>
<td>From day 7 no significant difference in amount of extra oxygen needed between HC-treated infants and controls</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>3.75 mg/kg 5 days</td>
<td>2.5 mg/kg 5 days</td>
<td>1.25 mg/kg 5 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.0 mg/kg 9 days</td>
<td>12 days</td>
<td>10.5 mg/kg</td>
<td>&lt;48 h</td>
<td>HC prophylaxis improved oxygen-free survival and early cardiocirculatory function</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.5 mg/kg 3 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

did not improve survival without CLD or mortality at 56 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 indomethacin 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. 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 indomethacin/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). 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; χ² with Yates correction) was found between the occurrence of intraventricular haemorrhage and hydrocortisone treatment. At the age of 1 year, 24 survivors (12 in both groups) were examined. There was a tendency to slightly increased incidence of gross neurologial 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.

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.

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).

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. A subgroup of these patients underwent proton magnetic resonance spectroscopy of the hippocampus: 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. 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 dexam-
ethasone 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 haemor-
hage. 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.56

**DISCUSSION**

Compared with preterm infants not treated with hydrocorti-
sone, 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.26–30 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 adminis-
tration 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,57 and hydrocortisone binds preferen-
tially to the mineralocorticoid receptor. Animal studies have
shown that activation of the glucocorticoid receptor leads to
adverse neuronal effects.58–59 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 glucocorti-
coid 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).60 Yet another mechanism may have a role. The
enzyme 11β-hydroxysteroid dehydrogenase type 2, which
catalyses rapid inactivation of cortisol to inert 11-keto derivates,
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.61–62 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.63 There may be less risk
of accumulation of medication with hydrocortisone. The
-pressor 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.64 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.65

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.66 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.67

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 was on children with a mean
gestational age of 29.8 (2.5) 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 dexametha-
sone 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.68

In two early treatment (prophylactic) hydrocortisone studies,
enrolment stopped because of an increased incidence of
spontaneous gastrointestinal perforation with combined hydro-
cortisone–indometacin treatment.67–68 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.69 In very low
birthweight infants, low-dose hydrocortisone alone (in the
absence of co-treatment with prophylactic indomethacin) did not
lead to gastrointestinal perforation.70 Peltoniemi et al found that
pretreatment serum cortisol levels were associated with treat-
ment effects and with the risk of intestinal perforations.71 Hallinan 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. Treatment with hydrocortisone beyond 2 weeks of postnatal age will avoid the interactive effect of dexamethasone 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, 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 therapy were not supported by the 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.

Competing interests: None.

REFERENCES


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