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Functional outcome at school age of preterm-born children treated with low-dose dexamethasone in infancy


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ABSTRACT

Background: Surviving preterm born children, postnatally exposed to high doses of dexamethasone, show an increased risk of neurodevelopmental impairments. Regarding treatment with low doses of dexamethasone, no data exist on outcomes at school age.

Aim: To assess the functional outcome at school age of preterm-born children treated with low-dose dexamethasone.

Study design: In this cohort study, twenty-seven very preterm-born infants treated with dexamethasone from eight days after birth, underwent neuropsychological assessments at age 6–13 years. Their scores were compared with those of the norm population, and scores on total IQ and motor functioning also with those of a preterm reference group, using one-sample-chi-square and student’s t-tests.

Results: Compared with the norm population, performance of dexamethasone-treated children was poorer, particularly in the motor domain (mean z-score −1.81). Dexamethasone-treated children also had lower scores on IQ (−0.29 to −1.12), verbal memory (−0.41 to −0.56), attention (−0.90 to −1.28), and word generation (−0.75). Their parents reported behavioral problems more often. Compared with preterm peers, motor skills remained poor, but total IQs were similar. Adjustment for bronchopulmonary dysplasia did not change our results, because all surviving children had bronchopulmonary dysplasia.

Conclusions: At school age, the prevalence of adverse motor, cognitive, and behavioral outcomes of preterm-born children treated with low-dose dexamethasone is increased. This could be the consequence of either dexamethasone or BPD.

1. Introduction

Bronchopulmonary dysplasia (BPD) is a major cause of long-term pulmonary and neurodevelopmental morbidity in preterm infants [1]. Since 1990, many preterm infants at risk of BPD were treated with high doses of dexamethasone (DXM), starting with ≥0.5 mg/kg/day [2]. This treatment strategy facilitated extubation and reduced the incidence and severity of BPD as well as neonatal mortality [3,4]. Nevertheless, subsequent concern about the potential adverse effects on neurodevelopmental outcomes in children who had been exposed to early and high doses of DXM, contributed to the 2002 recommendation of the American Academy of Pediatrics against using DXM routinely [5]. Even though its use has declined since then, very low birth weight infants are still frequently treated with DXM [6]. Lower doses seem to be equally effective in facilitating earlier extubation [7]. The optimal dose to reduce the severity of BPD is, however, unknown [8,9]. Studies investigating neurodevelopmental outcomes after low-dose DXM are scarce [8,10,11] and, to our best knowledge, nothing is known about its effect on neurodevelopmental outcomes at school age.

The first aim of our study was therefore to assess motor, cognitive, and behavioral outcomes at school age of preterm-born children who were treated with low-dose DXM for pulmonary problems, adjusted for the presence of BPD. Our second aim was to assess whether cumulative DXM doses, longer treatment duration with DXM, starting DXM treatment later (postnatal days), or longer duration of mechanical ventilation, were risk factors for poor outcomes.

2. Materials and methods

2.1. Study design and participants

Our design was a retrospective observational cohort study. From our
NICU patient database, we selected all infants born before 32 weeks' gestation who had been admitted between 2002 and 2008 and who had been given DXM, starting with a dose of 0.25 mg/kg/day, for the prevention or treatment of BPD. Treatment indications per protocol were ventilator-dependency after the seventh postnatal day in preterm infants with signs of BPD seen on chest radiography with a Ventilation Efficiency Index (MAPFiFO2) of > 4, and in whom weaning stagnated despite optimal supportive therapy. We excluded infants with major congenital anomalies as well as infants with tracheostomy, because of its influence on functional outcomes independent of DXM treatment.

The presence of BPD was defined as treatment with supplemental oxygen or continuous positive airway pressure (CPAP) at 36 weeks' postmenstrual age. Cerebral pathology was determined using cranial ultrasound. In accordance with our treatment protocol DXM was administered after the first postnatal week. The starting dose was 0.25 mg/kg/d for three days. On the fourth day, the attending neonatologist decided to continue DXM treatment in a tapering course of either 6 days (amounting to a total dose of 1.125 mg/kg) or 14 days (amounting to a total dose of 2.075 mg/kg). Depending on the clinical condition of the individual patient, the course was sometimes prolonged or shortened. For the purpose of this study we reviewed the medical charts for neonatal characteristics, cumulative doses, the age at which DXM treatment started, and treatment duration.

