Original Paper

Neonatology

Neonatology 2015;108:8–15
DOI: 10.1159/000376566

Received: September 15, 2014
Accepted after revision: January 29, 2015
Published online: April 11, 2015

Prematurity, Opioid Exposure and Neonatal Pain: Do They Affect the Developing Brain?

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Key Words
Children · Magnetic resonance imaging · Neuropsychological functioning · Opioids · Pain · Prematurity

Abstract
Background: Traditionally, 10 years ago, children born preterm often routinely received morphine, especially during mechanical ventilation. Studies in neonatal rats, whose stage of brain development roughly corresponds to that of children born preterm, found negative long-term effects after pain and opioid exposure. ***Objectives:*** We studied possible effects of prematurity, procedural pain and opioids in humans 10 years later. We hypothesized that these factors would negatively influence neurobiological, neuropsychological and sensory development later in life. ***Methods:*** We included 19 children born preterm who as neonates participated in an RCT on the short-term effects of morphine administration and who previously participated in our follow-up studies at ages 5 and 8/9 years. We assessed associations between brain morphology (n = 11), neuropsychological functioning (n = 19) and thermal sensitivity (n = 17) and prematurity, opioid exposure and neonatal pain. ***Results:*** Significant correlations (coefficients 0.60–0.85) of gestational age, number of painful procedures and morphine exposure with brain volumes were observed. Significant correlations between these factors and thermal sensitivity were not established. Neuropsychological outcome was significantly moderately correlated with morphine exposure in only two subtests, and children performed in general 'average' by Dutch norms. ***Conclusions:*** Although prematurity, opioid exposure and neonatal pain were significantly associated with brain volume, no major associations with neuropsychological functioning or thermal sensitivity were detected. Our findings suggest that morphine administration during neonatal life does not affect neurocognitive performance or thermal sensitivity during childhood in children born preterm without brain damage during early life. Future studies with larger sample sizes are needed to confirm these findings.

KARGER 125

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1661–7800/15/1081–0008$39.50/0

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Introduction

Children born preterm spend part of the third trimester outside the protective environment of the uterus when the brain is vulnerable to external perturbations [1]. Moreover, admitted to the neonatal intensive care unit (NICU), they undergo many potentially painful procedures – estimated at 11 daily [2]. This may cause pain-related stress and alterations in the intracranial blood volume and blood pressure, with the risk of intraventricular hemorrhage and periventricular leukomalacia [3]. Pain management traditionally consisted of opioids, but many NICUs nowadays are reluctant to use these because of potential negative long-term effects. Furthermore, previous RCTs have not found beneficial effects of the routine use of morphine in ventilated preterm newborns [4, 5].

Studies in neonatal rats have found increased neuroapoptosis and impaired cognitive functioning after exposure to pain and opioids [6–8]. However, these effects mainly occurred in response to an induced chronic inflammatory response – not necessarily mimicking the human situation. In humans, neurological and developmental disabilities were found in almost half of a cohort of toddlers born extremely preterm [9]. The long-term effects of prematurity include region-specific reductions in brain volume [10] and alterations in pain sensitivity [11]. A greater number of invasive procedures in children born preterm are associated with abnormalities in white matter brain structure associated with lower intelligence [12]. Pain-related stress is associated with a thinner cortex [13] and with changes in functional cortical activity that are negatively correlated with visual-perceptual functioning during childhood [14].

As previous studies found short- and long-term effects of pain and pain treatment in brain development, cognition and pain sensitivity, our goal was to study all these long-term consequences in a well-defined cohort of children born preterm who participated in an RCT as neonates [4] and whom we have followed up for about 10 years [15, 16]. We conducted structural magnetic resonance imaging (MRI) to study brain morphology and assessed neuropsychological functioning and thermal sensitivity.

Patients and Methods

Study Population

Subjects were recruited from a cohort of children born preterm who at neonatal age had participated in an RCT comparing continuous infusion of morphine with placebo [4, 17]. Some of them participated in two follow-up studies (online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000376566) [15, 16]. In the previous follow-up study of this same group of children, IQ, visual motor integration, behavior, and executive functioning were assessed at the age of 8/9 years [16]. Therefore, it was not found necessary to include behavior and IQ again in the present study.

