The effect of respiratory management on neurodevelopmental outcome in preterm infants
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Long-term neurodevelopmental outcome after doxapram for apnea of prematurity

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ABSTRACT

Background
Doxapram has been advocated as a treatment for persistent apnea of prematurity.

Objective
To evaluate the effect of doxapram on long-term neurodevelopmental outcome in preterm infants as its safety still needs to be established.

Methods
From a retrospective cohort of preterm infants with a gestational age (GA) < 30 weeks and/or a birth weight < 1250 g, born between 2000 and 2010, infants treated with doxapram (n = 142) and a nontreated control group were selected (n = 284). Patient characteristics and clinical and neurodevelopmental outcome data at 24 months corrected age were collected. Neurodevelopmental delay (ND) was defined as having a Mental or Psychomotor Developmental Index (MDI/PDI) < -1 standard deviation (SD), cerebral palsy, or a hearing or visual impairment. Odds ratios (OR) were calculated using multiple logistic regression analyses adjusting for potential confounders.

Results
Infants treated with doxapram had a lower GA compared to controls. The number of infants with an MDI or PDI < -1 SD was not different between the groups. The risk of the combined outcome death or ND was significantly lower in the doxapram group after adjusting for confounding factors (OR = 0.54, 95% CI 0.37, 0.78). Doxapram-treated infants had a higher risk of bronchopulmonary dysplasia and patent ductus arteriosus, but a lower risk of spontaneous intestinal perforation. All other morbidities were not different between the groups.

Conclusion
This study suggests that doxapram is not associated with an increased risk of ND. These findings need to be confirmed or refuted by a large, well-designed, placebo-controlled randomized trial.
INTRODUCTION

Apnea of prematurity (AOP) is very common in preterm infants with a gestational age (GA) < 34 weeks. AOP may be caused by a reduced or absent inspiratory effort (central AOP), obstruction of the (upper) airways (obstructive AOP) or a combination of both (mixed AOP). In case of central AOP, pharmacological treatment with the methylxanthine caffeine is the first choice of treatment. When central apnea persists despite the use of caffeine, intubation and positive pressure ventilation is surely an effective treatment for AOP but increases the risk of secondary lung injury and subsequent bronchopulmonary dysplasia (BPD). For this reason, some clinicians use doxapram. Doxapram is an analeptic that stimulates the breathing center in the brain, ensuring an 80% reduction in apnea frequency in preterm infants. Large placebo-controlled trials investigating the efficacy on clinical outcomes are currently lacking.

Doxapram has also been associated with short-term adverse effects, such as hypertension, QT interval prolongation and gastrointestinal disturbances. Furthermore, a case-control study in preterm patients with isolated mental developmental delay and a follow-up (telephone interviews) study reported a possible association between doxapram treatment and long-term neurodevelopmental delay (ND). However, the sample size of doxapram-treated infants in both studies was relatively small and the results were not (fully) corrected for possible confounders, such as BPD and duration of ventilation.

Therefore, the aim of the present study was to explore the possible association between doxapram and ND at 24 months corrected age in a large group of doxapram-treated preterm infants, correcting for known potential confounders.

METHODS

Study Population
This study is a retrospective cohort study conducted at the Academic Medical Center (AMC) in Amsterdam and the Leiden University Medical Center (LUMC), the Netherlands. The initial cohort consisted of all patients born between 2000 and 2010 at AMC and between 2005 and 2010 at LUMC with a GA < 30 weeks and a birth weight < 1250 g. From this cohort, we extracted all infants treated with doxapram at some point of time during their admission. These cases were compared to randomly selected nontreated controls selected from the same cohort using the identical GA and birth weight cutoff in a ratio of 1:2. Some methodologists nowadays considered this superior to a design using a matched control group, as the latter might lead to selection bias. As per protocol, all infants were treated with caffeine. The institutional review board approved the study.
Data Collection

