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ORIGINAL ARTICLE

Morphine exposure and neurodevelopmental outcome in infants born extremely preterm

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Abstract

Aim: To investigate the association between morphine exposure in the neonatal period and neurodevelopment at 2 and 5 years of age while controlling for potential confounders.

Method: We performed a retrospective, single-centre cohort study on 106 infants (60 males, 46 females; mean gestational age 26 weeks [SD 1]) born extremely preterm (gestational age < 28 weeks). Morphine administration was expressed as cumulative dose (mg/kg) until term-equivalent age. Neurodevelopmental outcome was assessed at 2 years with the Bayley Scales of Infant and Toddler Development, Third Edition, Dutch version and at 5 years with the Wechsler Preschool and Primary Scale of Intelligence, Third Edition, Dutch version. Multiple linear regression analysis was used to assess the association between morphine exposure and outcome.

Results: Sixty-four out of 106 (60.4%) infants included in the study received morphine. Morphine exposure was not associated with poorer motor, cognitive, and language subscores of the Bayley Scales of Infant and Toddler Development, Third Edition, Dutch version at 2 years. Morphine exposure was associated with lower Full-Scale IQ scores ($p = 0.008$, $B = -9.3$, 95% confidence interval [CI] = −15.6 to −3.1) and Performance IQ scores ($p = 0.005$, $B = -17.5$, 95% CI = −27.9 to −7) at 5 years of age.

Interpretation: Morphine exposure in infants born preterm is associated with poorer Full-Scale IQ and Performance IQ at 5 years. Individualized morphine administration is advised in infants born extremely preterm.

Infants born preterm (i.e. born at <37 weeks of gestation) have a greater risk for difficulty in attention and learning, as well as behavioural problems when reaching school age.[1] Infants born extremely preterm (i.e. born at <28 weeks of gestation) can spend several weeks in a neonatal intensive care unit (NICU) while undergoing a phase of rapid brain growth and development. In this setting, they may experience stressful medical interventions to prevent, diagnose, and treat critical conditions. Infants born preterm are exposed to approximately 5 to 15 noxious invasive procedures per day during their NICU stay and this number is inversely correlated with gestational age.[2,3] Exposure to repeated painful procedures during this critical period may negatively affect the normal growth[4] of head circumference, white matter volume, and subcortical grey matter maturation at term-equivalent age (TEA).[5] Furthermore, early pain experiences in newborns can negatively affect short-term cognitive scores, long-term neurosensory and cognitive abilities, and might have negative impacts on their psychosocial behaviours.[6,7] Thus, analgesic and sedative practices, aimed at minimizing the pain and stress associated with clinical procedures, are strongly recommended.[8]

Abbreviations: IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; TEA, term-equivalent age; WMI, white matter injury.

Morphine is the most common opioid analgesic drug used to treat pain and manage distress in infants receiving mechanical ventilation to reduce oxygen need and hypoxaemic episodes.[9,10] Its analgesic effect on procedural pain is controversial and the few available studies did not find a significant analgesic efficacy.[3] Concerns regarding its role in short- and long-term neurological outcomes have been reported previously.[9] Animal studies showed that chronic exposure to morphine decreased the metabolic activity in motor areas of the brain, restricted cortical cell proliferation and maturation, and promoted apoptosis.[11,12] In the absence of stress or pain, morphine contributed to delayed maturation of the hippocampus in the rat brain inducing adverse neurodevelopmental effects.[11] Using amplitude-integrated electroencephalogram, Tataranno et al.[13] demonstrated that early morphine administration caused reduction of spontaneous early brain activity in infants born preterm. In addition, the cumulative morphine dose was negatively correlated with total brain volume[14] and cerebellar growth at TEA.[13] Randomized controlled trials reported that routine morphine infusion did not influence poor short-term neurological outcomes.[15,16] Studies analysing long-term neurodevelopmental outcomes demonstrated no overall positive or negative effects of neonatal morphine exposure on motor, cognitive, and behavioural abilities at various ages.[2,17–20] However, evaluating the association between morphine administration and neurodevelopmental outcomes is a major challenge because preterm birth, and its associated complications, can play an important role on future neurological abilities. In addition, increasing evidence about the post-NICU environmental impact on the neurodevelopmental outcomes of infants born preterm has been reported.[21]

With this in mind, we conducted this study to better understand if morphine administration and its cumulative dose could negatively affect long-term neurodevelopmental outcomes at 2 and 5 years' corrected age in a cohort of infants born extremely preterm.