2.2. Follow-up

When the children had reached the age of 6 to 13 years we invited the parents and the children who met the inclusion criteria to take part in the extension of our NICU follow-up program. This program consisted of an array of neuropsychological tests and questionnaires. Parents gave their written consent prior to taking part in the extension of the follow-up program. The study was approved by our local Medical Ethical Committee of the University Medical Center. The parents of children with severe functional limitations, i.e. Level 3 or more on the Gross Motor Function Classification System (GMFCS), were invited to only complete the questionnaires. Their children were not required to do the neuropsychological tests.

Motor outcome was assessed with the Movement Assessment Battery for Children (Movement ABC). Total, verbal, and performance intelligence were assessed using a shortened version of the Wechsler Intelligence Scale for Children, Third edition, Dutch version (WISC-III). We assessed verbal memory with a standardized Dutch version of Rey’s Auditory Verbal Learning Test (AVLT) that tests immediate recall of words (learning capacity), delayed recall (long-term memory), and delayed recognition [12]. Selective attention was assessed with the subtest Map Mission and attentional control with the subtest Opposite Worlds of the Test of Everyday Attention for Children, Dutch version (TEA-Ch-NL) [13]. To assess the visual perceptual ability we used three subtests of the Test of Visual and Perceptual Skills (TVPS): Visual Discrimination, Form Constancy, and Visual Closure [14]. Language was assessed with the subtests Comprehension of Instructions, Speeded Naming, and Word Generation of the Developmental Neuropsychological Assessment test, Second edition (NEPSY-II-NL) [15]. Visual-motor deficits were assessed with the Beery-Buktenica Developmental Test of Visual-Motor Integration (BEERY-VMl) [16]. For all the tests administered, we excluded the scores obtained if, according to the trained and experienced investigators, a child had been inattentive or too tired to perform adequately.

We obtained information on the children’s behavioral and emotional competence and problems with the parental version of the Child Behavior Checklist (CBCL) and the parental version of the Behavior Rating Inventory of Executive Functioning (BRIEF) Questionnaire [17]. Information about the child’s attentional functioning in daily life was obtained with the Attention Deficit Hyperactivity Disorder Questionnaire (AVL) [18].

2.3. Data and statistical analysis

We used descriptive statistics summarizing continuous variables using medians and interquartile ranges. Percentages and absolute numbers are reported for categorical variables. We used the criteria in the test and questionnaire manuals to determine standard scores, percentiles, t scores, as appropriate. For each test we calculated the z scores from the percentiles, standard scores, and t scores.

We also classified the test scores as normal, borderline, or abnormal. For IQs, normal was an IQ of 85 or more, borderline was an IQ of 70 to 84, and abnormal was an IQ of < 70. We classified the results on the other cognitive tests into normal (≥ −1 SD), borderline (−1 SD to −2 SDs), or abnormal (< −2 SDs). We used the percentiles on the standardization samples of the Movement ABC to classify raw scores into normal (≥ P 15), borderline (P 5 to P 14) and abnormal (< P 5). For the AVL and CBCL, we used a similar classification following the criteria in the manuals.

Next, we used the one sample chi-square test to compare the z scores of the study group with the norm scores of the general population. To compare the outcome on total IQ, Movement ABC and CBCL with a preterm reference group, we used adapted cut-off points using Cohen’s d statistic as reported in three meta-analyses [19–21].

To relate motor, cognitive, and behavioral outcomes to DXM-related risk factors we used the Mann-Whitney test. We were not able to adjust for BPD, as this was present in all the DXM-treated children. P < .05 was considered to be statistically significant. We used SPSS for Windows, Version 23 (SPSS Inc., Chicago, IL, USA) for the analyses.

3. Results

Between 2002 and 2008, 1320 patients born before 32 weeks’ gestational age were admitted to our NICU, 56 (4.2%) of whom had been treated with DXM. Seventeen died during the neonatal period; two infants had major congenital anomalies and two infants required tracheostomies because of glottic stenosis due to trauma related to prolonged endotracheal intubation. Of the remaining 35 patients, eight could not be included for various reasons (Fig. 1). Eventually, 27 children were included in this cohort. Of them, one could not be tested because of a severe eyesight handicap. Two children with a GMFCS ≥ 3 were not tested, but we classified them as abnormal on the Movement ABC.

