Dexamethasone for treatment of patients mechanically ventilated for lower respiratory tract infection caused by respiratory syncytial virus


Background: A study was undertaken to evaluate the efficacy of dexamethasone in patients mechanically ventilated for lower respiratory infection caused by respiratory syncytial virus (RSV-LRTI).

Methods: In a multicentre randomised controlled trial patients were randomised to receive either intravenous dexamethasone (0.15 mg/kg 6 hourly for 48 hours) or placebo. End points were the duration of mechanical ventilation, length of stay (LOS) in the intensive care unit (PICU) and in hospital, and the duration of supplemental oxygen administration.

Results: Thirty seven patients received dexamethasone and 45 received placebo. There was no significant difference in any of the end points between the two groups. In a post hoc analysis patients were stratified into those with mild gas exchange anomalies (PaO2/FiO2 >200 mm Hg and/or mean airway pressure \( \leq 10 \) cm H2O, bronchiolitis group) and those with severe gas exchange anomalies (PaO2/FiO2 \( \leq 200 \) mm Hg and mean airway pressure >10 cm H2O, pneumonia group). In the 39 patients with bronchiolitis the duration of mechanical ventilation was 4.3 days shorter in the dexamethasone group than in the placebo group (4.9 v 9.2 days, 95% CI –7.8 to –0.8, p=0.02) and the duration of supplemental oxygen was 3.6 days shorter (7.7 v 11.3 days, 95% CI –8.0 to –0.1, p=0.048). No differences in end points were found in the pneumonia group.

Conclusions: Dexamethasone had no beneficial effect in patients mechanically ventilated for RSV-LRTI but was found to have a beneficial effect in patients with bronchiolitis.
of viral shedding, RSV immunofluorescence assay of nasopharyngeal aspirate was repeated on days 2, 3, 7, 10 and 14 while the patient was an inpatient. If two consecutive assays were negative the viral shedding was considered to be negative.

**Statistical analysis**

The previously found difference of 1.5 days in mechanical ventilation was considered to be clinically relevant; in order for this difference to be detected, 60 patients (30 in each arm) would be needed (α=0.05, β=80%).

Statistical analysis was performed with SPSS for Windows, version 10.1 (SPSS Inc). The Student’s t test was used to compare group means for normally distributed data; otherwise the Mann-Whitney U test was applied. Proportions were compared by the \( \chi^2 \) test. A two sided p value of <0.05 was considered statistically significant. Data were analysed according to the intention to treat principle. Data in the tables are given as mean (SE) unless otherwise stated.

**RESULTS**

**Eligible patients**

From December 1997 to March 2001 155 patients met the inclusion criteria and were eligible for enrolment. Seventy patients were not randomised for reasons shown in Fig 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of patients on admission in the PICU according to treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dexamethasone (n=37)</td>
</tr>
<tr>
<td>Male</td>
<td>30</td>
</tr>
<tr>
<td>Age (weeks)</td>
<td>5.9 (0.9)</td>
</tr>
<tr>
<td>Risk group</td>
<td>12</td>
</tr>
<tr>
<td>Premature*</td>
<td>10</td>
</tr>
<tr>
<td>CLD</td>
<td>1</td>
</tr>
<tr>
<td>CHD</td>
<td>1</td>
</tr>
<tr>
<td>Other†</td>
<td>0</td>
</tr>
<tr>
<td>Family history of asthma‡</td>
<td>9</td>
</tr>
<tr>
<td>Duration of symptoms (days)</td>
<td>3.3 (0.3)</td>
</tr>
<tr>
<td>Apnoea</td>
<td>5</td>
</tr>
<tr>
<td>Wheezing</td>
<td>16</td>
</tr>
<tr>
<td>Admission weight (kg)</td>
<td>4.1 (0.2)</td>
</tr>
<tr>
<td>Median (IQR) PRISM score</td>
<td>9 (7–12)</td>
</tr>
<tr>
<td>SIMV/PC</td>
<td>28</td>
</tr>
<tr>
<td>Median (IQR) PIP (cm H(_2)O)§</td>
<td>24 (20–26)</td>
</tr>
<tr>
<td>Median (IQR) PEEP (cm H(_2)O)§</td>
<td>4 (4–5)</td>
</tr>
<tr>
<td>Pa(<em>{O_2})/Fi(</em>{O_2}) ratio (mm Hg)</td>
<td>180 (9)</td>
</tr>
<tr>
<td>Time elapsed between start mechanical ventilation and start trial medication (h)</td>
<td>15 (1.2)</td>
</tr>
</tbody>
</table>

CLD=chronic lung disease; CHD=congenital heart disease; SIMV/PC=synchronised intermittent mandatory ventilation, pressure controlled; PIP=positive inspiratory pressure; PEEP=positive end expiratory pressure.  
*Prematurity was defined as a gestational duration of less than 36 weeks.  
†One patient with cardiomyopathy, one patient with lung hypoplasia.  
‡Mother, father or sibling with asthma.  
§Only in patients with SIMV/PC ventilation.
the 85 patients who were enrolled, 39 were randomised to receive dexamethasone and 46 to receive placebo. After enrolment three patients were withdrawn, one (dexamethasone group) because she died 4 days after admission due to severe cerebral oedema in combination with refractory seizures existing already before inclusion, and two because their medication vials (one containing dexamethasone and the other placebo) were accidentally interchanged. Eighty two patients therefore completed the trial, 37 of whom received dexamethasone and 45 placebo.

