Routine Morphine Infusion in Preterm Newborns Who Received Ventilatory Support
A Randomized Controlled Trial

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Morphine has been one of the most frequently used drugs to relieve pain in many age groups. Nevertheless, debate continues about whether morphine and analgesic therapy should serve as standard of care for preterm newborns who have received ventilatory support,1 despite the recognition that all preterm neonates feel pain.

Lack of a gold standard to assess neonatal pain, fear of adverse effects, and uncertainty about the long-term effects of opioids in the neurodevelopmental outcome of newborns contribute to this clinical conundrum. Although numerous neonatal pain instruments have been validated on models of acute pain,2 it is difficult, therefore, to measure the analgesic effect of morphine in neonates. Suggested adverse effects of morphine are hypotension,3-6 sei-
zures,7 bradycardia, decreased gastrointestinal motility,8 intestinal obstruction, urinary retention, and respiratory depression.9,10 Although a few long-term effects of neonatal morphine exposure have been suggested from animal studies,11-13 the effects seem to be minimal at 5 to 6 years in a cohort of former preterm infants.14 On the other hand, morphine administration may decrease morbidity, such as intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL).15 We hypothesized that continuous morphine infusions may improve outcomes and diminish pain responses of nonsurgical neonates who have received ventilatory support in stressful conditions. Furthermore, repeated pain exposure may cause hypersensitivity and lower pain threshold in preterm neonates,16-20 and morphine administration might protect preterm neonates from the harmful effects of pain on their short- and long-term outcomes.21,22

Consensus statements on the analgesic treatment of neonatal pain23,24 have suggested the use of continuous opioid infusions for preterm neonates who have received ventilatory support. Studies25-28 investigating intravenous opioids in neonates who have received ventilatory support do not provide conclusive evidence. Therefore, double-blind randomized controlled trials have been suggested as a means to resolve the uncertainty over whether and when to administer analgesics to critically ill neonates.1,20

Based on the protocol of a multicenter trial (NEOPAIN study [Neurologic Outcomes and Pre-emptive Analgesia In Neonates]), we performed a randomized, double-blind, placebo-controlled trial to evaluate the effect of continuous intravenous morphine infusion on pain responses, the incidence of IVH, and poor neurologic outcomes (severe IVH, PVL, or death) in preterm neonates who had received ventilatory support. We tested the hypothesis that continuous morphine administration in neonates who had received ventilatory support would reduce both the degree of pain experienced and the incidence of poor neurologic outcome and IVH (all grades).

METHODS

Patients

All neonates admitted to the neonatal intensive care unit (NICU) who required mechanical ventilation were eligible for inclusion. Other inclusion criteria were postnatal age younger than 3 days, artificial ventilation for less than 8 hours, and indwelling (peripheral or umbilical) arterial catheter. Excluded were neonates with severe asphyxia (Apgar score after 5 minutes of <4 or cord blood pH <7.0),30 severe IVH (grade III or IVH plus apparent periventricular hemorrhagic infarction), major congenital malformations and facial malformations (eg, cleft lip and palate), neurologic disorders, or receiving continuous or intermittent neuromuscular blockers.

Patients were recruited from 2 level III NICUs in the Netherlands: Erasmus MC-Sophia, Rotterdam (center 1), a university hospital, and the Isala Clinics in Zwolle, a nonuniversity hospital (center 2). Seventy-four percent of neonates admitted to the NICUs were born in the study hospital. The local ethics committees of the participating centers approved the study protocol.

The parents of eligible patients were asked to give written informed consent within 8 hours after endotracheal intubation. If possible, parents were informed about the study before the birth of their child. If consent was refused, information about morphine use of the patient involved was collected retrospectively and compared with information on the participants. Data from nonenrolled patients were not incorporated into other outcome analyses or pooled with that from any other patients. Enrolled patients were randomly allocated to receive a loading dose (100 µg/kg) followed by a continuous infusion (10 µg/kg per hour) of either morphine hydrochloride or placebo (sodium chloride), both dissolved in 5% glucose. To prevent possible overdosing, the study medication loading dose was not given if a preintubation morphine loading dose had been given less than 3 hours before the start of the study. The use of masked study medication was continued for 7 days or less, as required by the patient’s clinical condition. After 7 days, study medication was weaned and stopped or replaced by open-label morphine infusion.