What this paper adds

- A significant association between morphine exposure and neurodevelopmental impairment at 5 years was observed.
- Higher exposure to painful and stressful procedures during the neonatal period was associated with poorer abilities at 5 years of age.
- Differently from previous studies on morphine, this association was also considered in the statistical analysis.
- A more individualized morphine administration is advised in infants born extremely preterm to counteract the negative effects of high stress without affecting neurodevelopment.

METHOD

Patients

A retrospective, observational, single-centre cohort study was carried out at the NICU of the Wilhelmina Children's Hospital, Utrecht, the Netherlands. Infants born extremely preterm (gestational age < 28 weeks) born between 2008 and 2011 were enrolled. This cohort was previously included in the NEOBRAIN (Neonatal Estimation Of Brain Damage Risk And Identification of Neuroprotectants) project.[22] A brain magnetic resonance imaging (MRI) scan was acquired at TEA and a follow-up examination was performed at 2 and 5 years.

Exclusion criteria were the presence of major congenital malformations, chromosomal disorders, and inherited metabolic diseases. The study was approved by the local ethics committee of the University Medical Center of Utrecht, the Netherlands.

Clinical data collection

Variables of interest were collected from patients' medical charts, including gestational age, birthweight, birthweight below the 10th centile, sex, mode of delivery, Apgar score at 5 minutes of life, duration of mechanical ventilation, sepsis, patent ductus arteriosus (PDA) requiring treatment, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular haemorrhage (IVH), and length of stay in the hospital. Sepsis was defined as a positive blood culture. PDA was diagnosed by echocardiography. IVH was classified according to Papile et al.[23] Exposure to stress was evaluated by recording the number of the following painful and stressful procedures during the first 4 weeks after birth: heel pricks; intravenous or central line insertion; endotracheal intubation; intramuscular injection; chest tube insertion; nasal and oral suctioning; urinary catheter insertion; subdermal needle insertion; and nasogastric tube insertion. All infants underwent brain MRI at TEA performed on a 3 T MRI scanner (ACHIEVA, Philips Medical Systems, Best, the Netherlands), according to the NEOBRAIN protocol (www.clinicaltrials.gov/ct2/show/NCT00544895). The severity of brain injury was assessed using the Kidokoro scoring system[24] by a group of experienced neonatologists (MB, MLT).

Motor development, language, and cognitive outcomes were assessed at 2 years of corrected age using the Bayley Scales of Infant and Toddler Development, Third Edition, Dutch version.[25] Children's developmental abilities were assessed at 5 years of age using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition, Dutch version, which yields Full-Scale IQ, processing speed quotient, Verbal IQ, and Performance IQ scores.[26] Socioeconomic status was determined based on maternal educational level.

Pain management

During the NICU stay, the severity of stress and level of sedation was measured using the COMFORTneo Scale.

Health care providers evaluated strategies to prevent the pain and stress associated with procedures using non-pharmacological and pharmacological therapies. Pain prevention techniques included oral sucrose, non-nutritive sucking, facilitated tuck (holding the arms and legs in a flexed position), and swaddling. Kangaroo care, light and noise restriction, and clustered nursing were standards of care. Kangaroo care was done for at least 1 to 2 hours per day if permitted by the clinical condition; it consisted of chest-to-chest, upright placement of the infant wearing only a nappy with a blanket over the infant's back and the mother in a reclined position behind a privacy curtain. Health care providers avoided infant's exposure to light and noise as much as possible and clustered tasks such as checking vital signs, toileting, and medication administration simultaneously rather than at different times. Paracetamol was used for mild pain or as an adjunct to other measures. The use of morphine for each patient was prescribed by the responsible physician and based on the best available evidence[10] and clinical experience. Morphine was used to treat chronic severe pain and postsurgical pain and was considered as the first-choice treatment for infants who needed to undergo invasive procedures on a regular basis. Morphine was administered intravenously starting with a loading dose or bolus (0.05–0.1 mg/kg) followed by a continuous infusion (0.01–0.03 mg/kg/hour) when recommended according to pain scores and clinical indication (i.e. sedation, intubation, mechanical ventilation, or analgesia). Higher doses were required in cases of severe clinical conditions and high pain scores, despite the current dose. The morphine cumulative dose (mg/kg) during the whole hospitalization period was calculated as the average daily dose adjusted for the patient's weight until TEA. Fentanyl, an opioid with rapid metabolism and action, was adopted as the first-choice treatment only in cases of time-limited stress or pain.