Multiple demographic and short-term clinical data were collected (Table 1), and follow-up at 24 months postmenstrual age consisted of a complete physical examination including weight, length, head circumference, a standardized neurological examination, and assessment of mental and psychomotor development using the Bayley Scales of Infant and Toddler Development (BSID). Trained developmental psychologists performed the Bayley assessments. Due to the time period in which the outcome data were collected, both the second and third editions of the BSID were used, yielding the Mental Development Index (MDI) of the BSID-II and the composite cognitive score of the BSID-III, as well as the Psychomotor Development Index (PDI) of the BSID-II and the composite motor score of the BSID-III. Recent publications indicate that the two versions are not completely comparable. In order to combine the results of the two Bayley scores, we added 5 points to both the MDI and PDI of the BSID-II, so as to conform to the methods of the TRUFFLE study. These scores were then grouped with the composite cognitive score and composite motor scores from the BSID-III, while MDI and PDI were used for the cognitive and motor domains, respectively, for the grouped Bayley-II and -III measures. MDI (the adjusted MDI of the BSID-II and the unadjusted composite cognitive score of the BSID-III) and PDI (the adjusted PDI of the BSID-II and the unadjusted composite motor scores of the BSID-III) scores with < -1 standard deviation (SD) below the mean (< 85 points) were defined as abnormal. Cerebral palsy (CP) was diagnosed according to international standards. All levels of CP were included. ND was defined as one or more of the following outcomes: MDI and/or PDI score < 85, CP, hearing loss despite amplification, and visual impairment leading to blindness or only light perception in at least one eye.

Statistical Analysis

We used frequency and descriptive tables to describe the demographic, perinatal and clinical characteristics. Bivariate analyses were done using the Chi square test (for discrete data) and the independent samples t test or a Mann-Whitney U test (for continuous data) to compare sample means of variables between the doxapram-treated and nontreated group. Incidence of BPD, duration of hospitalization and ventilation days were also analyzed, but only in survivors of the two groups. Multiple logistic regression analysis was performed first without and then with correction for GA, BPD, small for gestational age (SGA), intraventricular hemorrhage (IVH), postnatal steroids and sepsis. These patient characteristics and short-term clinical outcomes were chosen because of their established adverse effect on the primary outcome of this study, i.e. long-term neurodevelopmental outcome. We did not correct for cystic periventricular leukomalacia (cPVL) since the incidence of this outcome was extremely low in both groups. Correction for maternal education was not possible due to the large amount of missing
data. The difference in the association between the two hospitals was explored in the multiple logistic regression analysis. To assess the impact of missing data on the primary outcome, we performed a sensitivity analysis, in which all patients lost to follow-up were considered abnormal in the doxapram group and normal in the nontreated control group for MDI and ND. Within the doxapram-exposed infants, the association between the cumulative dose and duration of therapy and the different neurodevelopmental outcomes was tested using a Pearson correlation for the continuous outcomes and Student’s t test for the categorical outcomes. Differences were considered statistically significant when the two-tailed p value was < 0.05. All statistical analyses were performed with Statistical Package for the Social Sciences, version 20.0.0.1 (SPSS Inc., Chicago, Ill., USA).

**RESULTS**

A total of 1447 eligible patients were born at both neonatal intensive care units. The overall mortality rate of the population was 16.8% in the study period. 142 (9.8%) patients were treated with doxapram of whom 65 (46%) were admitted in the AMC and 77 (54%) in the LUMC. Fourteen (9.9%) infants died, of whom one died after hospital discharge (Figure 1). Thirteen infants (9.2%) were lost to follow-up. Neurodevelopmental follow-up data were available for 115 (90%) of the surviving doxapram-treated patients. From the 284 randomly selected nontreated controls, 60 (21.1%) died during hospitalization and 54 were lost to follow-up (19.0%). Compared to the infants seen at follow-up, the group lost to follow-up had a slightly higher GA (28.0 ± 1.4 vs. 27.6 ± 1.5 weeks), a lower incidence of BPD (18.9 vs. 5.8%) and a shorter duration of hospitalization (43.5 ± 18.9 vs. 29.1 ± 26.0 days). Because the difference in mortality might lead to bias, the data

**Figure 1.** Population flow sheet: doxapram-treated versus nontreated patients. FU follow up.
on the incidence of BPD, the duration of hospitalization and the ventilation days were also analyzed for the two groups, but only in survivors. Similar significant results were seen comparable to the analyses of the total group (data not shown).

### Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Doxapram (n = 142)</th>
<th>Nontreated (n = 284)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td>26.9±1.6</td>
<td>27.7±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>953±243</td>
<td>946±190</td>
<td>0.743</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>24.8±2.8</td>
<td>25.1±2.5</td>
<td>0.352</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>6 (4.2)</td>
<td>25 (8.8)</td>
<td>0.086</td>
</tr>
<tr>
<td>Male</td>
<td>74 (52.1)</td>
<td>140 (49.2)</td>
<td>0.584</td>
</tr>
<tr>
<td>Caucasian</td>
<td>23 (62.1)</td>
<td>50 (69.4)</td>
<td>0.444</td>
</tr>
<tr>
<td>5-min Apgar score</td>
<td>7.2±1.9</td>
<td>7.6±2.2</td>
<td>0.108</td>
</tr>
</tbody>
</table>

### Doxapram therapy

<table>
<thead>
<tr>
<th></th>
<th>Doxapram</th>
<th>Nontreated</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnatal age at initiation, days</td>
<td>12 (14) (1-48)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Average dosage, mg.kg⁻¹.h⁻¹</td>
<td>1.0 (0.75) (0.04-2.51)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total duration, days</td>
<td>6 (10) (1-39)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total cumulative dosage, mg</td>
<td>123 (242) (1.0-984)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Culture proven sepsis</td>
<td>60 (42.3)</td>
<td>123 (43.3)</td>
<td>0.850</td>
</tr>
<tr>
<td>PDA</td>
<td>76 (54.2)</td>
<td>101 (37.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>NEC &gt; grade IIa</td>
<td>11 (7.9)</td>
<td>17 (6.3)</td>
<td>0.533</td>
</tr>
<tr>
<td>Spontaneous intestinal perforation</td>
<td>0 (0)</td>
<td>12 (4.4)</td>
<td>0.012</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>0.474</td>
</tr>
<tr>
<td>IVH &gt; grade II</td>
<td>24 (17.0)</td>
<td>53 (18.9)</td>
<td>0.644</td>
</tr>
<tr>
<td>PHVD</td>
<td>9 (6.3)</td>
<td>10 (3.5)</td>
<td>0.190</td>
</tr>
<tr>
<td>cPVL</td>
<td>5 (3.5)</td>
<td>5 (1.8)</td>
<td>0.286</td>
</tr>
<tr>
<td>Ventilation days</td>
<td>9.1±8.7</td>
<td>5.6±7.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postnatal steroids</td>
<td>24 (16.9)</td>
<td>27 (9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPD 36 weeks</td>
<td>39 (27.5)</td>
<td>18 (6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td>53.4±28.1</td>
<td>28.3±21.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>14 (9.9)</td>
<td>60 (21.1)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD, n(%) or median (interquartile range)(min-max). PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; PHVD, post hemorrhage ventricular distension; cPVL, cystic periventricular leukomalacia; BPD 36 weeks, bronchopulmonary dysplasia defined as the need for supplemental oxygen at 36 weeks’ postmenstrual age.

As shown in Table 1, the doxapram-treated group had a significantly lower GA, mortality rate and spontaneous intestinal perforation incidence compared to the nontreated group. Furthermore, infants treated with doxapram had a higher incidence of patent
Table 2. Long-term neurodevelopmental outcome.

<table>
<thead>
<tr>
<th></th>
<th>Doxapram (n=115)</th>
<th>Nontreated (n=170)</th>
<th>Unadjusted OR</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI p</td>
<td>OR 95% CI p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDI &lt; -1SD</td>
<td>0.53 (0.22, 1.28)</td>
<td>0.160 (0.054)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDI &lt; -1SD</td>
<td>0.77 (0.36, 1.63)</td>
<td>0.498 (0.162)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP</td>
<td>1.55 (0.46, 5.25)</td>
<td>0.447 (0.479)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ND</td>
<td>0.67 (0.37, 1.20)</td>
<td>0.174 (0.058)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death/ND</td>
<td>0.58 (0.42, 0.84)</td>
<td>0.003 (0.003)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are n(%) unless otherwise indicated. *ND* Neurodevelopmental Delay, defined as having MDI or PDI < -1SD, CP, or hearing or visual impairment. Corrected for gestational age, bronchopulmonary dysplasia, small for gestational age, intraventricular hemorrhage, postnatal steroids and sepsis.

Table 3. Correlations and associations of doxapram therapy and long-term neurodevelopmental outcomes.