If patients from either group were judged to be in pain or distress during masked study medication use, they were given additional morphine based on decisions of the attending physician (independent of the study). Allowed additional doses were 50 µg/kg followed by 5 to 10 µg/kg per hour of continuous open-label morphine.

Outcomes

Primary outcomes were defined as the analgesic effects of morphine, assessed by validated pain measurement instruments at baseline, before study medication, 30 minutes after the loading dose, and twice daily at a standardized time point before, during, and after endotracheal suctioning. At each time point, we videotaped the infants for 2 minutes with 2 cameras: one obtaining a whole-body image and the other focused on the patient’s face. Simultaneously, the caregiving nurse applied the visual analog scale (VAS) for pain at bedside. The VAS score ranges from 0 to 10 on a horizontal, continuous line with “no pain” on the left and “extreme pain” on the right; observers indicated the level of pain by marking the line. All nurses had been trained to assess neonatal pain. The videotapes were analyzed afterward using the Neonatal Infant Pain Scale (NIPS)31 and the VAS during all moments and the Premature Infant Pain Profile (PIPP)32 during suctioning. Videotapes were assessed by 2 researchers (N.J. and S.H.P.S) with acceptable interrater reliability (intraclass correlation coefficient of 0.70 and 0.73 for the NIPS and PIPP, respectively, and 0.67 for the VAS score).

Secondary outcome measures were poor neurologic outcome defined as severe IVH, PVL, or death within 28 days and the incidence of all grades of IVH.
Other clinical outcome measures were also compared between the morphine and placebo groups, including duration of artificial ventilation, length of NICU stay, incidence of comorbidity, and number of painful procedures. Regarding duration of artificial ventilation, we distinguished between the first ventilation period (including further periods of ventilation if the infant was extubated in between for <24 hours) and the second ventilation period (all further periods of artificial ventilation, after extubation for >24 hours). During the first 14 days of a patient’s NICU admission, we recorded all painful procedures.

A power analysis showed that 75 patients per group were needed to achieve a medium effect size (Cohen $d=0.55$), with an $\alpha$ error of .05 (2-tailed) and a power of 90%. Neonates had an equal probability of being assigned to either condition. The randomization code was developed using a computer random-number generator to select random permuted blocks. These blocks of 10 were stratified into 5 groups of gestational age ranges (<27, 27-30, 31-33, 34-36, and ≥37 weeks) to obtain a balanced number of infants within each stratum.

Using the computer-generated randomization list, independent pharmacists placed ampules of either 1 mL of morphine hydrochloride or 1 mL of placebo into boxes. These boxes were numbered with the study numbers and stored with increasing numbers for the different gestational age groups in a locked closet accessible only to the researchers. At a patient’s enrollment, the next box in line for the specific group was taken out by one of the researchers. All research and clinical staff, as well as the parents of the infants, were blinded to treatment.

**Statistical Analyses**

Data were analyzed using SPSS statistical software version 10.1 (SPSS Inc, Chicago, Ill). Nonparametric tests were used and results are shown as medians and interquartile ranges (IQRs) when variables deviated from the normal distribution. Background characteristics between the 2 treatment groups were compared using nonparametric Mann-Whitney $U$ tests or Fisher exact tests (in case of low incidences). Characteristics of the nonparticipating patients were compared with data from study infants using Kruskal-Wallis tests.

**Pain Scores.** Multiple regression analyses were performed with VAS-bedside and NIPS (scored 30 minutes after study medication loading dose) as outcome variables predicted by treatment group, having received a morphine dose before intubation, gestational age, Clinical Risk Index for Babies (CRIB) score, center, sex, and postnatal age in hours corrected by the pain score before the bolus was given. Pain scores were log 10 transformed to approximate a normal distribution.

Across all assessments, mean PIPP, NIPS, and VAS scores, scored during endotracheal suctioning, were calculated for each patient and used as outcome variables in multiple regression analyses. Summary statistics (mean scores for each patient) were used to increase reliability and to take repeated measures into account during analyses. Predictors were treatment group, mean amount of additional morphine, center, sex, and duration in study. The importance of the predictors is shown by unstandardized coefficients.

**Clinical Outcome.** Logistic regression analyses were used with poor neurologic outcome (death within 28 days, IVH grade III or IVH plus apparent periventricular hemorrhagic infarction, and/or PVL) and IVH (all grades) as outcome variables; treatment condition and additional morphine use as predictor variables; and center, gestational age, sex, CRIB score, deviation from mean birth weight for gestational age,33 prenatal corticosteroid use, preeclampsia and/or HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, and the use of indomethacin as covariates.