Baseline characteristics
The baseline characteristics of the study participants are shown in table 1. The proportion of males was higher in the dexamethasone group than in the placebo group and the dexamethasone group was significantly younger than the placebo group. There were no other differences in baseline characteristics between the two treatment groups.

Outcome
The mean duration of mechanical ventilation in the dexamethasone group was 1.6 days shorter than in the placebo group; this difference was not statistically significant (table 2). There was no difference in either the mean LOS in the PICU and in the hospital or the mean duration of supplemental oxygen. The results were not different after correction for sex or age (data not shown). Five patients (two in the dexamethasone group and three in the placebo group) needed to be re-intubated because of upper airway obstruction following intubation.

During the course of the trial Tasker et al published a study in which they reported that mechanically ventilated patients with RSV-LRTI may present with two patterns of disease which can be distinguished on the basis of early respiratory parameters. In order to determine whether the effect of dexamethasone was dependent on these clinical patterns we performed a post hoc subgroup analysis. Patients were stratified according to the PaO2/FiO2 ratio and the mean airway pressure (MAP) on the day of admission, analogous to the criteria described by Tasker et al. Arterial blood gas analysis data were available for 80 patients during the first 24 hours of admission (in case more blood gas analyses were available the worst PaO2/FiO2 was chosen). These patients were stratified into a bronchiolitis group (mild gas exchange anomalies: PaO2/FiO2 >200 mm Hg and/or MAP >10 cm H2O) and a pneumonia group (severe gas exchange anomalies: PaO2/FiO2 ≤200 mm Hg and MAP >10 cm H2O, n=39) and a pneumonia group. There were no differences in baseline characteristics between the dexamethasone and placebo treated patients within the bronchiolitis and pneumonia groups. The results of the end point analyses in these subgroups are shown in table 3. In the bronchiolitis group the mean duration of mechanical ventilation in the patients who received dexamethasone was 4.3 days shorter than in those who received placebo (4.9 v 9.2 days, 95% CI 7.8 to –0.8 days, p=0.02). The mean LOS in the PICU was 2.4 days shorter in the dexamethasone group than in the placebo group but this difference was not statistically significant (7.9 v 10.3 days, 95% CI –6.8 to 2.0, p=0.28). However, in the mild group three patients (two of whom received dexamethasone and one placebo) needed to be re-intubated because of upper airway obstruction following intubation. If these three patients were excluded from the analysis there was a significant difference of 3.9 days in mean LOS in the PICU (6.6 v 10.5 days, 95% CI 7.6 to –0.2, p=0.039) The mean LOS in hospital and the mean duration of supplemental oxygen were also shorter in the dexamethasone group than in the placebo group, but only the difference in duration of supplemental oxygen reached statistical significance. In the pneumonia group there was no significant

### Table 2
Mean (SE) duration of mechanical ventilation, length of stay (LOS) in the paediatric intensive care unit (PICU) and hospital, and duration of supplemental oxygen in the two treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone (n=37)</th>
<th>Placebo (n=45)</th>
<th>95% CI for difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of mechanical ventilation (days)</td>
<td>6.9 (0.7)</td>
<td>8.5 (0.9)</td>
<td>–3.8 to 0.8</td>
<td>0.19</td>
</tr>
<tr>
<td>LOS in PICU (days)</td>
<td>9.1 (0.9)</td>
<td>9.9 (0.9)</td>
<td>–3.4 to 1.8</td>
<td>0.53</td>
</tr>
<tr>
<td>LOS in hospital (days)</td>
<td>15.9 (1.5)</td>
<td>14.9 (1.2)</td>
<td>–2.8 to 4.7</td>
<td>0.52</td>
</tr>
<tr>
<td>Duration of supplemental oxygen (days)</td>
<td>10.0 (1.2)</td>
<td>10.9 (1.0)</td>
<td>–3.9 to 2.1</td>
<td>0.55</td>
</tr>
</tbody>
</table>

### Table 3
Mean (SE) duration of mechanical ventilation, length of stay (LOS) in the paediatric intensive care unit (PICU) and hospital, and duration of supplemental oxygen in days in the two treatment groups according to subgroup analysis