Since formal power analyses are hard to conduct in MRI studies, we aimed to include at least as many children as in a previous MRI pain study determining the long-term effects of neonatal pain, including 9 children per subgroup [18]. For feasibility reasons we chose to only include children of the original RCT who were recruited in Rotterdam and included in the local follow-up program (n = 44) [16]. Participants were recruited from both arms of the original RCT, as short-term survival and long-term cognition did not essentially differ between the groups [4, 15, 16]. Reasons for exclusion were as follows: term birth (n = 6), twins or triplets (n = 5), contraindications for an MRI or neuropsychological study (n = 11) such as intellectual disabilities (IQ of 80 or less), and brain abnormalities such as intraventricular hemorrhage (all grades), periventricular leukomalacia and subependymal cysts. Overall, 22 families were invited.

The study was performed at the Erasmus University Medical Center in Rotterdam in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the Institutional Review Board. Informed consent was obtained prior to participation. Children were recruited from July 2011 to February 2012.

Neuropsychological Testing

Neuropsychological functioning was tested with the NEPSY-II-NL test (a developmental neuropsychological assessment; Pearson). Norm scores and percentile scores were available for Dutch children. Participants completed nine subtests addressing areas of cognitive functioning such as attention and executive functioning, language, memory and learning, sensorimotor functioning, and visuospatial processing.

Chronic Pain Questionnaire

All participants filled out the Dutch chronic pain questionnaire, which addresses the presence of both current and chronic pain [19].

Examination of Detection and Pain Thresholds

Detection and pain thresholds were obtained using the Thermal Sensory Analyzer-II (TSA-II, Medoc Ltd., Ramat Yishai, Israel) with a Peltier contact thermode (30 × 30 mm). Detection thresholds were measured using both the reaction time-dependent method of limits and the reaction time-independent method of levels. For more details, see van den Bosch et al. [20].

Image Acquisition

MRIs were acquired on a 3-tesla scanner (Discovery MR750; General Electric, Milwaukee, Mich., USA) using an 8-channel head coil for signal reception. We obtained a high-resolution structural T1-weighted image using an inversion recovery fast-spoiled gradient recalled sequence with the following parameters: TR = 10.3 ms, TE = 4.2 ms, TI = 350 ms, NEX = 1, flip angle = 16°, readout bandwidth = 20.8 kHz, matrix 256 × 256, imaging acceleration factor of 2, and an isotropic resolution of $0.9 \times 0.9 \times 0.9$ mm^3.

Table 1. Demographic and clinical characteristics of children born preterm (n = 19)

General characteristics	
Age, years	10.2±0.4
Male	68.4
Western European ethnicity	68.4
Gestational age, weeks	31.1 (26.1–36.3)
Birth weight, g	1,415 (675–2,895)
Painful procedures per day[1], n	12 (4–18)
CRIB score	4 (0–8)
Age at ICU admission, days	0 (0–0)
Duration of ICU stay, days	15 (4–63)
Duration of mechanical ventilation, days	4 (2–26)
Pharmacological data	
Morphine administration	78.9
Cumulative use of intravenous morphine in the first 28 days, μg/kg	393.6 (0–4,873)

Data are presented as means ± SD, medians (with ranges) or percentages, as appropriate. CRIB = Clinical risk index for babies.

[1] Number of painful procedures per day: measured in the first 14 days, presented as mean per subject per day (based on n = 14 due to missing data).

Structural Imaging Analysis

We used the FreeSurfer image analysis suite version 5.1.0 (http://surfer.nmr.mgh.harvard.edu/) for cortical reconstruction and volumetric segmentation. FreeSurfer computes structural morphometric measures in an automated approach. Each image was visually inspected, and subjects with poor quality data were excluded. In subjects with small errors in the gray/white segmentation, control points and white matter edits were added to identify and correct misclassified white matter regions. Total brain volume and the volumes of a priori selected general and pain-related brain regions [21], including the thalamus and insula, were obtained. Additionally, these values were compared with control data. We used ANCOVAs, correcting for total brain volume, age and gender, with Bonferroni correction to account for multiple testing. Moreover, evaluation of surface-based cortical thickness was performed using the built-in FreeSurfer program QDEC with a smoothing filter of 10 mm. For the group analysis on cortical thickness a general linear model was fitted at each surface vertex. We corrected for age and gender and used a Monte Carlo correction ($p < 0.05$) to control for multiple testing.

Statistical Analysis

Normally distributed variables are presented as means (with standard deviations, SD) and nonnormally distributed variables as medians (with ranges or interquartile ranges, IQR). Spearman's rank-order correlation coefficient (with 95% confidence intervals, CI) was applied to calculate correlations of the nonnormally distributed variables of gestational age, number of painful procedures in the first 14 days of life (involving skin-breaking procedures as well as non-skin-breaking procedures such as endotracheal suctioning) and total morphine exposure in the first 28 days of life with brain volumes, NEPSY-II outcomes and detection and pain thresholds. A p value of 0.05 or less was considered statistically significant.

