Corticosteroids for the prevention of bronchopulmonary dysplasia in preterm infants: a network meta-analysis

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ABSTRACT

Objective To determine the comparative efficacy and safety of corticosteroids in the prevention of bronchopulmonary dysplasia (BPD) in preterm infants.

Study design We systematically searched PubMed, EMBASE and the Cochrane Library. Two reviewers independently selected randomised controlled trials (RCTs) of postnatal corticosteroids in preterm infants. A Bayesian network meta-analysis and subgroup analyses were performed.

Results We included 47 RCTs with 6747 participants. The use of dexamethasone at either high dose or low dose decreased the risk of BPD (OR 0.29, 95% credible interval (CrI) 0.14 to 0.52; OR 0.58, 95% CrI 0.39 to 0.76, respectively). High-dose dexamethasone was more effective than hydrocortisone, beclomethasone and low-dose dexamethasone. Early and long-term dexamethasone at either high dose or low dose decreased the risk of BPD (OR 0.11, 95% CrI 0.02 to 0.52; OR 0.58, 95% CrI 0.39 to 0.76, respectively). There were no statistically significant differences in the risk of cerebral palsy (CP) between different corticosteroids. However, high-dose and long-term dexamethasone ranked lower than placebo and other regimens in terms of CP. Subgroup analyses indicated budesonide was associated with a decreased risk of BPD in extremely preterm and extremely low birthweight infants (OR 0.60, 95% CrI 0.36 to 0.93).

Conclusions Dexamethasone can reduce the risk of BPD in preterm infants. Of the different dexamethasone regimens, aggressive initiation seems beneficial, while a combination of high-dose and long-term use should be avoided because of the possible adverse neurodevelopmental outcome. Dexamethasone and inhaled corticosteroids need to be further evaluated in large-scale RCTs with long-term follow-ups.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common serious pulmonary disease in premature infants.1 Approximately 20% of infants born at <30 weeks of gestation or with a weight <1500 g are diagnosed with BPD. In addition, the incidence of BPD appears to be growing in conjunction with the increased survival of infants with low birth weight.2–4 Premature infants with BPD are at an increased risk of death, and survivors often have lifelong morbidities, including delayed neurocognitive development.5

Postnatal systemic corticosteroid administration is controversial, mainly because of the concern for its adverse neurological effects.6–12 There were conflicting results from studies assessing the effects of diminished corticosteroid administration on the incidence and severity of BPD following the 2002 policy statements of the American Academy of Pediatrics (AAP).13–15 Although the AAP revised the statement in 2010, the role of corticosteroids in the management of BPD remains uncertain.16 However, clinicians still use corticosteroids in approximately 5%–32% of preterm infants to prevent and treat BPD.17 Therefore, identifying the optimal corticosteroid and regimen remains clinically relevant and important.

New clinical trials, meta-analyses and follow-up studies have been published since 2010, warranting an updated review of the available information. Due to different comparators used in clinical trials, a pair-wise meta-analysis cannot be used to evaluate comparative effects of different corticosteroids and regimens. Therefore, we conducted a network meta-analysis of all relevant randomised evidence to comprehensively compare and rank the different corticosteroids used to prevent BPD.
METHODS

Study search and selection

We systematically searched PubMed (1966 to June 2016), EMBASE (1974 to June 2016) and the Cochrane Library (Issue 6, 2016) to identify relevant randomised controlled trials (RCTs) in humans published in English. We also manually searched the reference lists of retrieved trials and systematic reviews (online supplementary appendix 1). Two reviewers independently assessed the trials for eligibility and included RCTs that evaluated the safety and efficacy of postnatal corticosteroid use for BPD prevention in preterm infants (<37 weeks). Studies that used postnatal surfactant and corticosteroids together were also included. Studies that assessed the combined use of corticosteroids and beta agonists were excluded.

