Analgesia and Sedation in Preterm Neonates Who Require Ventilatory Support

Results From the NOPAIN Trial

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Background: Preterm neonates are exposed to multiple painful procedures after birth and exhibit acute physiological responses to pain. Occurrence of early intraventricular hemorrhage within 24 to 72 hours after birth suggests a role of pain and stress in the multifactorial causation of severe intraventricular hemorrhage and periventricular leukomalacia. We proposed that such neurologic outcomes in preterm neonates who require ventilatory support may be reduced by morphine analgesia or midazolam sedation compared with a placebo.

Objectives: To define the incidence of clinical outcomes in the target study population, to estimate the effect size and adverse effects associated with analgesia and sedation, and to calculate the sample size for a definitive test of this hypothesis.

Methods: Sixty-seven preterm neonates were randomized in a pilot clinical trial from 9 centers. Neonates of 24 to 32 weeks’ gestation were eligible if they had been intubated and required ventilatory support for less than 8 hours and if they were enrolled within 72 hours after birth. Exclusion criteria included major congenital anomalies, severe intrapartum asphyxia, and participation in other research studies. Severity of illness was assessed by the Clinical Risk Index for Babies, and neonates were randomized to receive continuous infusions of morphine sulfate, midazolam hydrochloride, or 10% dextrose (placebo). Masked study medications were continued as long as clinically necessary, then weaned and stopped according to predefined criteria. Levels of sedation (COMFORT scores) and responses to pain (Premature Infant Pain Profile scores) were measured before, during, and 12 hours after discontinuation of drug infusion. Cranial ultrasound examinations were performed as part of routine practice, and poor neurologic outcomes were defined as neonatal death, severe intraventricular hemorrhage (grade III or IV), or periventricular leukomalacia.

Results: No significant differences occurred in the demographic, clinical, and socioeconomic variables related to mothers and neonates in the 3 groups or in the severity of illness at birth as measured by Clinical Risk Index for Babies scores. Two neonates in the placebo group and 1 neonate in the midazolam group died; no deaths occurred in the morphine group. Poor neurologic outcomes occurred in 24% of neonates in the placebo group, 32% in the midazolam group, and 4% in the morphine group (likelihood ratio $\chi^2 = 7.04, P = .03$). Secondary clinical outcomes and neurobehavioral outcomes at 36 weeks’ postconceptional age were similar in the 3 groups. Responses elicited by endotracheal tube suction (Premature Infant Pain Profile scores) were significantly reduced during the morphine ($P < .001$) and midazolam ($P = .002$) infusions compared with the placebo group.

Conclusions: This pilot trial suggests that preemptive analgesia given by continuous low-dose morphine infusion may reduce the incidence of poor neurologic outcomes in preterm neonates who require ventilatory support. Limitations in the sample size of this pilot study suggest that these results should be confirmed in a large multicenter randomized trial.


Despite improvements in clinical outcomes resulting from potent anesthesia and postoperative analgesia in neonates undergoing cardiac and noncardiac surgical operations, substantial variability exists in the routine clinical use of analgesia and sedation for newborns. Accumulating evidence indicates that exposure of preterm neonates to repetitive pain and stress in the neonatal intensive care unit (NICU) leads to clinical instability and complications. Justifications for the use of analgesic or sedative drugs include a functional pain system, the presence of acute physiological responses to pain and stress, and the potential for long-term changes in the developing nervous system. Conversely, clinical concerns that

The authors’ affiliations as well as a complete list of the centers and contributors of the NOPAIN Trial appear at the end of this article.
METHODS

From 9 participating Neonatal Outcome and Prolonged Analgesia in Neonates (NOPAIN) trial centers, 170 neonates were identified by the inclusion criteria: 37 of these fulfilled exclusion criteria, 37 were excluded because of parent refusal, and 9 patients were excluded because of other reasons; therefore, 67 neonates were recruited and completed the study procedures.