Collinearity for the logistic regression analyses was checked by performing a multiple regression analysis instead of the logistic regression analyses to calculate the variance inflation factors, which were all well below 2.0. The same was true for the multiple regression analyses. The risk of overfitting was controlled by using a ratio of 1:10 at least for the number of explanatory variables and sample size. To assess overfitting more precisely, the patients in these 2 groups were split into deciles. To cross-validate, the training sample was composed of 9 of the 10 deciles; the validation sample contained the remaining decile. The predicted values for the remaining decile were obtained by the parameters of the logistic regression analysis performed on 9 of the other deciles. This procedure was repeated 10 times because each decile functioned as a validation sample. The overall mean obtained from the 10 mean values and the pooled SD derived from the 10 SDs of the validation samples for each condition separately were compared with the overall mean and SD of the predicted values of the total sample. A high level of agreement between the overall solution and the cross-validation samples indicates high stability. Stepwise procedures were used.

Comorbidity (eg, chronic lung disease, necrotizing enterocolitis, duration of artificial ventilation) was compared using the Mann-Whitney $U$ test and Fisher exact test. Missing values were excluded listwise during all analyses in the sense that all cases that had any values missing on any of the variables used in the analyses were excluded. In all analyses, the intention-to-treat principle was used and involved all included infants who were randomly assigned to the morphine and placebo groups.

**RESULTS**

A total of 210 infants were eligible between December 2000 and October 2002; the parents of 60 newborns refused informed consent and 150 were randomized (FIGURE). The percentage of nonenrolled patients was 36% in center 1 ($n=51$) and 13% in center 2 ($n=9$). Seventy-three patients were allocated to receive continuous morphine infusion (44 in center 1 and 29 in center 2), and 77 patients were assigned to receive pla-
cebo (48 in center 1 and 29 in center 2). Median duration of study medication infusion was 48 hours (IQR, 19-96 hours). Use of the medication was stopped for the following reasons: extubation (n = 106), 7 days in study (n = 24), hypotension (n = 6), continuous use of neuromuscular blockers (n = 5), death (n = 4), surgery (n = 2), the need for too much additional morphine (n = 2), and overdosing (n = 1).

Patient characteristics for both treatment groups are shown in Table 1. All patient characteristics were comparable between the groups. Demographic characteristics of the nonparticipants also showed no significant difference compared with the participating infants. Painful procedures were counted for a median duration of 6 days (IQR, 3-10 days). The number of daily painful procedures was similar in the morphine group (median, 13; IQR, 10-16) and placebo group (median, 13; IQR, 9-16) (Mann-Whitney U test, 2479; P = .66).

### Pain Scores

At baseline, median NIPS scores in the morphine and placebo groups were 0.0 (IQR, 0.0-0.0) and 0.0 (IQR, 0.0-0.8) and median VAS scores were 0.6 (IQR, 0.3-2.2) and 0.7 (IQR, 0.3-1.5), respectively. Thirty minutes after study medication administration, median NIPS scores in the morphine and placebo groups were 0.0 (IQR, 0.0-0.0) and 0.0 (IQR, 0.0-1.0), and median VAS scores were 0.6 (IQR, 0.3-1.6) and 0.6 (IQR, 0.2-1.4), respectively.

During suctioning, median PIPP scores in the morphine and placebo groups were 10.1 (IQR, 8.2-11.6) and 10.0 (IQR, 8.2-12.0) (P = .94), median NIPS scores were 4.8 (IQR, 3.7-6.0) and 4.8 (IQR, 3.2-6.0) (P = .58), and median VAS scores were 2.8 (IQR, 2.0-3.9) and 2.6 (IQR, 1.8-4.3) (P = .14), respectively (Table 2). There were no significant differences between groups for pain scores. Of the 2530 VAS scores, only 293 values indicated moderate pain by exceeding 4 (69% were scored during suctioning), with 146 and 147 values noted in the morphine and placebo groups, respectively. Table 2 shows pain scores at the different time points for the morphine- and placebo-treated infants. The mean SDs of pain scores for those patients who underwent multiple procedures were 2.5 for the PIPP, 2.2 for the NIPS, and 2.2 for VAS scores.