Results

Study Population

A total of 22 families received an invitation. Of these, 2 families declined and 1 child was lost to follow-up. Therefore, 19 children participated (13 boys and 6 girls) with a mean age of 10.2 years (SD 0.4). The numbers of children included in the different analyses are presented in online supplementary figure 2. Of the 19 children, only 4 did not receive morphine (standard or additional open-label). One child had undergone surgery in the neonatal period (clipping of patent ductus arteriosus and ileostomy) and was not scanned. Other characteristics are presented in table 1. The 19 included children did not differ from the 25 excluded children with regard to gender ($p = 0.40$), gestational age ($p = 0.69$), number of painful procedures in the first 14 days of life ($p = 0.55$), or morphine exposure in the first 28 days of life ($p = 0.65$).

Correlation Coefficients

Gestational age, number of painful procedures and morphine exposure were not significantly correlated with each other, as seen by the following: gestational age and painful procedures: –0.40 ($p = 0.29$, 95% CI –0.84 to 0.36), gestational age and morphine exposure: –0.50 ($p = 0.12$, 95% CI –0.85 to 0.14) and painful procedures and morphine exposure: 0.30 ($p = 0.43$, 95% CI –0.45 to 0.80).

Table 2. Global brain volumes and volumes of pain-related brain regions (in cm^3) in children born preterm (n = 11)

Global brain volumes	
Total brain volume	1,129±111
Cerebral white matter	372±41
Total grey volume	713±64
Parietal lobe	
Left	72±8
Right	74±8
Frontal lobe	
Left	105±9
Right	103±10
Cerebellum (white matter)	
Left	13±2
Right	13±2
Cerebellum (cortex)	
Left	56±5
Right	57±6
Pain-related brain regions	
Thalamus	
Left	6.6±0.8
Right	6.6±0.9
Amygdala	
Left	1.6±0.2
Right	1.6±0.2
Anterior cingulate cortex	
Left	2.0±0.3
Right	2.7±0.5
Insula	
Left	6.9±0.7
Right	6.8±0.8

Data are presented as means ± SD.

Structural Imaging Results

No incidental brain anomalies were detected. Brain volumes are presented in table 2. We found statistically significant correlations between gestational age (range of correlation coefficients: 0.62 to 0.85), number of painful procedures (–0.73 to –0.83) and morphine exposure (–0.60 to –0.74) and volumes of brain regions (table 3).

Neuropsychological Functioning

No statistically significant correlations between gestational age and any of the NEPSY outcomes were found (range of correlation coefficients: –0.20 to –0.07 and 0.03 to 0.37). The number of painful procedures was also not significantly correlated with NEPSY outcomes (range of correlation coefficients: –0.41 to –0.10 and 0.03 to 0.47). A significant correlation was found between morphine exposure and the total amount of commission errors in the subtest of response set (coefficient –0.46, p = 0.05). Furthermore, there was a significant correlation between morphine exposure and the total score for recognition in the subtest of narrative memory (coefficient –0.46, p = 0.05). Children in general scored 'average' by Dutch norms (Pearson NEPSY-II-NL manual; table 4). Only the number of response set omission errors and visuomotor precision errors corresponded to a 'low average' score.

Detection and Pain Thresholds

Reliable data on detection and pain thresholds were obtained from 16/17 children (table 5). We found no statistically significant correlations of gestational age, number of painful procedures and morphine exposure with detection and pain thresholds. Moreover, the correlation was very weak to moderate (range of correlation coefficients: –0.44 to –0.07 and 0.01 to 0.40).

Chronic Pain

Of the 19 children, 13 (68.4%) had experienced pain in the 3 months before the visit; 3 children (15.8%) had chronic pain (longer than 3 months).

Discussion

Our findings suggest that gestational age, neonatal pain and morphine exposure were correlated with brain volume but not with cognitive performance or thermal detection and pain thresholds. The associations with respect to brain volume indicated that lower gestational age, a higher number of painful procedures in the first 14 days of life and higher exposure to morphine in the first 28 days of life were correlated with smaller brain volumes. Interestingly, we found average scores in general on cognitive functioning, in contrast to our expectations based on animal studies but in line with previous follow-up studies in children born preterm at our department [15, 16].