<table>
<thead>
<tr>
<th>Reason for Nonenrollment</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental consent refused or withdrawn</td>
<td>57*</td>
</tr>
<tr>
<td>Exubated in &lt;24 h</td>
<td>13</td>
</tr>
<tr>
<td>Continuous positive airway pressure only, ventilation not required</td>
<td>10</td>
</tr>
<tr>
<td>Intubated &gt;8 h before randomization</td>
<td>10</td>
</tr>
<tr>
<td>Research staff not notified</td>
<td>4</td>
</tr>
<tr>
<td>Moved; health maintenance organization assignment</td>
<td>2</td>
</tr>
<tr>
<td>Difficulty with central lines</td>
<td>2</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
<td>4</td>
</tr>
<tr>
<td>Religious objections</td>
<td>1</td>
</tr>
</tbody>
</table>

Asterisk indicates that consent was withdrawn after randomization and before initiation of study drug therapy for 2 neonates.

Approvals from the human research review boards of all participating institutions and informed written parental consent were obtained before enrollment. Randomization procedures, data entry, and statistical analyses were coordinated by the Maryland Medical Research Institute, Baltimore.

TRIAL DESIGN AND THERAPEUTIC PROCEDURES

Preterm neonates born between 24 and 32 weeks’ gestation were enrolled if they had been intubated and required ventilatory support for less than 8 hours. Exclusion criteria included postnatal age greater than 72 hours, positive pressure ventilation for 8 or more hours, major congenital anomalies (defined as having surgical, medical, or cosmetic importance and requiring therapeutic interventions within 7 days after birth), severe intrapartum asphyxia (defined as a 5-minute Apgar score ≤3), and participation in other research studies that interfered with the NOPAIN study procedures or outcomes. To monitor for clinical bias and recruitment problems, all participating centers reported eligible neonates who were not enrolled.

Balanced randomization in blocks, stratified by each center, was performed through an automated telephone response system available 24 hours a day for authorized users at each site. Following enrollment, the randomized group allocation was faxed to the participating NICU and hospital pharmacy. Only one pharmacist at each site had access to the codes regarding drug assignment. Neonates were assigned to 3 groups, receiving midazolam hydrochloride (0.1 mg/mL in 10% dextrose), morphine sulfate (0.05 mg/mL in 10% dextrose), or placebo (10% dextrose) infusions. Physicians, nurses, and all NICU staff were masked to the identity of the study drug.

Loading and maintenance doses for the study drug (Table 1) were initially based on birth weight of the neonate then changed to current body weight after it exceeded the neonate’s birth weight. These doses were justified by recent clinical and pharmacokinetic studies in neonates that reported effective analgesia with morphine doses of 50 to 200 µg/kg and infusion rates of 7.5 to 50 µg/kg per hour. These data illustrated the variability of morphine pharmacokinetics in preterm neonates, with the potential for underdosing or overdosing these patients. Optimum midazolam doses for preterm neonates have not been defined. Most clinical experience and studies report that doses between 50 and 200 µg/kg are safe and effective in preterm neonates.

RESULTS

DEMOGRAPHIC AND CLINICAL VARIABLES

The demographic and clinical variables for the neonates and their mothers were similar in the 3 randomized groups (Table 3). Maternal diagnoses and use of medications before delivery were not significantly different in the 3 groups. Fetal distress occurred more frequently in the morphine group (P = .05), whereas trends for an increased incidence of preeclampsia (P = .15) in the morphine group or antepartum hemorrhage (P = .13) in the dextrose group were not significant. Duration for infusion of the study drug was determined by the clinical requirements for analgesia or sedation and based on specific criteria for stopping drug infusion (Table 2). No differences occurred in duration of treatment between the 3 groups (P = .37).
A fresh study drug syringe was prepared by the hospital pharmacy every 12 or 24 hours. Bolus doses or increases in the rate of infusion of the study drug were not allowed. Study drug infusions were continued for as long as clinically necessary or for a maximum of 14 days. Predefined clinical guidelines (Table 2) were followed for weaning and stopping the study drug infusion. Because of the inclusion of a placebo group, withholding additional analgesia from these neonates was considered unethical. At the discretion of the clinical team, additional analgesia was provided with intravenous morphine doses, and the amount and frequency of analgesia were recorded as outcome measures. Therapies that might interact with the use of analgesia (eg, the use of muscle relaxants, naloxone hydrochloride, flumazenil, enteral feeds, or anticonvulsants) were standardized for all neonates.