Multiple regression analyses revealed that VAS and NIPS scores after the loading dose of study medication did not significantly differ between the 2 groups (unstandardized regression coefficient [B]=-0.019; 95% confidence interval [CI], −0.071 to 0.032; P = .66). Pain scores were not influenced by withholding the loading dose (B = −0.014; 95% CI, −0.075 to 0.047; P = .47) and were not significantly predicted, however, by the pain scores before bolus administration (B = 0.65; 95% CI, 0.53 to 0.78; P < .001; and B = 0.54; 95% CI, 0.34 to 0.73; P < .001). VAS scores were higher in girls compared with boys (B = −0.057; 95% CI, −0.11 to −0.005; P = .03) and higher in center 2 compared with center 1 (B = −0.065; 95% CI, −0.12 to −0.010; P = .02). Pain scores tended to be higher when no morphine was given before intubation (B = −0.054; 95% CI, −0.11 to 0.002; P = .06; and B = −0.11; 95% CI, −0.20 to 0.018; P = .02).

The PIPP, NIPS, and VAS scores during suctioning were not predicted in multiple regression analyses by treat-
ment group or by the amount of additional morphine used (TABLE 3). Mean NIPS and VAS scores decreased with increasing length of study, and VAS scores were lower in center 1 compared with center 2. Spearman r correlation coefficients between the different pain scores were 0.44 (NIPS vs PIPP, P<.001), 0.31 (NIPS vs VAS, P<.001), and 0.22 (PIPP vs VAS, P=.02).

**Clinical Outcome**

TABLE 4 lists the clinical outcomes and incidences of morbidity and mortality for the 2 groups. Overall, 11 infants died within 28 days, and 48 were diagnosed as having IVH, 10 of which had the severe type (grade III or IVH plus apparent periventricular hemorrhagic infarction). Four infants had PVL. Logistic regression analysis showed that the incidence of poor neurologic outcome was not related to treatment group or to additional morphine use (TABLE 5). It was, however, associated with lower gestational ages (P=.005) and higher CRIB scores (P=.004) and was more apparent in boys compared with girls (P=.003).

The incidence of IVH (all grades), also evaluated with logistic regression analysis, was significantly higher in the placebo group compared with the morphine group (adjusted odds ratio, 2.36; 95% CI, 1.05-5.28; P=.04). Furthermore, the incidence of IVH was associated with lower gestational ages (P=.006) and was higher in those born small for gestational age (P=.05) and in infants born outside the study hospital (P=.04). Median duration of the first period of artificial ventilation, median total duration of ventilation, and median length of NICU stay did not significantly differ between groups (P=.72, P=.81, and P=.92, respectively).

**Morphine Use**

Open-label morphine was administered to 20 infants (27%) in the morphine group and 31 (40%) in the placebo group (TABLE 5). It was, however, associated with lower gestational ages (P=.005) and higher CRIB scores (P=.004) and was more apparent in boys compared with girls (P=.003).

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**COMMENT**

We hypothesized that continuous morphine infusion in preterm neonates would reduce pain experience and incidences of poor neurologic outcome and IVH. However, pain measurements validated for this age group did not reveal any analgesic effects of morphine. Al-
though routine morphine infusions did not affect poor neurologic outcomes or any other clinical outcome measure, preemptive morphine analgesia significantly decreased the incidence of IVH. These findings suggest that routine morphine infusion in preterm newborns who have received ventilatory support neither improves pain relief nor protects against poor neurologic outcome. The impact of decreased IVH in the morphine-treated neonates, however, should be evaluated with their long-term neurobehavioral outcomes.

Overall, we found that pain scores did not significantly differ between the 2 randomized groups. Although the results of pain scores should be viewed with some caution, the PIPP and NIPS have both been validated for the assessment of procedural pain in preterm neonates. The sensitivity and specificity of these methods for measuring acute or chronic pain in preterm infants remain unknown. The VAS has not been specifically validated for this group of patients but appears to reflect the intensity of pain. In this study, the VAS was applied by experienced NICU nurses who were specifically trained for assessing neonatal pain. Measuring the effect of morphine on the pain experienced by preterm neonates remains difficult because of the lack of a gold standard to assess neonatal pain. The absence of a measurable analgesic effect of morphine, as established by these validated pain scores, may be explained by several reasons.