Statistical analysis

Patients' characteristics were summarized as the mean (SD), median and interquartile range, range, percentages, and absolute frequencies depending on the nature of the variables involved. Univariate regression analyses were performed to assess the association between morphine administration and neurodevelopmental outcomes (Tables S1 and S2). Infant composite scores from the Bayley Scales of Infant and Toddler Development, Third Edition, Dutch version were entered into three separate models as dependent variables (cognitive, language, and motor). Equally, models using the subscores of the Wechsler Preschool and Primary Scale of Intelligence, Third Edition, Dutch version were analysed. A multiple linear regression analysis was performed, adjusting for gestational age, PDA, ventilation lasting more than 7 days, postnatal corticosteroids, sum of total stressful and painful procedures, white matter injury (WMI) defined by the Kidokoro scoring system,[24] IVH (any grade), cerebellar haemorrhage, maternal education, and cumulative morphine dose until TEA. A $p < 0.05$ was considered statistically significant. Results were presented as coefficients of the independent variables with 95% confidence intervals. Condition indexes and the variance inflation factor were calculated to detect the multicollinearity of the regression model. A condition index lower than 30 and variance inflation factor values lower than 5 denoted models that did not have significant multicollinearity. Data analysis was performed using SPSS v27 (IBM Corp., Armonk, NY, USA).

RESULTS

The clinical characteristics of the enrolled infants ($n = 106$) are summarized in Table 1. The mean number of painful and stressful procedures collected until 28 days of age was 202 (SD 53). Sixty-four infants received morphine (60.4%) at a mean dose of 2.03 mg/kg (SD 2.09) during their NICU stay. Two groups were identified based on whether or not neonates received morphine (Table 2). Infants exposed to morphine were more frequently male, had lower gestational age and birthweight, were ventilated for a longer period, had higher incidence of PDA, IVH, and bronchopulmonary dysplasia, WMI at TEA, surgery, and a longer stay in the NICU (Table 2). The developmental outcomes of the studied population are summarized in Table 3. No statistically significant difference was observed between the mean neurodevelopmental score values on the *t*-test in infants exposed and not exposed to morphine (Table 3). In 49 out 106 cases (46%), data about language outcome at 2 years of age were not available. In 31 out 106 cases (29%), data about neurodevelopmental outcomes at 5 years were missing.

Multiple regression analysis showed that morphine exposure was not associated with neurodevelopmental outcome at 2 years of age after adjusting for gestational age, PDA, long-term mechanical ventilation (>7 days), postnatal corticosteroids, number of painful and stressful procedures, IVH, WMI, cerebellar haemorrhage, and maternal education. Maternal education level was associated with higher cognitive scores ($p = 0.04$). Mechanical ventilation lasting for longer than 7 days showed a negative association with cognitive and language scores. Lower gestational age and higher WMI scores were associated with poorer motor development ($p = 0.028$ and $p = 0.003$ respectively) (Table 4).

After adjustment for the aforementioned clinical confounders, linear regression analysis showed that exposure to morphine was associated with lower Full-Scale IQ and Performance IQ scores at 5 years of age (Table 5) ($p = 0.008$ and $p = 0.005$ respectively). Mechanical ventilation lasting for longer than 7 days was negatively associated with Performance IQ ($p = 0.03$) and processing speed quotient ($p = 0.002$). Higher WMI scores and a higher number of painful and stressful procedures were associated with a worse Performance IQ score (Table 5).