ASSESSMENT METHODS

Severity of illness was measured by the Clinical Risk Index for Babies,\(^1\) which uses clinical data from the day of birth and predicts the long-term clinical outcomes of preterm neonates,\(^2\) with the Neonatal Medical Index, which assesses a few clinically salient items at the time of hospital discharge,\(^3\) and was also found to be predictive of neurobehavioral status and subsequent developmental outcome.\(^4\) Level of sedation was assessed by the COMFORT score,\(^5\) and responses to pain were measured by the Premature Infant Pain Profile (PIPP) score.\(^6\) These measurements were obtained before starting the study drug infusion, after 24 hours of continued infusion, and at 10 to 12 hours after stopping infusion. Responses to tracheal suction were assessed by the PIPP score, selected because it is the only method developed and validated from clinical data in preterm neonates\(^7\) and has proven reliability for routine NICU monitoring.\(^8\)

SEVERITY OF ILLNESS

Severity of illness at birth was similar among the 3 randomized groups (P = .24) as measured by the Clinical Risk Index for Babies (Table 3). The distribution of Neonatal Medical Index risk categories at time of hospital discharge was significantly different in the 3 groups of neonates (P = .01).

POOR NEUROLOGIC OUTCOMES

Poor neurologic outcomes occurred in 24% of neonates in the placebo group, 32% of neonates in the midazolam group, and 4% of neonates in the morphine group (likelihood ratio \( \chi^2 = 7.04, P = .03 \)) (Figure 1). Two neonates in the placebo group and 1 neonate in the midazolam died; no deaths occurred in the morphine group (Table 4).

ADEQUACY OF ANALGESIA AND SEDATION

COMFORT scores were not significantly altered from baseline in any of the randomized groups. At 12 hours after stopping the drug infusion, decreased sedation was noted by significantly elevated COMFORT scores in the morphine group (P = .005), but remained unchanged in the midazolam and dextrose groups. Pain responses elicited by endotracheal tube suction (PIPP scores) were significantly reduced during the morphine (P < .001) and midazolam (P = .002) infusions compared with the placebo group (Table 4). Within-group comparisons showed significantly reduced PIPP scores during morphine infusion compared with baseline (P = .002); such changes were not noted in the midazolam or dextrose groups. Similar amounts of additional analgesia during the study drug infusion were prescribed by clinical staff according to predefined clinical criteria (Figure 2).

DATA MANAGEMENT AND STATISTICAL ANALYSES

Data forms were faxed to the NOPAIN Coordinating Center, reviewed for completeness, and entered into a database (Access; Microsoft Corp, Redmond, Wash). Weekly lists for patient recruitment and delinquent form status were sent to all participating NICUs. All datasheets were tracked and obtained from the participating centers before initiating statistical analyses with an SAS program (SAS Institute, Cary, NC).

Intention-to-treat data analyses were performed for the patients in this study. Poor neurologic outcomes were defined as neonatal death (occurring at 0-28 days of age without discharge from the NICU), IVH grade III or IV, or PVL. Satisfactory outcomes were defined as survival with IVH absent or maximum grade II and no PVL. To investigate the secondary effects of analgesia and sedation, we also collected data on weight gain, incidence of pneumothorax, durations of respiratory support, length of NICU stay and hospital stay, and neurobehavioral assessment scores at 36 weeks after conception.

Binary and categorical outcomes were compared among treatment groups using a likelihood ratio \( \chi^2 \) procedure.\(^9\) Logistic regression techniques were used to investigate the effects of treatment group allocation and other clinical variables on binary outcomes,\(^10\) with treatment group included as 2 indicator variables (placebo as the reference group). Comparisons of mean outcome levels among treatment groups were performed using linear regression analyses to calculate means adjusted for gestational age. Differences in baseline characteristics among the 3 treatment groups were assessed using the same techniques. All analyses were performed using SAS 6.12.\(^11\) Type I error level of P < .05 was used for the primary clinical outcome, but more stringent type I error levels were specified for the secondary outcome measures. For example, P < .01 represented evidence of differences and P < .001 represented strong evidence of differences in the secondary outcomes. SECON DARY CLINICAL OUTCOM ES