Data extraction and quality assessment

The primary outcome assessed was BPD at 36 weeks’ postmenstrual age (PMA). Secondary outcomes included BPD at 28 days’ postnatal age (PNA), death at 36 weeks’ PMA and 28 days PNA, and a diagnosis of cerebral palsy (CP) in a long-term follow-up. Two independent reviewers extracted the baseline characteristics, methods and outcomes of the included studies. Patients were categorised by gestational weeks (extremely preterm: <28 weeks; preterm: 28–37 weeks) and by birth weight (extremely low birth weight: <1000 g; very low birth weight: 1000–1500 g; low birth weight: 1500–2500 g). Dexamethasone regimens were categorised by the timing of initiation (early initiation: ≤7 days’ PNA; late initiation: >7 days’ PNA), total dose (low dose: ≤3.0 mg/kg; high dose: >3.0 mg/kg) and duration (short term: ≤3 days; long term: >3 days). Intention-to-treat analysis data were used whenever available. We contacted the authors of the included studies for missing data by email. Two independent reviewers assessed the risk of bias in trials using the Cochrane risk of bias tool, with any discrepancies resolved by consensus.

Statistical analysis

We conducted a Bayesian network meta-analysis using the WinBUGS V.1.4.3 software (MRC Biostatistics Unit, Cambridge, UK) and adopted a random-effects model with vague priors for multiarm trials. Pooled estimates and the probability of each treatment being the best were obtained by the Markov chain Monte Carlo method. Model convergence was assessed by trace plots and Brooks-Gelman-Rubin plots. The results of dichotomous outcomes were reported as posterior medians or ORs with 95% credible intervals (CrIs). The surface under the cumulative ranking curve (SUCRA) was calculated as a percentage to estimate the probability that an intervention was the best. Prespecified subgroup analyses were performed according to gestational age and birth weight. The interactions between the intervention effect and subgroups were assessed using a heterogeneity test in meta-analysis. Network geometry was performed with STATA V.13.0 software, in which the size of the nodes and thickness of the edges were proportional to sample sizes and numbers of trials involved, respectively.

RESULTS

Literature search

Of the 557 citations initially identified by searching bibliographical databases, 449 were excluded through title and abstract screening. We examined the full text of 108 reports, and identified 66 publications describing 47 RCTs that were eligible for network meta-analysis (online supplementary appendix 2). We contacted 19 corresponding authors of the included studies with missing data, and received additional data from 6 of the 19 authors (online supplementary appendix 3).

Characteristics of the included studies

The included trials evaluated five corticosteroids and involved a total of 6747 randomly assigned participants. The sample...
size of the trials ranged from 23 to 856 participants (median 60). The included studies recruited preterm infants with similar ranges of gestational age and birth weight, including extremely preterm with birth weights <1000 g (gestational age: median 26.7, IQR 26.0–27.9; birth weight: median 850, IQR 790–1010). According to data from 15 (31.9%) of the included trials, the average PNA at study entry ranged from 1.9 to 2.8 weeks' PMA. The results of network comparisons for BPD at 36 weeks' PMA showed direct evidence supporting BPD prevention (≤7 days after birth) with a high total dose (>3.0 mg/kg) and a long-term duration (>3 days), and early initiation of dexamethasone prevention (>7 days after birth) with a high total dose (>3.0 mg/kg) and a long-term duration (>3 days); EHL, early initiation of dexamethasone prevention (≤7 days after birth) with a low total dose (≤3.0 mg/kg) and a short-term duration (>3 days); LHL, late initiation of dexamethasone prevention (>7 days after birth) with a high total dose (>3.0 mg/kg) and a long-term duration (>3 days); LHS, late initiation of dexamethasone prevention (>7 days after birth) with a low total dose (≤3.0 mg/kg) and a short-term duration (>3 days); LLL, late initiation of dexamethasone prevention (>7 days after birth) with a low total dose (≤3.0 mg/kg) and a long-term duration (>3 days); LHS, late initiation of dexamethasone prevention (>7 days after birth) with a low total dose (≤3.0 mg/kg) and a short-term duration (>3 days); ELL, late initiation of dexamethasone prevention (>7 days after birth) with a low total dose (≤3.0 mg/kg) and a short-term duration (>3 days); LHS, late initiation of dexamethasone prevention (>7 days after birth) with a low total dose (≤3.0 mg/kg) and a short-term duration (>3 days); PMMA, postmenstrual age.