Table 1 provides an overview of the patient characteristics. No baseline differences were detected between DXM-treated children who participated and the eight survivors who did not (median gestational age 27.50 weeks, birth weight 830 g). For six patients information on mothers’ level of education was not obtained. Age at follow-up ranged from 6 to 13 years, median 9 years. Information about education was obtained for 25 children. Five of them required special education. Ten children had repeated a class. Seven children had developed CP of whom three were classified as GMFCS Level 1, two as GMFCS Level 2, and two as GMFSC Level 5. One child was too tired to complete the Movement ABC. In the speeded naming test, one child was excluded because of his young age, and another child could not complete the speeded naming test because he did not yet know several letters.

Table 2 contains the scores on the tests with the concomitant z scores. Particularly total Movement ABC scores were poorer in DXM-treated children compared with both the norm population and preterm peers. Total, verbal, and performance IQs were normally distributed in our study population. Mean (SD) total IQ was 89 (17), mean verbal IQ was 96 (17) and mean performance IQ was 82 (20). The z scores of total and performance IQ, verbal long-term memory, attention, and word generation all were lower than the norm group. When compared with preterm peers the z scores of total IQ did not differ. The z scores of the behavioral questionnaires that were completed by the parents were not significantly different from the norm population. There was no difference regarding internalizing and externalizing problems between our
Fig. 1. Flow chart of dexamethasone-treated children who were included for follow-up at school age.

Table 1
Clinical characteristics of DXM-treated children.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DXM-treated N = 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys/girls</td>
<td>14/13</td>
</tr>
<tr>
<td>Twin pairs</td>
<td>9 (33.3%)</td>
</tr>
<tr>
<td>Gestational age (GA) (weeks)</td>
<td>26.71 (25.57–27.29)</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>830 (750–960)</td>
</tr>
<tr>
<td>IUGR (birth weight &lt; P 10)</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Apgar score at 5 min</td>
<td>7 (5–9)</td>
</tr>
<tr>
<td>Patent ducus arteriosus</td>
<td>20 (74.1%)</td>
</tr>
<tr>
<td>Late-onset morbidity</td>
<td></td>
</tr>
<tr>
<td>Late-onset sepsis (positive blood culture)</td>
<td>12 (44.4%)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Retinopathy of prematurity (≥ Grade II)</td>
<td>9 (33.3%)</td>
</tr>
<tr>
<td>BPD (O2 at 36 weeks’ PMA)</td>
<td>27 (100%)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (days)</td>
<td>37 (23–51)</td>
</tr>
<tr>
<td>Cerebral pathology</td>
<td></td>
</tr>
<tr>
<td>No cerebral pathology</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>PVE &gt; 7 days</td>
<td>13 (48.1%)</td>
</tr>
<tr>
<td>Mild (GMH-IVH Grade I or II)</td>
<td>9 (33.3%)</td>
</tr>
<tr>
<td>Severe*</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Prenatal corticosteroids</td>
<td>25 (92.6%)</td>
</tr>
<tr>
<td>Treatment duration (days)</td>
<td>8.50 (6.00–14.00)</td>
</tr>
<tr>
<td>Postnatal day DXM started</td>
<td>24 (19–32)</td>
</tr>
<tr>
<td>Gestational age DXM started (wk)</td>
<td>30.43 (28.72–32.00)</td>
</tr>
<tr>
<td>Cumulative DXM dose (mg/kg)</td>
<td>1.35 (1.13–2.08)</td>
</tr>
<tr>
<td>Mothers level of education</td>
<td></td>
</tr>
<tr>
<td>&lt; 11 years</td>
<td>3 (14.3%)</td>
</tr>
<tr>
<td>12 to 13 years</td>
<td>5 (23.8%)</td>
</tr>
<tr>
<td>&gt; 14 years</td>
<td>13 (48.1%)</td>
</tr>
</tbody>
</table>

Data are given as numbers (percentages) or median (25th to 75th percentiles). IUGR, intra-uterine growth restriction; PVE, periventricular echodensities; GMH, germinal matrix hemorrhage; IVH, intraventricular hemorrhage. * Grade III GMH-IVH, periventricular hemorrhagic infarction, post hemorrhagic ventricular dilation (lateral ventricle size > 0.33 according to Evans’ index), and cystic periventricular leukomalacia.

cohort and the preterm reference group.

We present the proportions of children with normal, borderline, and abnormal scores in Table 3. In particular motor function, attention, and IQ were affected. Of the DXM-treated children, 18 out of 25 had abnormal total scores on the Movement ABC, with most problems encountered on balance. Regarding IQ, more DXM-treated children had abnormal total and performance IQs than the norm population (P < .001 for both). As for the other cognitive tests, the performance of DXM-treated children on verbal long-term memory, selective attention, attentional control, form constancy, word generation, and visuomotor integration was abnormal significantly more often compared to the children belonging to the norm population.