Process outcomes were measured by the number of days required for mechanical ventilation, continuous positive airway pressure or oxygen therapy, duration of NICU or hospital stay (Table 4), and tolerance of enteral feeds (Table 4). No significant differences occurred among

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the 3 randomized groups for any of these outcomes. Pneu-
mothorax occurred in 1 neonate from each of the mid-
azolam and dextrose groups but not in the morphine
group (Table 4). No differences occurred in daily weight
gain (normalized by birth weight) or neurobehavioral out-
comes of the neonates at 36 weeks (Neurobehavioral As-
sessment of the Premature Infant examination cluster
scores) after adjusting for differences in Neonatal Medi-
cal Index risk categories resulted from neonatal
complications during hospitalization (Table 4) and may
be related to the effects of therapy. Differences in mater-
nal use of prenatal medications were similar in all groups. CRIB
indicates Clinical Risk Index for Babies.

Demographic variables for neonates and mothers in
the 3 groups were remarkably similar despite the small
sample size. Clinical Risk Index for Babies scores in the 3
randomized groups showed that the severity of illness was
similar at birth, although significant differences occurred
at the end of hospitalization. Significant differences in Neo-
natal Medical Index risk categories resulted from neon-
al complications during hospitalization (Table 4) and may
be related to the effects of therapy. Differences in mater-
nal exposure to nonprescription drugs was not signifi-
cantly different between the randomized groups (Table 3),
although a greater proportion of mothers in the dextrose
group reported drug abuse during pregnancy. The im-
 pact of drug abuse during pregnancy on the risk of brain
injury in preterm neonates is determined by the drugs used
(increased risks with alcohol, cocaine, or nicotine abuse),
reduced risks with opiate abuse, and duration and degree of
exposure (ie, doses used, route of administration), and

Table 1. Loading and Maintenance Doses for the Study Drugs

<table>
<thead>
<tr>
<th>Gestation, wk</th>
<th>Loading Dose (&gt;1 h)</th>
<th>Maintenance Dose (Continuous Infusion), per Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume Infused, mL/kg</td>
<td>Morphine Sulfate Dose, µg/kg</td>
</tr>
<tr>
<td>24-26</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>27-29</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>30-33</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2. Guidelines for Stopping and Weaning the Study Drug Infusion

Criteria for Stopping the Study Drug Infusion
- Withdrawal of parental consent
- Planned extubation in the next 24 h
- No spontaneous respiration under predefined conditions*  
- Clinical condition such that death is imminent
- Severe hypotension or life-threatening effects
- Drug infusion continued for 14 d
- Surgical operation or exchange transfusion

Approach to Weaning the Study Drug Infusion
- Neonates receiving the study drug for ≤4 d were weaned in 1-2 d, initial doses reduced by 30%-50%, then by 20%-30% every 6-8 h†
- Neonates receiving the study drug for >4 d
- Decrease infusion rate by 25%-50% every 12 h
- Convert to intermittent intravenous doses every 4 h
- Increase the dose interval to every 8 h
- Treat withdrawal symptoms with morphine sulfate, phenobarbital, or lorazepam as necessary