<table>
<thead>
<tr>
<th></th>
<th>MDI 1</th>
<th>MDI &lt; -1SD 2</th>
<th>PDI 1</th>
<th>PDI &lt; -1SD 2</th>
<th>ND 2</th>
<th>Death or ND 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total duration (days)</td>
<td>-0.09 (0.45)</td>
<td>-0.12 (-0.99, 0.73) (0.77)</td>
<td>0.03 (0.81)</td>
<td>0.35 (-0.32, 1.01) (0.31)</td>
<td>0.27 (-0.20, 0.73) (0.26)</td>
<td>0.47 (-0.014, 0.94) (0.05)</td>
</tr>
<tr>
<td>Total cumulative dosage (mg)</td>
<td>-0.10 (0.39)</td>
<td>-0.22 (-1.47, 1.02) (0.72)</td>
<td>-0.04 (0.74)</td>
<td>0.32 (-0.66, 1.29) (0.52)</td>
<td>-0.14 (-0.82, 0.54) (0.68)</td>
<td>0.08 (-0.59, 0.76) (0.81)</td>
</tr>
<tr>
<td>Total cumulative dosage (mg.kg^-1)</td>
<td>-0.12 (0.32)</td>
<td>-0.34 (-1.62, 0.93) (0.59)</td>
<td>-0.07 (0.59)</td>
<td>0.31 (-0.69, 1.32) (0.54)</td>
<td>-0.22 (-0.92, 0.48) (0.53)</td>
<td>-0.013 (-0.7, 0.72) (0.97)</td>
</tr>
</tbody>
</table>

*ND* neurodevelopmental delay, defined as having MDI or PDI < -1SD, CP, hearing or visual impairment.

1 Continuous variable (MDI, PDI): Pearson correlation (p value). 2 binary variable (MDI < -1SD, PDI < -1SD, ND, death or ND): mean difference, 95% confidence interval (p value).
ductus arteriosus, BPD and postnatal steroid use, and were ventilated and hospitalized longer. There was no difference in the incidence of necrotizing enterocolitis (NEC), gastrointestinal hemorrhage or IVH between the groups. As shown in Table 1, the median duration of doxapram therapy and the cumulative dosage was 6 days and 125 mg.kg⁻¹, respectively.

The postmenstrual age at follow-up was similar in both groups (24.0 ± 2.4 vs. 24.3 ± 2.4 months), and there were no differences in weight, length and head circumference. The mean MDI and PDI were similar in the doxapram group compared to the nontreated group (MDI: 99.3 ± 15.5 vs. 97.4 ± 13.8, and PDI: 95.4 ± 14 vs. 94.3 ± 11.4, respectively). There were no infants with a hearing impairment in either group, and only one infant with visual impairment (doxapram group). Univariate analysis of infants with an MDI/PDI < -1 SD, CP, visual impairment, and the combined outcome NDI showed no significant differences between both groups (Table 2). However, there was a significant reduction of the combined outcome death or ND in favor of the doxapram group (odds ratio (OR) = 0.58, 95% CI 0.41, 0.83).

Repeating this analysis with correction for possible confounders (GA, BPD, SGA, IVH, postnatal steroids and sepsis) resulted in a clear trend towards a beneficial effect of doxapram on MDI < -1 SD (OR = 0.35, 95% CI 0.12, 1.02) and ND (OR = 0.53, 95% CI 0.28, 1.02). This correction did not impact the beneficial effect of doxapram on the combined outcome death or ND (OR = 0.54, 95% CI 0.37, 0.78). No changes of the point estimates were seen, putting the variable center into the equation. The sensitivity analyses, in which infants in the doxapram group who were lost to follow-up were labeled as having ND and all nontreated infants as normal, revealed no significant differences in ND between the groups. As shown in Table 3, no correlation was found in the cumulative dose, the duration of therapy and the MDI/PDI, or the combined outcomes ND, or death or ND in the treated group.

**DISCUSSION**

To our knowledge, this is the largest study exploring the effect of doxapram on neurodevelopmental outcome in preterm infants. Our main finding is that doxapram is not associated with an increased risk of the combined outcome death or ND at a corrected age of 24 months. In fact, our study suggests that doxapram might have a positive effect on this outcome.