Risk of bias
In approximately 65% of the trials, the risk of selection bias (sequence generation and allocation concealment) was determined to be low. Blinding of both participants and outcome assessors occurred in 21 trials (44.7%). Incomplete data were appropriately tackled for the primary outcome (BPD), with 73.3% (33/45) assessed as having a low risk of bias. Forty-two trials (89%) were at a low risk of selective outcome reporting. Ten trials (20%) were deemed to have a high risk of other biases, for reasons that include early trial termination and unbalanced patient characteristics at baseline (online supplementary appendix 5). 37-38

Table 1 Results of network meta-analysis: relative effects of different corticosteroids versus placebo on BPD and CP

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Direct drug comparison studies/participants (n/N)</th>
<th>OR: median (95% CrI)</th>
<th>Direct evidence</th>
<th>All evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD at 36 weeks' PMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone (high dose)</td>
<td>6/659</td>
<td>0.34 (0.20 to 0.57)</td>
<td>0.29 (0.14 to 0.52)</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone (low dose)</td>
<td>13/2180</td>
<td>0.66 (0.54 to 0.80)</td>
<td>0.59 (0.39 to 0.77)</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>5/1022</td>
<td>0.80 (0.61 to 1.05)</td>
<td>0.74 (0.43 to 1.4)</td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>2/886</td>
<td>0.60 (0.45 to 0.81)</td>
<td>0.58 (0.29 to 1.06)</td>
<td></td>
</tr>
<tr>
<td>Fluticasone</td>
<td>1/53</td>
<td>0.32 (0.08 to 1.29)</td>
<td>0.32 (0.08 to 1.29)</td>
<td></td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>3/352</td>
<td>0.78 (0.46 to 1.35)</td>
<td>0.81 (0.40 to 1.55)</td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone (high dose)</td>
<td>5/307</td>
<td>2.30 (1.22 to 4.36)</td>
<td>2.02 (0.60 to 6.67)</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone (low dose)</td>
<td>3/245</td>
<td>0.61 (0.28 to 1.34)</td>
<td>0.81 (0.26 to 3.13)</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>3/334</td>
<td>1.09 (0.57 to 2.11)</td>
<td>1.79 (0.64 to 15.96)</td>
<td></td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>1/56</td>
<td>1.47 (0.12 to 18.47)</td>
<td>1.47 (0.12 to 18.47)</td>
<td></td>
</tr>
</tbody>
</table>

Network comparisons of the different corticosteroids
Efficacy: BPD and death
Networks of eligible comparisons for the prevention of BPD are presented in figure 1. Nine (32.1%) of the 28 available pair-wise comparisons showed direct evidence supporting BPD prevention at 36 weeks' PMA. The results of network comparisons for BPD

Table 2 SUCRA ranking probabilities of corticosteroids for primary and secondary outcomes

<table>
<thead>
<tr>
<th>Corticosteroids or placebo</th>
<th>SUCRA (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD at 36 weeks' PMA (%)</td>
<td>Death at 36 weeks' PMA (%)</td>
</tr>
<tr>
<td>Dexamethasone (high dose)</td>
<td>91.2</td>
</tr>
<tr>
<td>Dexamethasone (low dose)</td>
<td>56.0</td>
</tr>
<tr>
<td>Budesonide</td>
<td>54.9</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>78.8</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>28.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.9</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>34.2</td>
</tr>
</tbody>
</table>

* Larger SUCRA values denote more effective interventions. BPD, bronchopulmonary dysplasia; CP, cerebral palsy; PMA, postmenstrual age; SUCRA, surface under the cumulative ranking curve.
and CP are shown in table 1, and the results for other outcomes
are available in online supplementary appendix 6A.

The use of dexamethasone, at either high or low dose,
decreased the risk of BPD compared with placebo (OR 0.29,
95% CrI 0.14 to 0.52; OR 0.58, 95% CrI 0.39 to 0.76, respec-
tively). High-dose dexamethasone was associated with a lower
risk of BPD at 36 weeks' PMA, as compared with hydrocortisone
(OR 2.53, 95% CrI 1.20 to 5.68), beclomethasone (OR 2.75,
95% CrI 1.23 to 6.78) and low-dose dexamethasone (OR 1.99,
95% CrI 1.04 to 3.91) (online supplementary appendix 6A).
According to the estimated probability of being the best for BPD
prevention at 36 weeks' PMA, high-dose dexamethasone ranked
first (91.2%) and beclomethasone ranked last (28.0%) (table 2).