Table 3. Demographic and Clinical Variables for Neonates and Mothers*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Midazolam (n = 22)</th>
<th>Morphine Sulfate (n = 24)</th>
<th>Dextrose (n = 21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation, mean (SD), wk</td>
<td>28.6 (2.5)</td>
<td>29.2 (2.2)</td>
<td>28.1 (2.2)</td>
<td>.33</td>
</tr>
<tr>
<td>Male, %</td>
<td>54.5</td>
<td>46.2</td>
<td>57.1</td>
<td>.73</td>
</tr>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>1245 (445)</td>
<td>1230 (475)</td>
<td>1049 (419)</td>
<td>.36</td>
</tr>
<tr>
<td>Entry weight, mean (SD), g</td>
<td>1224 (491)</td>
<td>1265 (501)</td>
<td>1188 (524)</td>
<td>.91</td>
</tr>
<tr>
<td>Duration of study drug, mean (SD), hours of infusion</td>
<td>122.2 (122.1)</td>
<td>81.0 (94.1)</td>
<td>121.1 (120.8)</td>
<td>.37</td>
</tr>
<tr>
<td>CRIB score, mean (SD)</td>
<td>5.7 (3.5)</td>
<td>4.5 (3.1)</td>
<td>6.6 (4.0)</td>
<td>.24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Midazolam (n = 22)</th>
<th>Morphine Sulfate (n = 24)</th>
<th>Dextrose (n = 21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>28.0 (5.9)</td>
<td>28.7 (5.3)</td>
<td>25.2 (4.8)</td>
<td>.25</td>
</tr>
<tr>
<td>Education, %</td>
<td>High school</td>
<td>College</td>
<td>Postgraduate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>44.4</td>
<td>42.1</td>
<td>44.4</td>
<td>.86</td>
</tr>
<tr>
<td>College</td>
<td>38.9</td>
<td>47.4</td>
<td>50.0</td>
<td></td>
</tr>
<tr>
<td>Postgraduate</td>
<td>16.7</td>
<td>10.5</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Income, $, %</td>
<td>&lt;20 000</td>
<td>28.5</td>
<td>35.3</td>
<td>.21</td>
</tr>
<tr>
<td></td>
<td>20 000-39 999</td>
<td>28.5</td>
<td>35.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;40 000</td>
<td>42.9</td>
<td>29.4</td>
<td></td>
</tr>
<tr>
<td>Drug use, %</td>
<td>Prescription</td>
<td>Nonprescription</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>63.6</td>
<td>46.4</td>
<td>71.4</td>
<td>.85</td>
</tr>
<tr>
<td></td>
<td>13.6</td>
<td>19.2</td>
<td>28.6</td>
<td>.47</td>
</tr>
</tbody>
</table>

