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Long-Term Effects of Neonatal Morphine Infusion on Pain Sensitivity: Follow-Up of a Randomized Controlled Trial

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Abstract: Short-term and long-term effects of neonatal pain and its analgesic treatment have been topics of translational research over the years. This study aimed to identify the long-term effects of continuous morphine infusion in the neonatal period on thermal pain sensitivity, the incidence of chronic pain, and neurological functioning. Eighty-nine of the 150 participants of a neonatal randomized controlled trial on continuous morphine infusion versus placebo during mechanical ventilation underwent quantitative sensory testing and neurological examination at the age of 8 or 9 years. Forty-three children from the morphine group and 46 children from the placebo group participated in this follow-up study. Thermal detection and pain thresholds were compared with data from 28 healthy controls. Multivariate analyses revealed no statistically significant differences in thermal detection thresholds and pain thresholds between the morphine and placebo groups. The incidence of chronic pain was comparable between both groups. The neurological examination was normal in 29 (76%) of the children in the morphine group and 25 (61%) of the children in the control group ($P = .14$). We found that neonatal continuous morphine infusion (10 μg/kg/h) has no adverse effects on thermal detection and pain thresholds, the incidence of chronic pain, or overall neurological functioning 8 to 9 years later.

***Perspective:** This unique long-term follow-up study shows that neonatal continuous morphine infusion (10 μg/kg/h) has no long-term adverse effects on thermal detection and pain thresholds or overall neurological functioning. These findings will help clinicians to find the most adequate and safe analgesic dosing regimens for neonates and infants.*

***Key words:** Morphine, quantitative sensory testing, neonatal intensive care, follow-up, randomized controlled trial.*

Providing adequate and evidence-based analgesia and sedation to neonates receiving intensive care is an ongoing challenge; one has to account for developmental changes in drug pharmacokinetics and pharmacodynamics as well as in the human nervous system.[13,23] The repeated painful procedures in intensive care can lead to short-term hyperalgesia.[22] Long-term follow-up of extremely preterm neonates showed a generalized decrease in thermal sensitivity, probably caused by tissue injury and modulation of nociceptor pathways.[26] Therefore, analgesic treatment plays an important role in the neonatal intensive care unit (NICU). Opioids such as morphine are commonly used in the NICU and have both beneficial and adverse short-term effects. Morphine is an effective analgesic agent for neonates' postoperative pain but not for acute procedural pain.[1,4,5,20] However, continuous morphine infusion does not decrease the risk of poor neurological outcome after intensive care treatment.[20]

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Animal studies on long-term cognitive functioning and neurodevelopmental outcome after neonatal morphine exposure found impaired learning abilities, neuronal degeneration,[2] increased neuroapoptosis,[3] and enhanced hippocampal gliosis (proliferation of damaged astrocytes) in rodents treated with morphine.[14,21,25] In humans, participants of 2 randomized controlled trials (RCTs) on neonatal morphine administration were studied 5 years after the original RCT was conducted.[1,20] The first, a small-scale follow-up of the NEOPAIN (Neurologic Outcomes and Pre-emptive Analgesia in Neonates) trial,[9] showed that children who had received morphine (n = 14) had a smaller head circumference, weighed less, and had more social problems than children who had received placebo (n = 5). The second, performed in our institution, showed that children who had received morphine (n = 49) performed more poorly on 1 subtest of the intelligence scale than did the children who had received placebo (n = 41); other neurobehavioral outcomes and the incidences of chronic pain were comparable between the 2 groups.[7] This unique cohort is being followed, and at the age of 8 years, participants were old enough for quantitative sensory testing (QST).[6]

Morphine is used worldwide for opioid analgesia in neonates, infants, and children; therefore, it is important to confirm that it does not have any negative long-term effects. In the current study, we evaluated thermal sensitivity, the occurrence of chronic pain, and neurological outcome in 8- to 9-year-old children who at neonatal age had received continuous morphine infusion. Our null hypothesis is that continuous morphine infusion at neonatal age has no adverse effects on thermal detection and pain thresholds, incidence of chronic pain, and neurological functioning at 8 to 9 years of age.

Methods

Original Study

Between 2000 and 2002, 150 term- and preterm-born neonates who received mechanical ventilation in 2 level III NICUs participated in a multicenter RCT. Morphine is one of the most frequently used analgesics across all age groups worldwide. At the time of the study,[20] the debate was whether preterm newborns on ventilatory support should routinely receive a continuous morphine infusion. The aim of the RCT was to evaluate the effects of continuous intravenous morphine infusion on pain responses, incidence of intraventricular hemorrhage, and poor neurologic outcome (severe intraventricular hemorrhage, periventricular leukomalacia, or death). Seventy-three neonates were randomly assigned to the continuous morphine group (loading dose of 100 μg/kg followed by infusion of 10 μg/kg/h) and 77 to the placebo group (normal saline infusion). If pain or distress was noted, children in both groups received an open-label morphine bolus of 50 μg/kg and, if indicated, an open-label morphine infusion (5–10 μg/kg/h) as rescue medication. Open-label morphine was administered to 27% of the children in the morphine group versus 40% of the placebo group (P = .10). Further details, including the background characteristics of the participants, can be found in the original article.[20]

Follow-Up Study (8–9 Years)

The institutional ethics review boards of the 2 study sites (Erasmus University Medical Center–Sophia Children's Hospital, Rotterdam, The Netherlands, and Isala Clinics, Zwolle, The Netherlands) approved the study plan. Parents of the 132 survivors were informed of the study and were asked for written informed consent. Seventeen participants from the morphine group were lost to follow-up and 5 parents refused to provide informed consent for the follow-up study. Sixteen patients of the placebo group were lost to follow-up and 5 parents refused informed consent for the follow-up study. The remaining 89 children and their parents were then invited for a follow-up visit in their hospital (either Rotterdam or Zwolle) (Fig 1). The nonparticipants had a lower birth weight and their first hospital stay was longer compared with the participants.[8]

Parents were asked to complete several questionnaires (see later discussion) before the visit. The visit consisted of 3 parts: QST by a trained researcher (A.J.V.), medical examination by a pediatrician (D.T.), and neuropsychological testing by a psychologist (M.vD.). These health professionals were blinded to the participants' study condition (continuous morphine infusion versus placebo) in the original RCT.

QST

Participants underwent QST (see Supplementary Material) in a quiet hospital room, with a stable room temperature (20–22°C). Parents were present in the room and were instructed not to interfere during the test. Reaction time was measured using the baseline speed task for the dominant hand (Amsterdam Neuropsychological Tasks, Version 3.1; Boom Test Publishers, Amsterdam, The Netherlands).

Reference Data QST (Control Group)

We compared the detection and pain thresholds of both the placebo and the morphine group with detection and pain thresholds of 28 healthy control individuals (aged 8–10 years). The control values were collected by our research group and obtained using the same protocol as for QST.[24]

Healthy term-born controls without a history of intensive care admission or severe early pain were recruited. Participants of other studies were asked whether they could recommend someone in the age range of 8–18 years who would be interested in volunteering. Furthermore, children were recruited at primary schools in Rotterdam. Eventually, we selected the children aged 8 to 10 years as the reference group for the present study.

Control individuals were included at Erasmus Medical Center in Rotterdam from October 2011 to March 2013. The local institutional review board approved this study. Informed consent from the parents and assent of the children was obtained before participation.