Parents of DXM-treated children also reported significantly more behavioral problems on the CBCL than did the parents of the norm population. Of the DXM-treated children, four out of 27 were in the abnormal range for total behavior (P < .001, Table III), eight for internalizing problems (P < .001), and three for externalizing problems (P = .001). The parents did not report more problems on the BRIEF than did parents of the norm group. On the AVL, four out of 27 children fell in the abnormal range for total ADHD score, as well as for attentional problems, hyperactivity, and impulsivity (all P = .019).

As all of the DXM-treated children had BPD at 36 weeks’ post-menstrual age, adjusting our analyses for BPD did not change our results. Starting DXM treatment later and longer duration of mechanical ventilation, were associated with abnormal visuomotor integration (P = .029 and P = .007, respectively). Longer treatment duration with DXM was associated with abnormal hyperactivity in the AVL (P = .034). Higher cumulative doses of DXM were not associated with any abnormal test results.

4. Discussion

We found that at school age, children who had been treated with low-dose DXM in infancy obtained lower scores on motor skills, performance and total IQs, and attention. Their scores were three quarters to nearly 2 SDs below the norm. Memory and language were also affected, but less so. On these skills they scored approximately one half SD below the norm. Parents’ reports on behavioral problems also revealed scores of around one third lower than the norm, with the exception of externalizing behavioral problems and executive functioning. In comparison to their preterm peers, motor functioning was still considerably poorer at school age, but scores on total IQ did not differ from the preterm reference group. Longer treatment duration with DXM, starting DXM treatment later and longer duration of mechanical ventilation were all associated with a poorer outcome on a single item, but not on overall outcome. All children developed BPD.

We had not expected such large numbers to score so poorly in several domains. Several studies reported that high doses of postnatal steroids are associated with an increased risk of neurodevelopmental impairments, especially motor impairments [4,22–24]. To the best of our knowledge, however, there are only a few studies on the use of low-dose DXM and none report any significant abnormal neurological outcomes [10,11,25]. Of note, all these studies concerned children who had been tested only at pre-school age. Compared with children treated with high doses of DXM, McEvoy et al. found no difference in neurodevelopmental outcome at the corrected age of one year in children treated with low doses, whereas Hitzert et al. found normal neurodevelopment at the age of 12 to 36 months in the majority of children treated with low-dose DXM [10,25]. The Dexamethasone: A Randomized Trial (DART) study [11] showed no significant differences between low-dose DXM treatment and placebo in the mental developmental index (MDI), psychomotor developmental index (PDI), and rate of CP at the age of two years. In this study, however, the chances of finding substantial harmful effects were slim, given the fact that the study had to be abandoned after only 10% of the target sample size had been recruited.
We offer several explanations for the poor performance of our children. First, following the recommendations regarding the use of DXM in 2002 [5], much stricter criteria applied to commencing DXM treatment, if at all. Only 4.3% of our 1320 subjects received DXM. Undoubtedly therefore the children in the low-dose DXM group were more severely ill than the children treated before 2002 with high-dose DXM. This implies that our population had a higher risk of poor outcomes due to factors besides the low-dose DXM treatment. This suggestion is emphasized by the high mortality rate (30%) and the fact that all of the surviving children in our cohort developed BPD, which itself is associated with negative neurocognitive outcomes [26]. The increased illness severity is also suggested by the relatively high rate of neonatal sepsis (44.4% versus 22% reported in literature [27]). Neonatal sepsis is also associated with poor neurodevelopmental outcome in early childhood [28].

Second, despite their origin early in life, the functional implications of motor problems may become clearer at school age when children have to cope with more complex tasks. Third, to a certain extent the poorer outcome for overall cognitive performance could result from poor motor performance, because adequate locomotion is required for proper cognitive functioning. It may also result from abnormal attentional problems in children as associated with postnatal exposition to DXM [29], but they may also be due to very preterm birth in itself [21].

There are indications that attentional problems in children are associated with negative neurocognitive outcomes [26]. The increased illness severity is also suggested by the relatively high rate of neonatal sepsis (44.4% versus 22% reported in literature [27]). Neonatal sepsis is also associated with poor neurodevelopmental outcome in early childhood [28].