Previous studies found signs of altered brain development [10, 22] and altered brain functioning during pain in children born preterm [18]. Comparing the MRI scans of the children born preterm with those of healthy controls, which were obtained for other follow-up studies of our department [23], we found no differences in either cortical thickness or brain volumes after correction for age, gender, total brain volume, and multiple testing (data not shown). We expected thinning of the cortex, as this was found in a study in 42 children born preterm with a

Table 3. Correlations between brain volumes and gestational age, morphine exposure and number of painful procedures in children born preterm

	Gestational age (n = 11)	Morphine exposure (n = 11)	Painful procedures[1] (n = 9)
Global brain volumes			
Total brain volume	*0.76 (0.30 to 0.93)*	*–0.67 (–0.91 to –0.12)*	–0.47 (–0.86 to 0.28)
Cerebral white matter	*0.62 (0.03 to 0.89)*	*–0.74 (–0.93 to –0.25)*	–0.45 (–0.86 to 0.31)
Total grey volume	*0.73 (0.23 to 0.92)*	*–0.60 (–0.88 to –0.001)*	–0.43 (–0.85 to 0.33)
Parietal lobe			
Left	*0.67 (0.12 to 0.91)*	*–0.68 (–0.91 to –0.14)*	–0.37 (–0.83 to 0.39)
Right	*0.76 (0.30 to 0.93)*	–0.47 (–0.83 to 0.18)	–0.42 (–0.85 to 0.34)
Frontal lobe			
Left	*0.85 (0.51 to 0.96)*	–0.44 (–0.82 to 0.22)	–0.13 (–0.73 to 0.58)
Right	*0.79 (0.36 to 0.94)*	–0.60 (–0.88 to 0.01)	0.10 (–0.60 to 0.72)
Cerebellum (white matter)			
Left	*0.67 (0.12 to 0.91)*	*–0.65 (–0.90 to –0.08)*	*–0.83 (–0.96 to –0.37)*
Right	0.49 (–0.16 to 0.84)	–0.52 (–0.85 to 0.12)	*–0.80 (–0.96 to –0.29)*
Cerebellum (cortex)			
Left	0.53 (–0.10 to 0.86)	–0.47 (–0.83 to 0.18)	–0.65 (–0.92 to 0.02)
Right	0.36 (–0.31 to 0.79)	–0.18 (–0.70 to 0.47)	–0.35 (–0.82 to 0.41)
Pain-related brain regions			
Thalamus			
Left	0.40 (–0.26 to 0.81)	–0.46 (–0.83 to 0.19)	*–0.73 (–0.94 to –0.13)*
Right	0.52 (–0.12 to 0.85)	–0.53 (–0.86 to 0.10)	–0.52 (–0.88 to 0.22)
Amygdala			
Left	0.27 (–0.39 to 0.75)	–0.35 (–0.79 to 0.32)	0.28 (–0.47 to 0.80)
Right	0.35 (–0.32 to 0.79)	*–0.67 (–0.91 to –0.12)*	0.00 (–0.66 to 0.66)
Anterior cingulate cortex			
Left	0.08 (–0.55 to 0.65)	0.39 (–0.27 to 0.80)	0.35 (–0.41 to 0.82)
Right	*0.66 (0.10 to 0.90)*	–0.45 (–0.83 to 0.21)	–0.22 (–0.77 to 0.52)
Insula			
Left	–0.17 (–0.70 to 0.48)	–0.37 (–0.79 to 0.30)	–0.10 (–0.72 to 0.60)
Right	0.11 (–0.52 to 0.67)	–0.57 (–0.87 to 0.05)	–0.27 (–0.79 to 0.48)

Values in parentheses are 95% CI. Correlation coefficients were derived from Spearman's correlation test.
[1] Painful procedures: based on n = 9 due to missing data. Italics represent statistically significant results.

median age of 7.8 years (IQR 7.7–8) [13]. The explanation possibly lies in the fact that the median gestational age in our study group was higher: 31.1 weeks (range 26.1–36.3) versus 29.7 weeks (range 24–32).