The effect of doxapram on ND was corrected for possible confounders, as the characteristics of the doxapram-treated and nontreated infants were clearly different. The increased incidence of short-term morbidity in the doxapram-treated patients was most likely due to the fact that these infants had a lower GA as shown by regression analyses.
correcting for BPD, patent ductus arteriosus and ventilation days for GA. This clearly showed that doxapram use was confounded by indication and should be controlled for by performing a multiple regression analysis. This analysis resulted in a nonsignificant reduction in the OR for outcome ND attributed to the effects of doxapram treatment. Looking at the different components of this combined outcome, this effect was mainly due to a reduction in the number of infants with an MDI < -1 SD. These results are in contrast with two previously published reports. Sreenan et al.\textsuperscript{11} performed a cohort study comparing 40 preterm infants with an MDI < 70 to matched controls with an MDI > 85 at a corrected age of 18 months. The authors reported an association between the total dose and duration of doxapram therapy and mental delay. Although the controls were matched for some possible confounders, important factors such as BPD or prolonged ventilation were not taken into account\textsuperscript{21,22}. Lando et al.\textsuperscript{12} found a negative effect of doxapram treatment on developmental outcome in 53 preterm infants. Again, this study did not correct for the potential confounders BPD and duration of mechanical ventilation. Furthermore, development was assessed via a structured telephone interview, which can only be used as a screening tool. These studies, similar to the present study, are at risk for confounding by indication. However, the methodology used in the present study allows adjusting this risk by correction for known confounders, which makes the results not only more accurate, but also more valid.

Although selection bias in the nontreatment group is unlikely considering the overall mortality rate during the study period (16.8%), our finding that mortality was significantly less in the doxapram-treated group needs to be interpreted with extreme caution. A possible explanation for this finding could be that infants not receiving doxapram died earlier during the course of their hospitalization. It is unclear if doxapram might have a direct effect on mortality and if so by what mechanism. Therefore, this finding needs to be confirmed by future studies before drawing any conclusions. The reduction in mortality in the treated group is, however, important when interpreting our finding on ND. It shows that the reduction in NDI in the doxapram-treated group is not caused by an increased mortality.

Many clinicians are reluctant to use doxapram in preterm infants because of possible gastrointestinal side effects\textsuperscript{7,8}. In line with previous reports, we did not observe more cases of NEC or spontaneous intestinal perforation in the doxapram group\textsuperscript{5,9}. Future studies need to assess if this is also true for other gastrointestinal side effects, such as feeding intolerance and abdominal distension.

This study has several limitations that need to be addressed. First, because of the retrospective nature, the pediatricians and psychologists were not blinded to the medical history. Second, the number of infants lost to follow-up for long-term neurodevelopmental assessment was substantial in the nontreated control group. To ensure that this did not conceal a potential adverse effect of doxapram on MDI and ND, we reanalyzed our
data after imputing outcomes in those infants who were lost to follow-up. Those in the
doxapram group were imputed with an abnormal outcome, whereas those not treated
were imputed as normal at follow-up. Even in this unlikely situation, the analyses did not
show a significant adverse effect of doxapram on neurodevelopmental outcome. Third,
during the study period, respiratory management in the delivery room and the intensive
care unit became increasingly noninvasive over time. Although there is no evidence
suggesting these changes have an impact neurodevelopmental outcome, potential
bias cannot be ruled out. This risk was minimized as much as possible by selecting the
nontreated controls over the exact same study period and separately for each including
hospital. Finally, we did not correct the logistic regression analyses for the variables cPVL
and maternal education. This may have affected the results of our study, although the
impact is probably limited as the incidence of cPVL was extremely small and similar in
both groups. Unfortunately, information on maternal education was not available in this
study. This may have confounded our results.

The present study has important implications for clinical practice and research. De-
spite the lack of convincing evidence of efficacy and the concerns on adverse effects,
doxapram is increasingly being used in daily clinical practice5–22. The results of this study
seem to be reassuring in terms of adverse effect, as they show no increase in short-
term gastrointestinal complications and long-term ND. However, these findings need
to be confirmed or refuted by an adequately powered, double-blinded and placebo-
controlled randomized controlled trial with long-term neurodevelopmental outcome as
the primary outcome.
REFERENCES