Our patients seemed to experience only minor pain. Most patients showed no evidence of pain before or 30 minutes after the loading dose. Taking the limited time span from birth to study enrollment (median, 8 hours; IQR, 5-12 hours) into consideration, the low pain scores may be explained by release of endorphins, resulting from birth and postnatal stress. Since severe pain was mostly absent, it need not be relieved by morphine.

Pain scores were obtained during an invasive, presumably noxious procedure. Endotracheal suctioning was the only repetitively, frequently, and routinely performed invasive procedure during our study. Heel lances were not performed routinely because all patients had arterial catheters. Furthermore, previous studies have shown that tracheal suctioning was related to increased pain scores and stress responses and is considered painful. In our study, tracheal suctioning was associated with a median PIPP score of 10, NIPS score of 4.8, and VAS score of 2.7, indicating mild to moderate pain. These physiologic and behavioral responses are indicators of neonatal pain, but they are also influenced by factors such as gestational age, severity of illness, and time.
from the previous painful procedure. Previous studies using these measures have reported large interindividual variability.

The low correlation between the different pain scores also underlines the difficulty of pain assessment in this group of patients, as was recently reviewed by our group. However, multivariate analyses, adjusting for these covariates, did not show any statistically or clinically significant decrease in pain scores resulting from continuous morphine administration. The explained variance of these analyses was low, probably the result of low variability of pain scores. The few previous studies on this subject present conflicting findings. The decrease in pain that resulted from higher morphine doses compared with the ones used in our study during endotracheal suctioning and heel lances was not confirmed in another study using morphine doses of the same magnitude.

The samples sizes in our study were considerably larger and the amounts of morphine used in our study conformed to internationally recommended doses.

Despite the low pain scores, a number of infants were given additional morphine (27% in the morphine group and 40% in the placebo group). Because this study aimed to evaluate the effect of routine continuous morphine infusion in newborns who received ventilatory support on primary and secondary outcome measures, placebo-treated infants received open-label morphine if deemed to be in pain. By reflecting variations among patients that occur in real clinical practice, this study is a pragmatic trial that aimed to inform choices between treatments (routine morphine administration or no routine morphine infusion). In pragmatic trials, the treatment response is the total difference between 2 treatments, including both treatment and associated placebo effects, since this will best reflect the likely clinical response in practice. Because the intention-to-treat principle was used in our study, patients in both groups receiving open-label morphine were not dropped out but included in the analyses. In daily practice, a newborn in pain who receives ventilatory support needs to receive analgesic treatment, independent of any routine morphine administration. If an infant was in pain, morphine was given. In this way, our study was a realistic reflection of 2 different strategies of daily NICU practice.

Clinical bias was minimized via randomization of patients and binding of physicians, parents, and investigators. The attending physicians and nurses obviously considered these infants to be uncomfortable and in need of extra pain relief, although this was not reflected in their pain scores. The use of extra morphine was not significantly different between the randomized groups, as reported previously. The nonparticipating infants received open-label morphine somewhat more frequently than those in the study group, suggesting that participation in this trial was not a causative factor for additional morphine prescription. Furthermore, additional morphine could be used only according to the protocol. Therefore, physicians were allowed to administer additional doses of 50 µg/kg followed by 5 to 10 µg/kg per hour continuous open-label morphine. The nonparticipants, however, often received standard morphine boluses of 100 µg/kg. Additional morphine use in nonparticipants differed between the 2 centers perhaps due to different prescribing policies or to different patient characteristics.

Our results are indicative of nonstandardized pain management under which lack of decision rules results in prescribing analgesics on the basis of personal clinical experience. This is not only the case in our centers but also representative of clinical practice in most NICUs worldwide. Implementation of pain scores (ie, using cutoff points for prescribing additional analgesics that are integrated in clinical algorithms or flowcharts) may be required for rationalizing the use of opioid analgesics in the NICU. The development of new techniques, such as functional magnetic resonance imaging and positron emission tomographic scans, might be useful in the near future to further objectify the analgesic effects of opioids in newborns, but they are not applicable in daily NICU care.