TABLE 1 Clinical characteristics of the study cohort

Clinical characteristics	*n* = 106
Gestational age (weeks), mean (SD)	26 (1)
Male, *n* (%)	60 (56.6)
Birthweight (g), mean (SD)	896.9 (172.7)
PDA, *n* (%)	
Medical treatment	44 (41)
Surgery	13 (12.3)
Mechanical ventilation, *n* (%)	90 (84.9)
Mechanical ventilation (days), mean (SD)	11.6 (10.4)
BPD, *n* (%)	37 (39)
Surgery, *n* (%)	23 (21.6)
Morphine dose (mg/kg), mean (SD)	2.03 (2.09)
n days, mean (SD)	7 (6)
Number of painful or stressful procedures, mean (SD)	202 (53)
IVH, *n* (%)	
Grades I and II	31 (29.3)
Grades III and IV	2 (1.9)
White matter injury, mean (SD)	
No injury or mild injury	40 (37.7)
Moderate to severe	5 (4.7)
Cerebellar haemorrhage, *n* (%)	9 (8.5)
NICU stay (days), mean (SD)	61 (27)
Bayley-III, mean (SD)[a]	
Cognitive score	102.1 (13.7)
Motor score	105.8 (14.3)
Language score	102.05 (14.7)
WPPSI-III-NL, mean (SD)[b]	
Full-Scale IQ	97.4 (12.6)
Verbal IQ	99.1 (13.8)
Performance IQ	98.9 (11.9)
Processing speed quotient	92.4 (14.5)

Abbreviations: Bayley-III-NL, Bayley Scales of Infant and Toddler Development, Third Edition, Dutch version; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; WPPSI-III-NL, Wechsler Preschool and Primary Scale of Intelligence, Third Edition, Dutch version.

[a] Combined scores <80 provide the best definition of moderate-to-severe neurodevelopmental delay.

[b] The Wechsler Preschool and Primary Scale of Intelligence yields a standard score with a mean of 100 and an SD of 15.

DISCUSSION

Our study investigated the association between morphine exposure up to term age and neurological outcomes at 2 and 5 years of age in infants born extremely preterm. Mean neurodevelopmental scores in infants exposed and not exposed to morphine were not significantly different at the *t*-test. However, after correction for the number of stressful procedures and major comorbidities, infants exposed to morphine showed poorer outcomes at 5 years of age. Nevertheless, the mean scores between the two groups were within the normal range. Morphine exposure did not predict neurodevelopmental impairment at 2 years of age. As in previous studies that reported a negative effect of procedural pain on brain development in infants born preterm,[5,7] in our cohort higher exposure to painful and stressful procedures during the neonatal period was associated with poorer abilities at 5 years of age.

These different results might be explained by the difficulty in providing an objective measure of neurodevelopmental abilities in early childhood. Neurodevelopmental scores at 2 years of age have a poor predictive value and recording a normal value does not rule out impairment at an older age when more complex tasks are carried out.

To date, few studies have investigated the short- and long-term effects of morphine on neonatal brain maturation and conflicting results have been reported about the role of morphine on the neurodevelopmental outcomes of infants born preterm.[2,18,27–29]

Two large randomized controlled trials analysing the effect of morphine on brain injury in mechanically ventilated infants born preterm did not show significant differences in short-term outcomes, including severe IVH, periventricular leukomalacia, or death.[15,30] However, subgroup analyses of the NEOPAIN trial revealed an increased incidence of IVH, periventricular leukomalacia, or death associated with open-label morphine related to the risk for hypotension. In our cohort, morphine-exposed infants experienced a higher incidence of IVH compared to controls (placebo). However, selection bias should be considered because morphine exposure could potentially be higher in infants with comorbidities. Therefore, we adjusted our statistical comparative analysis for the major neonatal risk factors.

Only a few studies evaluated the long-term effects of morphine on infants born preterm. Kocek et al.[28] retrospectively analysed morphine use in infants with extremely low birthweight, finding an association between higher exposure to morphine and poorer outcomes at 20 months of corrected age. However, these patients received significantly longer mechanical ventilation and consequently a higher cumulative morphine dose (82.44 mg/kg) compared to our study cohort.

Zwicker et al.[27] reported that morphine exposure was independently associated with poorer neurodevelopmental outcomes (i.e. motor and cognitive subscores) at 18 months of corrected age. The median cumulative dose of morphine was comparable to that of our cohort.