In terms of mortality, all corticosteroids failed to show any
superiority compared with placebo, and no statistically signif-
cicant difference was found between different corticosteroids
(online supplementary appendix 6A).

Safety: CP
Compared with placebo, high-dose dexamethasone, hydrocort-
sisone and beclomethasone tended to have a higher risk of CP
although the difference was statistically non-significant (ORs
ranging from 1.47 to 2.02). No statistically significant difference
was found between the five corticosteroids (online supplemen-
tary appendix 6A). According to SUCRA probabilities, low-dose
dexamethasone was the first (76.8%), ranked higher than hy-
drocortisone, while high-dose dexamethasone was the last (26.9%).

Of note, two dexamethasone trials and three hydrocorti-
sone trials were discontinued early due to safety consid-
erations.29-34 Of the five prematurely terminated trials,
two were stopped due to an increased incidence of sponta-
nous gastrointestinal perforation in participants of the trials,31 32
while the others were terminated because of the serious adverse effects reported in other studies and in the
2002 statement from the AAP.31 35 36

Comparisons of different dexamethasone regimens
We compared different regimens of dexamethasone, one of
commonly used corticosteroids in clinical practice, to determine
its optimal regimen.39

Efficacy: BPD and death
Compared with placebo, early-initiation, high-dose, long-term
(EHL), and early-initiation, low-dose, long-term (ELL) dexa-
methasone regimens were associated with a decreased risk of
BPD at 36 weeks' PMA (OR 0.11, 95% CrI 0.02 to 0.41; OR
0.37, 95% CrI 0.16 to 0.67) (table 1). In addition, EHL was
more effective than early-initiation, low-dose, short-term (OR
7.24, 95% CrI 1.60 to 34.15), early-initiation, high-dose, short-
term (OR 8.56, 95% CrI 1.14 to 62.62), and late-initiation,
low-dose, long-term (LLL) (OR 6.07, 95% CrI 1.09 to 37.88).
No statistically significant differences were found between
different dexamethasone regimens in terms of mortality (online
supplementary appendix 6B).

Safety: CP
No statistically significant differences in the risk of CP were
detected between different dexamethasone regimens (online
supplementary appendix 6B). According to SUCRA probabil-
ities, high-dose and long-term regimens, late-initiation, high-
dose, long-term (LHL) and EHL, ranked lower than placebo
in terms of CP (online supplementary appendix 7).

Results of subgroup analyses
By gestational week
For extremely preterm infants, both doses of dexamethasone
and budesonide were effective in decreasing the risk of BPD at
36 weeks' PMA compared with placebo (OR 0.06, 95% CrI 0.01
to 0.33; OR 0.73, 95% CrI 0.55 to 0.97; OR 0.60, 95% CrI
0.36 to 0.93), even though budesonide failed to show efficacy
in general preterm infants. Moreover, high-dose dexamethasone
was superior to low-dose dexamethasone and budesonide in
this population (OR 11.48, 95% CrI 2.16 to 93.39; OR 9.29,
95% CrI 1.63 to 79.07). No statistically significant difference
was found in terms of mortality and CP between the five corti-
costeroids (online supplementary appendix 8).

By birth weight
For extremely low birthweight infants, only budesonide signifi-
cantly reduced the risk of BPD at 36 weeks' PMA compared
with placebo (OR 0.60, 95% CrI 0.34 to 0.95). For very low
birthweight infants, both doses of dexamethasone were associ-
ated with a decreased risk of BPD at 36 weeks' PMA (high
dose: OR 0.23, 95% CrI 0.07 to 0.56; low dose: OR 0.36, 95% CrI
0.16 to 0.70). There were no statistically significant differences
in the risk of CP detected between the five corticosteroids in any
subgroups.

DISCUSSION
Summary of findings
Our network meta-analysis provides unified hierarchies of
evidence for corticosteroid use in BPD, overcoming the problem
due to inadequate evidence from head-to-head trials. Compared
with placebo, both high-dose and low-dose dexamethasone
reduced the risk of BPD at 36 weeks' PMA. In addition,
high-dose dexamethasone significantly decreased the risk of BPD
compared with hydrocortisone and beclomethasone. The attempt
to explore the optimal regimens of dexamethasone revealed that
early initiation and a high dose of dexamethasone decreased the
risk of BPD, but high-dose and long-term dexamethasone might
increase the risk of CP. For the extremely preterm and extremely
low birthweight infants, budesonide showed a decreased risk of
BPD, compared with placebo.