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone</th>
<th>Placebo</th>
<th>95% CI for difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolitis group‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>18</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of mechanical ventilation (days)</td>
<td>4.9 (0.5)</td>
<td>9.2 (1.6)</td>
<td>–7.8 to –0.8</td>
<td>0.02</td>
</tr>
<tr>
<td>LOS PICU</td>
<td>7.9 (1.4)</td>
<td>10.3 (1.6)</td>
<td>–6.8 to 2.0</td>
<td>0.28</td>
</tr>
<tr>
<td>LOS hospital</td>
<td>14.9 (2.0)</td>
<td>16.0 (1.9)</td>
<td>–6.7 to 4.5</td>
<td>0.11</td>
</tr>
<tr>
<td>Duration of supplemental oxygen (days)</td>
<td>7.7 (0.9)</td>
<td>11.3 (1.6)</td>
<td>–8.0 to –0.1</td>
<td>0.048</td>
</tr>
<tr>
<td>Pneumonia group†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>19</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of mechanical ventilation (days)</td>
<td>8.9 (1.1)</td>
<td>8.1 (1.0)</td>
<td>–2.2 to 3.6</td>
<td>0.61</td>
</tr>
<tr>
<td>LOS PICU</td>
<td>10.1 (1.1)</td>
<td>9.9 (1.2)</td>
<td>0.1 to 3.5</td>
<td>0.90</td>
</tr>
<tr>
<td>LOS hospital</td>
<td>16.7 (2.2)</td>
<td>14.1 (1.5)</td>
<td>–2.8 to 8.0</td>
<td>0.34</td>
</tr>
<tr>
<td>Duration of supplemental oxygen (days)</td>
<td>12.1 (1.9)</td>
<td>10.4 (1.0)</td>
<td>–2.7 to 6.1</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Arterial blood gas analysis was available for 37 patients in the dexamethasone group and 43 patients in the placebo group.
‡Bronchiolitis group: patients with PaO2/FiO2 >200 mm Hg and/or mean airway pressure ≤10 cm H2O.
†Pneumonia group: patients with PaO2/FiO2 ≤200 mm Hg and MAP >10 cm H2O.
difference in any of the end points between the dexamethasone
and placebo treated patients.

Concomitant treatment
There were no differences in concomitant treatment with
antibiotics, bronchodilators or paralysing agents between the
two treatment groups (table 4). None of the patients received
palivizumab before admission or ribavirin during admission.
Three patients received corticosteroids after randomisation;
two (one from each treatment group) were started after 8 days
with the aim of getting them off the ventilator earlier and one
in the dexamethasone group was started on corticosteroids
after 2 days because of suspicion of adrenal insufficiency.

Side effects
Mean blood pressure both before the start of trial medication
(59 ± 58 mm Hg in the dexamethasone and placebo group,
respectively, p=0.72) and during the first 5 days of admission
(42 mm Hg in both groups, p=0.36) did not differ between the
two treatment groups. In one patient (dexamethasone group)
malignant hypertension developed 3 days after start of the
trial medication which later proved to be caused by a renal
vein thrombosis. During the first 5 days of admission gluco-
uria was found on 7 of the 146 days when urine was checked
in the dexamethasone group and on 5 of the 163 days when
urine was checked in the placebo group (p=0.56).

During the first 2 weeks of admission at least two RSV
immunofluorescence assays were repeated in 58 patients (23
in the dexamethasone group and 35 in the placebo group).
In six patients in the dexamethasone group and in nine in the
placebo group the test became negative (p=0.60).

DISCUSSION
The results of this trial show that dexamethasone does not
lead to a shorter duration of mechanical ventilation in patients
with RSV-LRTI. Although dexamethasone shortened the
duration of mechanical ventilation by more than 1 day in the
whole study cohort, this difference did not reach statistical
significance. Our results confirm a very recently published
trial that also evaluated the efficacy of dexamethasone in
mechanically ventilated patients with RSV-LRTI. However, this
trial was primarily designed to evaluate differences in virus
quantity and the authors stated that it was underpowered to
detect differences of <50% between the two groups.

RSV induced respiratory insufficiency may present with two
different patterns. The first pattern, classically referred to as
bronchiolitis, is characterised predominantly by obstruction of
the airways while the second pattern, classically referred to as
pneumonia, is characterised by a predominantly restrictive
pulmonary function pattern (i.e. bronchiolitis) while severe gas exchange anomalies are consistent with a severe
restrictive pulmonary function pattern (i.e. pneumonia). By combining the results of lung function studies in patients with RSV-LRTI with the results of the study by Tasker et al, Newth concluded
that patients with mild gas anomalies may reflect a mainly
obstructive pulmonary function pattern (i.e. bronchiolitis) while severe gas exchange anomalies are consistent with a
severe restrictive pulmonary function pattern (i.e. pneumonia). In addition, Newth showed that the AaDO2 value of >400 mm Hg that was used corresponds to a PaO2/FiO2 ratio of approximately <200 mm Hg which is used to define
ARDS. By applying a cut off value of 200 mm Hg for the
PaO2/FiO2 ratio and of 10 cm H2O for the MAP to differentiate
between patients with RSV bronchiolitis and those with
pneumonia (who did not fulfil both criteria), we found a
marked difference in the efficacy of dexamethasone between
these subgroups. Dexamethasone reduced mechanical ventila-
tion by more than 4 days and LOS in the PICU by more than 3 days in the bronchiolitis group. In addition, the LOS in hospital
and the duration of supplemental oxygen were reduced by
dexamethasone, only the latter end point being statistically
significant.