In a pilot study, Ferguson et al.[2] suggested that preemptive (regularly administered during mechanical ventilation) morphine analgesia did not affect neuropsychological outcomes assessed at 5 to 7 years of age. However, infants had a smaller head circumference and exhibited increased latencies when answering in the short memory task compared to controls (placebo). De Graaf et al.[19] found that short-term (<5–7 days) morphine analgesia in the NICU did not affect neurodevelopmental outcomes at 5 to 6 years of age. In the same cohort of patients at 8 to 9 years of age, the morphine-treated group exhibited better executive function compared to the control

TABLE 2 Group identification based on whether or not neonates received morphine

	No morphine (n = 42, 39.6%)	Morphine (n = 64, 60.4%)	p
Gestational age (weeks), mean (SD)	27 (1)	26 (1)	0.015
Male, n (%)	18 (42.9)	42 (65.6)	0.021
Birthweight (g), mean (SD)	940 (163.7)	868 (173.9)	0.036
Birthweight, z-score	0.48 (0.66)	0.20 (0.88)	0.072
Caesarean section, n (%)	15 (36.8)	34 (53.2)	0.39
Apgar score at 5 minutes, mean (SD)	8 (2)	7.5 (1.75)	0.07
PDA, n (%)			0.020
Medical treatment	15 (35)	29 (45)	
Surgery	1 (2)	12 (19)	
Culture-proven sepsis, n (%)	13 (31)	20 (31)	0.360
Mechanical ventilation, n (%)	27 (64,3)	63 (98,4)	0.000
Mechanical ventilation (days), mean (SD)	6.7 (7.1)	13.6 (11)	0.004
Postnatal corticosteroids, n (%)	3 (7)	17 (27)	0.132
BPD, n (%)	9 (21)	28 (44)	0.03
NEC, n (%)			0.900
Conservative/medical treatment	2 (5)	1 (2)	
Surgery	0 (0)	2 (3)	
Surgery, n (%)	2 (5)	21 (33)	0.030
ROP, n (%)			0.185
Grade 1	1 (2)	7 (11)	
Grades 2 and 3	1 (2)	2 (3)	
Severe (laser therapy)	0 (0)	2 (3)	
IVH, n (%)			0.042
Grades I and II	7 (16)	24 (37)	
Grades III and IV	0 (0)	2 (3)	
White matter injury, n (%)			0.033
No injury or mild injury	18 (43)	22 (34)	
Moderate to severe	0 (0)	5 (8)	
Cerebellar haemorrhage, n (%)	3 (7)	6 (9)	0.730
PVL, n (%)	0	10 (16)	0.095
Number of painful and stressful procedures, mean (SD)	189 (55)	211 (50)	0.041
NICU stay (days), mean (SD)	49.9 (25.5)	67.8 (25.8)	0.001

Abbreviations: BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

(placebo) group without other significant differences.[20] In the latter study, median gestational age was significantly higher compared to our study population.

Conversely, an observational study of 223 infants born very preterm did not show a correlation between morphine use and neurodevelopmental performance at 7 years of age;[29] lower doses were used in this study than in other studies (e.g. NEOPAIN trial).[30] The EPIPAGE study revealed that prolonged (>7 days) sedative and/or opioid use was not related to a poor long-term cognitive outcome at 5 years of age.[18]

Therefore, controversial results about the negative impact of opioids on neurodevelopment have been reported and prospective randomized controlled trials specifically conducted with the aim of investigating the long-term effects of morphine are not yet available.

Morphine acts centrally through μ and κ receptors, causing interruption of nociceptive signals and activation of pain-modulating neurons. However, in vitro testing and animal models demonstrated that morphine administration may increase microglial and neuron apoptosis by means of the caspase-3-dependent pathway and can inhibit neuronal progenitor cell proliferation in a dose-dependent manner.[12] Its analgesic effect on procedural pain is controversial and the few available studies found a non-significant analgesic efficacy.[31] Nonetheless, morphine is one of the most used analgesic drugs in mechanically ventilated infants born preterm.[10,32]

Discrepancies between our findings and previously reported data might be explained by the wide variability in morphine dosage. The correlation between morphine exposure and neurological impairment is more often observed in

TABLE 3 Developmental outcomes of the study cohort

	No morphine (n = 42, 39.6%)	Morphine (n = 64, 60.4%)	p
Bayley-III-NL, mean (SD)			
Cognitive score	103 (10)	102 (11)	0.530
Motor score	111 (15)	105 (10)	0.030
Fine motor	12 (3)	11 (2)	0.630
Gross motor	10 (3)	9 (2.85)	0.130
Language score	108 (13)	106 (14)	0.610
WPPSI-III-NL, mean (SD)			
Full-Scale IQ	99 (12)	97 (13)	0.45
Verbal IQ	99 (14)	99 (14)	0.92
Performance IQ	101 (12)	98 (12)	0.26
Processing speed quotient	95 (16)	91 (13)	0.21
Maternal education			
No education	1 (2.4)	2 (3.1)	0.900
Low	7 (16.7)	15 (23.4)	
Middle	6 (14.3)	14 (21.9)	
High	8 (19)	18 (28.1)	

Abbreviations: Bayley-III-NL, Bayley Scales of Infant and Toddler Development, Third Edition, Dutch version; WPPSI-III-NL, Wechsler Preschool and Primary Scale of Intelligence, Third Edition, Dutch version.