A possible explanation for the lack of significant correlations in the present study with respect to cognitive development and thermal sensitivity would be the relatively low dose of morphine (10 μg/kg/h) administered to the morphine group in the original RCT. In the only other comparable RCT in neonates born between 30 and 32 weeks of gestation the dose was 30 μg/kg/h [5]. Another possible explanation is that brain volume at term-equivalent age had normalized over time due to the inherent plasticity of the human brain. A likely reason for our lack of results is the relatively small sample size which, however, should have permitted the detection of major differences and significant correlations. Still, our results suggest that gestational age, morphine exposure and painful procedures exert an effect mainly on brain volume but not on brain function. The previous follow-up studies in this unique cohort likewise did not evidence major negative effects of neonatal morphine exposure on cognition [15, 16]. The previous follow-up showed that neonatal morphine exposure had no significant negative effects on IQ, visual motor integration or behavior. Interestingly, children exposed to morphine in neonatal life showed fewer problems with executive functioning. Executive functioning as rated by the parents remained also signifi-

Table 4. Neuropsychological outcome

NEPSY-II subtests	Children born preterm (n = 19)	
	median (IQR)	minimum–maximum
Attention and executive functioning		
Auditory attention		
Commission errors	0 (0–0)	0–180
Omission errors	1 (0–2)	0–30
Inhibitory errors	0 (0–0)	0–35
Response set		
Commission errors	2 (1–4)	0–180
Omission errors	5 (2–8)	0–36
Inhibitory errors	1 (0–2)	0–37
Language		
Word generation (total score)	28 (24–36)	0–no maximum
Memory and learning		
Memory for faces (total score)	10 (7–12)	0–16
Memory for faces delayed (total score)	11 (9–13)	0–16
Narrative memory (total score)		
Free and cued recall	25 (23–28)	0–34
Recognition	15 (14–16)	0–16
Sensorimotor functioning		
Visuomotor precision (total errors)	12 (5–18)	0–382
Visuospatial processing		
Arrows (total score)	27 (24–31)	0–38
Geometric puzzles (total score)	30 (28–32)	0–40
Route finding (total score)	9 (8–10)	0–10

cantly better in morphine-treated children after adjustment for IQ and potential confounders [16]. The neuropsychological test results of all children in this current study were generally comparable with Dutch norm scores – in line with what we found previously [16]. Comparing the neuropsychological test results with those of a healthy age- and gender-matched control group, we found no significant differences in neuropsychological functioning (data not shown).

While previous studies found evidence of hypersensitivity for pain in children born preterm with a history of procedural pain and opioid exposure [11, 24], we did not find significant correlations between clinical characteristics and detection or pain thresholds. When comparing these children with healthy controls [23], no statistical differences were obtained (data not shown). Moreover, our obtained pain threshold for heat was roughly comparable with that of children born preterm as described in the literature [18].

The strength of this study is that relevant prospectively collected information regarding pain and mor-

Table 5. Detection and pain thresholds in children born preterm (n = 17)

Method of limits	
Cold detection threshold, °C	30.0±1.9
Warm detection threshold, °C	34.8±2.4
Cold pain threshold[1], °C	13.5±9.1
Threshold not reached[2]	6 (37.5)
Heat pain threshold[1], °C	45.0±4.4
Threshold not reached[2]	6 (37.5)
Method of levels	
Cold detection threshold, °C	30.6±1.3
Number of stimuli	10±3
Warm detection threshold, °C	33.6±1.3
Number of stimuli	10±3

Data are presented as means ± SD or n (%), as appropriate.
[1] n = 16 children.
[2] The child did not press the button before the minimum or maximum temperature of 0 or 50 °C at least once during the test.

phine exposure was available from the prior RCT. A limitation is the relatively small sample size. Therefore, our findings should be interpreted with caution. Moreover, the small sample size did not permit us to correct for possible confounding factors such as the duration of mechanical ventilation and neonatal infection. However, this unique cohort participated in previous follow-up studies of our department at younger ages [15, 16]. By adding neuroimaging to the previous follow-up programs, we present a comprehensive and unique view of the long-term effects of low-dose morphine administration and procedural pain in children born preterm. Larger studies are needed to confirm these important findings, and these will permit to correct for possible confounding factors.

Conclusion

We report strong to very strong correlations of prematurity, opioid exposure and neonatal pain with brain volumes. However, and in our view more importantly, we did not observe strong correlations with neurocognitive performance or thermal sensitivity. Furthermore, children born preterm scored average according to norm values on cognitive tests, indicating an effect mainly on brain volume but no major effects on brain function.

Acknowledgments

We thank Ko Hagoort of the Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands, for editorial assistance.

This study was supported by ZonMw Priority Medicines for Children (grant 40-41500-98.9020).

Disclosure Statement

The authors declare that they have no conflicts of interest, including financial interests, relationships or affiliations, relevant to this manuscript. The authors alone are responsible for the content and writing of the paper.

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