For several reasons our results should be interpreted with
cautious. Firstly, the efficacy of dexamethasone in patients with
RSV bronchiolitis was demonstrated by a post hoc analysis.
This only generates the hypothesis that corticosteroids may be
beneficial in patients with bronchiolitis and needs to be
confirmed in a prospectively conducted randomised trial.
Secondly, Tasker et al found an important difference in LOS in the
PICU between patients with mild gas exchange anomalies and
those with pneumonia. By applying their criteria we would have expected to find a similar difference
between these two subgroups in the placebo treated patients
but this was not the case, which underscores the need for fur-
ther studies on this topic.

The efficacy of corticosteroids in patients with RSV-LRTI
has been studied for decades with conflicting results. Like other workers, in an
earlier trial we were unable to show that oral prednisolone was
beneficial in patients with mild RSV-LRTI. However, pred-
nisolone shortened the duration of mechanical ventilation
and the LOS in hospital in a small group of patients on
mechanical ventilation. The results reported here support our
previous findings that corticosteroids are beneficial in a

<table>
<thead>
<tr>
<th>Antibiotic treatment*</th>
<th>Dexamethasone (n=37)</th>
<th>Placebo (n=46)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Started before or on admission</td>
<td>24</td>
<td>32</td>
<td>0.8</td>
</tr>
<tr>
<td>Started &gt;1 day after admission</td>
<td>10</td>
<td>12</td>
<td>1.0</td>
</tr>
<tr>
<td>Bronchodilator therapy during admission</td>
<td>19</td>
<td>27</td>
<td>0.65</td>
</tr>
<tr>
<td>Mean (SE) duration of bronchodilator treatment [days]</td>
<td>5.3 (0.6)</td>
<td>5.3 (0.7)</td>
<td>0.98</td>
</tr>
<tr>
<td>Additional corticosteroid therapy</td>
<td>2</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Paralysing agents during admission</td>
<td>9</td>
<td>15</td>
<td>0.47</td>
</tr>
<tr>
<td>Mean (SE) duration of paralysing agents [days]</td>
<td>3.8 (0.7)</td>
<td>4.5 (0.8)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

*Amoxicillin (with or without clavulanic acid) or a macrolide were the most frequently prescribed antibiotics.

92% v 75% in the dexamethasone and placebo groups respectively, p=0.36.
subgroup of patients with RSV bronchiolitis. Further research is needed to identify more precisely patients in the PICU with RSV-LRTI in whom corticosteroids are potentially beneficial.

Since no treatment is available for RSV-LRTI, our findings may indicate a step forward in the search for effective treatment. This may have an important socioeconomic impact since hospital admissions for bronchiolitis have increased substantially over the last decade and it is estimated that, in the USA, more than 120 000 children are admitted annually with RSV-LRTI.19

In our previous trial we used oral prednisolone in a dose of 1 mg/kg/day for 7 days. Because the beneficial effect of prednisolone was mainly seen in the first 3 days, in the current trial a shorter and higher dose of intravenous corticosteroids was used. On the basis of the dose used in patients with laryngitis subglottica and meningitis,20 the dose of dexamethasone chosen was 0.6 mg/kg/day (equivalent to 6 mg/kg/day prednisolone). The parenteral route was chosen because mechanically ventilated patients were studied.

The beneficial effects of intravenous dexamethasone should outweigh the potential side effects. No significant side effects were found in the present study, which is in accordance with what is known about short courses of steroid treatment.18

In conclusion, dexamethasone was not found to be beneficial in patients needing mechanical ventilation for RSV-LRTI. However, post hoc subgroup analysis suggested a beneficial effect of dexamethasone in a subgroup of patients with RSV bronchiolitis. Although our findings indicate a significant improvement in the therapeutic possibilities for patients with RSV bronchiolitis who need mechanical ventilation, this observation can only be considered hypothetical and should be tested in a prospective randomised controlled trial.

ACKNOWLEDGEMENTS
We thank the trial pharmacists and medical staff and nurses of all participating centres for their help with preparing the trial medication and including patients and completing the trial respectively, and the Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam for their statistical advice and support.

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