TABLE 4 Multiple linear regression analysis between morphine exposure and outcome at 24 months of corrected age

Bayley-III-NL	Cognitive score			Motor score			Language score		
	B [a]	95% CI	p	B	95% CI	p	B	95% CI	p
Gestational age	1.76	(−1.5 to 5)	0.28	3.6	(0.42–6.8)	0.028	3.06	(−1.2 to 8)	0.21
Mechanical ventilation >7 days	−6.4	(−12.6 to −0.175)	0.044	−1.6	(−9.8 to 6.5)	0.68	−13.2	(−23.04 to −3)	0.013
PDA	0.63	(−4.5 to 5.7)	0.80	3.5	(−0.57 to 7.7)	0.08	−2.6	(−11 to 5.7)	0.52
Postnatal corticosteroid use	0.36	(−4.7 to 5.5)	0.88	1.9	(−2.2 to 6.02)	0.35	0.3	(−7 to 7.6)	0.93
Number of painful and stressful procedures (4 weeks)	0.006	(−0.6 to −0.7)	0.86	−0.16	(−0.74 to 0.43)	0.59	0.075	(−0.16 to 0.18)	0.1
Morphine dose (mg/kg) until TEA	−0.35	(−2.2 to 1.5)	0.71	−0.64	(−2.3 to 1.07)	0.44	1.53	(−0.89 to 3.9)	0.2
IVH	2.6	(−2.08 to 7.3)	0.26	1.12	(−3.7 to 6.03)	0.64	4.6	(−1.8 to 11.2)	0.14
Cerebellar haemorrhage	−2.42	(−10.5 to 5.7)	0.54	−5.5	(−13.9 to 2.9)	0.19	0.027	(−15 to 15)	0.99
WMI score	−0.56	(−2.22 to 1.09)	0.49	−2.9	(−4.5 to −1.4)	0.003	−1.2	(−3.8 to 1.3)	0.32
Maternal education	3.1	(0.062–6.2)	0.046	−0.06	(−4.01 to 3.8)	0.97	1.4	(−4.12 to 6.9)	0.60

Abbreviations: Bayley-III-NL, Bayley Scales of Infant and Toddler Development, Third Edition; CI, confidence interval; IVH, intraventricular haemorrhage; PDA, patent ductus arteriosus; TEA, term-equivalent age; WMI, white matter injury.

[a]Unstandardized regression coefficient or beta value.

patients who receive higher dosages.[27,28] In addition, previous studies reported that morphine administration was based on the individual physician's clinical experience, which is not easily compared or reproducible. Moreover, several studies did not consider the number of stressful procedures, thus preventing the quantification of pain. A further explanation could be provided by individual susceptibility to morphine administration in infants born preterm. Recent evidence suggests that differences in the genes involved in morphine biotransformation may predict interindividual variations in terms of efficacy and susceptibility to adverse effects.[33]

Moreover, increasing evidence suggests that post-NICU environmental exposure may significantly contribute to neurodevelopmental outcomes in infants born preterm.

In our study, maternal educational level was associated with higher cognitive, Full-Scale IQ, and Performance IQ scores. These results confirm that maternal stimulus is a strong determinant against the negative impact of preterm birth. A lower education level could lead to a less sensitive response to the infant's needs, leading to less appropriate care and less frequent use of medical post-discharge services.[34]

Study limitations

The current study has several limitations. We attempted to isolate the effect of morphine, adjusting for major confounders

TABLE 5 Multiple linear regression analysis between morphine exposure and outcome at 5 years of age