Hydrocortisone versus dexamethasone
The AAP guideline discussed the difference between hydrocorti-
sone and dexamethasone in terms of safety, based mainly on
pharmacokinetic studies and animal studies.16 Our study showed
that hydrocortisone ranked lower than low-dose dexamethasone
in terms of both CP and BPD prevention at 36 weeks' PMA.
According to a recent in vivo experimental study, hydrocortisone
had similar neurotoxic effects to dexamethasone on neurons
in immature chicken cerebellum and it may not be safer than
dexamethasone.40

Different dexamethasone regimens
High-dose, long-term dexamethasone regimens appeared to
be associated with a higher risk of CP compared with placebo
(ORs range from 2.30 to 2.75) and low-dose, short-term regi-
ments (ORs range from 2.30 to 33.33), but without significant
differences. In addition, our findings appeared to support early
initiation, as both EHL and ELL were associated with a lower
risk of CP compared with LHL and LLL (OR: 0.82 and 0.62,
respectively). The possible explanations for the finding include
the following: early-initiation, low-dose dexamethasone was
found to suppress the expression of inflammatory mediators

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and decrease pulmonary oedema. The adverse neurodevelop-
mental outcomes of postnatal dexamethasone therapy were
shown to be associated with initiation time. Early initiation of
dexamethasone enhanced the acquisition of contextual fear and
spatial memory later in life of rat pups and increased dendritic
spine number. Hence, our findings challenge the use of high-
dose and long-term dexamethasone, but advocate a more aggres-
sive initiation of dexamethasone than current clinical practice.

Extremely preterm and low birth weight
In subgroup analyses, high-dose dexamethasone was shown to
be superior to low-dose dexamethasone, hydrocortisone and
beclomethasone in extremely preterm infants. However, the
recommendation of an increase in dose for extremely preterm
could not be made due to the lack of evidence on long-term
neurodevelopmental safety. It was found that budesonide signifi-
cantly reduced BPD at 36 weeks' PMA compared with placebo in
extremely preterm and extremely low birthweight infants. However, this finding was consistent with the point raised by Bassler, who predicted that inhaled budesonide may play a role in extremely
low birthweight infants. However, there was no convincing
evidence from RCTs on the effects of other inhaled corticoste-
roids for BPD prevention.\textsuperscript{11}

Limitations of this study
Our study has several potential limitations. First, variations in
corticosteroid regimens and participants resulted in signifi-
cant heterogeneity across the included studies. We therefore
planned a comparison of the different regimens of dexameth-
asone and beclomethasone in extremely preterm infants. However, the
counterpoint was raised by Bassler, who predicted that these regimens of
dexamethasone may play a role in extremely preterm infants. However, there was no convincing
evidence from RCTs on the effects of other inhaled corticoste-
roids for BPD prevention.\textsuperscript{11}

CONCLUSIONS
For preterm infants with risk of BPD, dexamethasone can reduce
the risk of BPD, and high-dose dexamethasone is more efficacious
than other regimens of corticosteroids. Of the different
dexamethasone regimens, aggressive initiation seems a favour-
able option, and a combination of high-dose and long-term use
should be avoided because of the possible long-term adverse
neurodevelopmental outcome. Budesonide is associated with
a decreased risk of BPD in extremely preterm and extremely low
birthweight infants, although recommendations cannot be made
due to the lack of long-term safety data. RCTs of early-initiation and
low-dose dexamethasone, budesonide and other inhaled
corticosteroids with factorial design and long-term follow-ups
are urgently needed to identify the optimal postnatal corticoste-
roid regimens.

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data, and drafted and revised the manuscript. JT revised the study protocol, and
analysed and interpreted the data. FS contributed to the conception and design of
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study protocol, interpreted the data and revised the manuscript. DM contributed to
the conception and design of the study and revised the manuscript. LZe conceived
the study, interpreted the data, and drafted and revised the study protocol and
manuscript.

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