Contrary to what we expected on the basis of our test results, only a few parents reported abnormal executive functioning. This finding differed from reports in the literature, as it is well-documented that preterm-born children are at greater risk of abnormal executive functioning [30]. The same is true for the results of the AVL, which contrast with the results of the TEA-Ch. We are unable to offer a good explanation for this observation. Possibly the parents reported fewer
problems because they had become used to certain difficulties in their children's behavior. Perhaps they took their child's preterm birth into account, while not recognizing the difficulties as constituting a problem for their children. The results might have been different if we had actually tested executive functions, similar to our contrasting results between the TEA-Ch and the AVL.

Regarding the CBCLs, considerably more children obtained abnormal scores, especially on internalizing problems. This is in line with the findings of Aarnoudse-Moens et al. who compared 4125 very preterm infants and/or very low birth weight infants with 3197 term-born controls and showed that regarding behavioral sequelae, especially attention and internalizing problems were cause for concern [21].

Except for the cumulative doses of DXM, each of the DXM-related risk factors (longer treatment duration, longer duration of mechanical ventilation or starting DXM treatment later) was a risk factor for poor performance on a single item. None were associated with overall poor performance. The median postnatal day at which DXM was provided was day 24 (19 to 32 days), which is relatively late. Contrary to earlier findings [31,32], the most recent Cochrane review [9] reported that delaying treatment, that is starting after 21 days postnatal age, compared to early and moderate early initiation of therapy, showed no difference in mortality, BPD, or long-term neurodevelopmental sequelae, including CP. In our study, delaying DXM treatment was only associated with abnormal visuomotor integration.

A dose-related effect of DXM on neurodevelopment at age 18 to 22 months was found by the National Institute of Child Health and Human Development (NICHD) network benchmarking study on extremely low birth weight (ELBW) infants [32]. This study showed that each additional 1 mg/kg of DXM was associated with a 2-point reduction in the Mental Developmental Index score and a 40% increase in disabling CP. This could imply that even low-dose DXM therapy could have influenced neurodevelopment. In our population, however, we could not replicate that a higher cumulative dose of DXM was associated with abnormal test results. This supports our speculation that DXM may not have any relationship to poorer neurodevelopmental outcome in our population.

In our opinion, the most likely explanation for the absence of a dose-related effect in our study, is that the potential side-effects of the DXM are negligible compared with those of BPD, which was highly prevalent in our population. Doyle et al. [33] conducted a meta-regression analysis of 24 RCTs of postnatal steroid therapy that included 1721 infants. They showed that in those studies where the risk of BPD in the control group at study entry was above 65%, the risk of BPD-associated CP would be higher than the risk associated with postnatal steroid therapy. Conversely, when the risk of BPD was low, postnatal steroid therapy was associated with greater risk than the disease.

The strength of our study was the broad array of motor, cognitive, and behavioral tests. We also recognize several limitations. First, we studied a small number of infants, which was due partly to the decline in use of DXM.
since 2002 and partly to a 20% refusal to participate in the follow-up. This makes it difficult to correct for any other factors that might relate to child outcomes. Second, we did not perform the complete battery of neuropsychological tests in severely disabled children in our follow-up. Our results regarding the poor outcomes on several neuropsychological domains could therefore have been underestimated. Third, we compared our population not only with the norm-population but also with a preterm ‘norm-group’ based on several meta-analyses. We chose this strategy because first, these results are more robust to compare our findings with, and second, a retrospectively composed preterm control group would easily create a selection bias, for example regarding disease severity. We acknowledge, however, that this remains a second best choice.

Our study might have implications. First, it underlines the importance of long-term follow-up of DXM-treated, preterm-born children, not only to detect motor impairments but cognitive and behavioral problems as well. Second, as we cannot rule out a direct effect of DXM on neurodevelopmental impairment, there is an urgent need for an alternative that reduces BPD equally well, but with fewer potential neurodevelopmental side-effects. Hydrocortisone may be such a strategy. So far, existing data are insufficient to make any recommendation. Nevertheless, a randomized, double-blind, placebo-controlled multicenter study including 400 very low birth weight infants is underway, including a two-year follow-up of each child [34]. Meanwhile, perhaps we should be less reluctant to start DXM treatment when the risk of BPD is high.

To conclude, our study demonstrated that at school age a large proportion of preterm-born children who had been treated with low-dose DXM in infancy had an increased risk of adverse motor, cognitive, and behavioral outcomes. Compared to their preterm peers, they have an increased risk of adverse motor outcome in particular, but not regarding total IQ. The question remains whether these poor outcomes are a direct effect of DXM, or whether they are the result of the underlying disease severity, BPD in particular.

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Conflict of interest

The authors declare that they have no conflict of interest.

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