WPPSI-III-NL	Full-Scale IQ score			Performance IQ score			Processing speed quotient score		
	B[a]	95% CI	*p*	*B*[a]	95% CI	*p*	*B*[a]	95% CI	*p*
Gestational age	−1.3	(−9.7 to 7)	0.7	2.4	(−3.1 to 7.9)	0.3	2.5	(−1.9 to 7)	0.2
Mechanical ventilation >7 days	1.4	(−18.4 to 21.4)	0.8	24	(3.1–44.8)	0.03	−21.5	(−32.9 to −10.1)	0.002
PDA	10.9	(1.4–20.3)	0.028	13.9	(3.5–24.2)	0.015	14.6	(5.2–23.9)	0.006
Postnatal corticosteroid use	0.5	(−24.2 to 25.2)	0.9	−2.7	(−18.4 to 12.9)	0.6	−3.7	(−24.3 to 16.7)	0.6
Number of painful and stressful procedures (4 weeks)	−0.04	(−0.2 to 0.1)	0.1	−0.15	(−0.3 to 0.009)	0.04	0.075	(−0.04 to 0.19)	0.2
Morphine dose (mg/kg) until TEA	−9.3	(−15.6 to −3.1)	0.008	−17.5	(−27.9 to −7)	0.005	2.3	(−8.2 to 13)	0.6
IVH	−1.7	(−19.8 to 16.3)	0.8	2.1	(−9.6 to 14)	0.6	−5.8	(−12.3 to 0.65)	0.07
Cerebellar haemorrhage	11.8	(−0.2 to 23.9)	0.54	16.8	(3.7–30.0)	0.019	−7.6	(−31 to 15.8)	0.4
WMI score	−3.8	(−8.3 to 0.5)	0.08	−8.9	(−14.0 to −3.7)	0.005	2.6	(−5.3 to 10.6)	0.4
Maternal education	5.6	(0.4–10.8)	0.037	5.5	(0.24–10.9)	0.04	−2.09	(−9.2 to 5)	0.5

Abbreviations: CI, confidence interval; IVH, intraventricular haemorrhage; PDA, patent ductus arteriosus; TEA, term-equivalent age; WMI, white matter injury; WPPSI-III-NL, Wechsler Preschool and Primary Scale of Intelligence, Third Edition, Dutch version.

[a]Unstandardized regression coefficient or beta value.

to counteract the difficult challenge of evaluating causality between morphine administration and neurodevelopmental impairment. However, the impact of severe comorbidities and the magnitude of pain during the NICU stay may affect the need for morphine and neurodevelopmental outcome.

Morphine exposure and several painful procedures could influence each other causing selection bias in the morphine-exposed group. However, unlike previous studies, we took into account the number of stressful procedures.

We hypothesize that the different impact of morphine exposure on neurodevelopmental outcomes at 2 and 5 years of age could be explained by the fact that activities performed at school age are more demanding than those of 2-year-old children, giving rise to developmental alterations that are not yet visible at a younger age. Fine abilities evaluated by the Wechsler Preschool and Primary Scale of Intelligence, Third Edition, Dutch version could be more sensitive in detecting neurodevelopmental impairment than the Bayley Scales of Infant and Toddler Development, Third Edition, Dutch version which may overestimate neurocognitive outcomes.[35] Moreover, despite the existence of a significant difference between the two groups at 5 years, the mean of the reported outcome score in the morphine group was still within the normal range. This makes it more difficult to evaluate the real impact and relevance of the effect of morphine administration on long-term outcomes.

CONCLUSIONS

We did not find evidence of a causal link between morphine exposure and cognitive, motor, and language abilities in infants born extremely preterm in our cohort at 2 years of age. Nevertheless, poorer Full-Scale IQ and Performance IQ scores at 5 years were observed, even if within the normal range. A systematic assessment of pain and stress may decrease the risk of oversedation and undersedation, leading to a more individualized use of morphine or alternative analgesics counteracting the negative effects of high stress without affecting neurodevelopment.

Emerging strategies based on monitoring facial expressions, body movement, crying sounds, and physiological signals using artificial intelligence could be a potential future avenue of investigation.[36]

Further prospective randomized controlled trials designed to investigate the effects of morphine on long-term outcomes are warranted to define the best recommended dosage and regimen to treat neonatal pain.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Univariate linear regression analysis between morphine exposure and neurological outcome at 24 months corrected age

Table S2: Univariate linear regression analysis between morphine exposure and neurological outcome at 5 years of age

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