Morphine use might decrease the fluctuations in cerebral blood volume and intracranial pressure caused by neonatal reactions to pain and painful procedures. Morphine may thus protect against the development of venous hemorrhage in the germinal matrix or brain parenchyma or against the extension of a small previous IVH. High pain scores were not related to the incidence of IVH or poor neurologic outcome. Oberlander et al also found that parenchymal brain injury did not cause a difference in pain response in premature neonates. Significantly fewer neonates in the morphine-treated group were found to have IVH compared with the placebo group. This effect of mor-

### Table 6. Use of Morphine in All Groups

<table>
<thead>
<tr>
<th></th>
<th>Morphine Group (n = 73)</th>
<th>Placebo Group (n = 77)</th>
<th>Nonparticipants (n = 60)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-label morphine, median (IQR), µg/kg per hour</td>
<td>0.0 (0.0-0.6)</td>
<td>0.0 (0-3.1)</td>
<td>0.8 (0-4.6)</td>
<td>.005</td>
</tr>
<tr>
<td>Total morphine amount, median (IQR), µg/kg per hour</td>
<td>10.0 (10.0-10.6)</td>
<td>0 (0-3.1)</td>
<td>0.8 (0-4.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patients receiving additional morphine, No. (%)</td>
<td>20 (27)</td>
<td>31 (40)</td>
<td>33 (55)</td>
<td></td>
</tr>
<tr>
<td>Amount of additional open-label morphine, median (IQR), µg/kg per hour</td>
<td>3.0 (1.3-6.8)</td>
<td>4.3 (1.6-7.7)</td>
<td>3.6 (1.7-6.7)</td>
<td>.80</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

*P values determined by Kruskal-Wallis tests comparing the use of morphine between groups.
phine can be partly explained by a decreased incidence of low-grade IVH. The impact of routine morphine administration, by reduction of low-grade IVH, on long-term outcome is hard to predict. Both PVL and IVH were diagnosed and staged from cranial ultrasounds by staff neonatologists, using standard criteria.579.58 It is difficult to determine the neurobehavioral outcome in infants with IVH because other confounding criteria, such as comorbidity, are involved. Mortality and major neurologic sequelae are generally related to the degree of hemorrhage and, to a greater extent, to the degree of associated parenchymal injury.58 Infants with IVH grade 1 and II, without venous infarction, seem to have little increased risk of adverse outcome compared with those without IVH.58.60.64-66 When we studied the impact of morphine infusion on poor neurologic outcomes (eg, death, PVL, IVH grade III, or IVH and apparent periventricular hemorrhagic infarction), there were no differences between the 2 groups.

The neurologic condition of our patients, however, needs to be reevaluated at older ages. A study by Quinn et al67 also showed comparable clinical outcomes between placebo- and morphine-treated neonates. A pilot study by Anand et al,15 with a slightly different study design, showed decreased poor neurologic outcomes on account of morphine compared with midazolam hydrochloride and placebo. Relatively small groups, numbering approximately 20, in those studies, as well as differences in morphine dose regimen, might explain the differing results. Further results of that study should conclusively show whether routine use of morphine reduces the incidences of IVH and poor neurologic outcome.

Overall, our results show a lack of measurable analgesic effect and absence of a beneficial effect on poor neurologic outcome from routine continuous morphine infusion in preterm neonates. Future research is needed to establish cutoff points and an algorithm for the administration of analgesic agents in this specific age group of children, which should be included in consensus statements.23.24 Furthermore, better understanding of individual differences in responses to morphine and pain is necessary to improve neonatal pain management.

Our findings suggest that morphine infusion in preterm newborns who receive ventilatory support should not be used as a standard of care. The long-term consequences of reduced IVH incidence in the morphine-treated neonates should be evaluated at predetermined time points at older ages, using validated assessment instruments for neurodevelopmental outcome.

Author Contributions: Study concept and design: Simons, vand Jijk, vanden Lingen, Roofthoef, Anand, van den Anker, Tibboel. Acquisition of data: Simons, vand Jijk, vanden Lingen, Jongeneel, Bunkers, Smink, Tibboel. Analysis and interpretation of data: Simons, vand Jijk, vanden Lingen, Roofhoef, Duivenvoorden, Anand, van den Anker, Tibboel. Drafting of the manuscript: Simons, vand Jijk, vanden Lingen, Jongeneel, Bunkers, Smink, van den Anker. Critical revision of the manuscript for important intellectual content: vanden Lingen, Roofhoef, Duivenvoorden, Anand, van den Anker, Tibboel. Statistical expertise: Simons, vand Jijk, Duivenvoorden, Obtained funding: vanden Lingen, Tibboel. Administrative, technical, or material support: Simons, vand Jijk, Roofhoef, Jongeneel, Bunkers, Smink, van den Anker. Study supervision: vanden Lingen, Rooffhoef, Anand, van den Anker, Tibboel.

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