*No spontaneous respiration noted at ventilator rates of 15/min or less, measured tidal volumes of 8 to 12 mL/kg, and Paco2 in the normal range (40-55 mm Hg or 5.3-6.7 kPa).
†At each step in weaning the study drug, careful attention was paid to avoid withdrawal symptoms; appropriate fluid therapy and adequate nutrition were given to support growth.
Table 4. Clinical Outcomes*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Midazolam</th>
<th>Morphone Sulfate</th>
<th>Dextrose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters Measuring the Severity of Illness in Neonates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal Medical Index Grade†</td>
<td>I</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>V</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Frequency of Neurologic Outcomes by Treatment Group, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (4.6)</td>
<td>0</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1 (4.6)</td>
<td>0</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>PVL</td>
<td>4 (18.2)</td>
<td>1 (4.2)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>IVH grade†</td>
<td>1</td>
<td>4 (18.2)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 (4.6)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3 (13.6)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2 (9.1)</td>
<td>0</td>
</tr>
<tr>
<td>Preterm Infant Pain Profile (PIPP) and COMFORT Scores, Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMFORT</td>
<td>Before drug</td>
<td>15.9 (3.8)</td>
<td>17.3 (4.6)</td>
</tr>
<tr>
<td></td>
<td>During drug</td>
<td>14.9 (4.6)</td>
<td>14.7 (3.2)</td>
</tr>
<tr>
<td></td>
<td>After drug</td>
<td>15.8 (4.7)</td>
<td>18.9 (4.0)</td>
</tr>
<tr>
<td>PIPP</td>
<td>Before drug</td>
<td>10.5 (4.1)</td>
<td>11.5 (4.0)</td>
</tr>
<tr>
<td></td>
<td>During drug</td>
<td>8.9 (3.3)§</td>
<td>7.9 (2.3)§</td>
</tr>
<tr>
<td></td>
<td>After drug</td>
<td>8.9 (4.4)</td>
<td>10.2 (2.9)</td>
</tr>
<tr>
<td>Secondary Clinical Outcomes, Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilatory support</td>
<td>14.2 (11.1)</td>
<td>7.5 (8.3)</td>
<td>12.2 (12.7)</td>
</tr>
<tr>
<td>Continuous positive airway pressure</td>
<td>12.1 (18.8)</td>
<td>7.1 (8.8)</td>
<td>9.8 (12.9)</td>
</tr>
<tr>
<td>Oxygen</td>
<td>35.0 (33.0)</td>
<td>27.6 (29.1)</td>
<td>32.3 (30.2)</td>
</tr>
<tr>
<td>Neonatal intensive care unit stay</td>
<td>48.6 (31.1)</td>
<td>32.2 (30.4)</td>
<td>37.5 (31.4)</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>78.0 (46.5)</td>
<td>56.1 (23.9)</td>
<td>57.5 (33.1)</td>
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<tr>
<td>Outcomes Related to Enteral Feeding, Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full strength</td>
<td>11.0 (7.1)</td>
<td>10.9 (7.8)</td>
<td>12.8 (17.4)</td>
</tr>
<tr>
<td>Full-volume NG</td>
<td>21.7 (14.0)</td>
<td>23.4 (16.4)</td>
<td>18.6 (15.5)</td>
</tr>
<tr>
<td>Full-volume PO</td>
<td>46.1 (20.7)</td>
<td>43.8 (18.2)</td>
<td>39.2 (28.4)</td>
</tr>
<tr>
<td>Daily Weight Gain Normalized by Birth Weight Treatment, Mean (SD), g/kg per Day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>0.91 (0.072)</td>
<td>0.97 (0.085)</td>
<td>0.92 (0.082)</td>
</tr>
<tr>
<td>14</td>
<td>0.97 (0.075)</td>
<td>1.00 (0.080)</td>
<td>0.98 (0.094)</td>
</tr>
<tr>
<td>21</td>
<td>1.08 (0.098)</td>
<td>1.12 (0.127)</td>
<td>1.08 (0.092)</td>
</tr>
<tr>
<td>28</td>
<td>1.17 (0.135)</td>
<td>1.26 (0.152)</td>
<td>1.15 (0.146)</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>1.97 (0.889)</td>
<td>1.78 (0.716)</td>
<td>1.96 (0.837)</td>
</tr>
<tr>
<td>NAPI Scores Adjusted for Neonatal Medical Index and Gestational Age, Mean (SEM)#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor development</td>
<td>54.9 (3.9)</td>
<td>57.4 (4.1)</td>
<td>55.6 (4.9)</td>
</tr>
<tr>
<td>Alertness and orientation</td>
<td>52.2 (5.4)</td>
<td>52.6 (5.7)</td>
<td>58.7 (6.7)</td>
</tr>
<tr>
<td>Irritability and crying</td>
<td>56.6 (7.3)</td>
<td>64.2 (7.7)</td>
<td>60.5 (9.2)</td>
</tr>
<tr>
<td>Scarf sign</td>
<td>59.9 (6.9)</td>
<td>62.8 (7.3)</td>
<td>52.1 (8.6)</td>
</tr>
<tr>
<td>Popliteal angle</td>
<td>44.8 (8.6)</td>
<td>56.9 (9.1)</td>
<td>51.6 (10.8)</td>
</tr>
<tr>
<td>Average NAPI score</td>
<td>53.6 (3.9)</td>
<td>58.6 (4.1)</td>
<td>55.7 (4.9)</td>
</tr>
</tbody>
</table>

*PVL indicates periventricular leukomalacia; IVH, intraventricular hemorrhage; NG, nasogastric; PO, by mouth; and NAPI, Neurobehavioral Assessment of the Premature Infant. No significant differences were noted on analysis of variance unless otherwise noted.
†Neonatal Medical Index risk classification likelihood ratio is $x^2 = 16.571, P = .01$; IVH incidence likelihood ratio is $x^2 = 11.818, P = .16$.
‡Dextrose vs midazolam during drug is $P < .01$, dextrose vs morphine during drug is $P < .001$, and morphine before vs during drug is $P < .01$.
§Morphine during drug vs morphine after drug is $P < .01$.
¶The daily weight gain was adjusted for birth weight in an analysis of covariance model. The only significant differences noted were between morphine vs midazolam on day 7 ($P = .03$), and morphine vs dextrose on day 28 ($P = .04$).
#NAPI scores were adjusted for Neonatal Medical Index and gestational age in an analysis of covariance model. F tests were performed to analyze differences among the treatment groups as well as to test placebo vs active treatment groups and midazolam vs morphine groups. No significant differences were noted. The adjusted NAPI scores are actually coefficients from regression equations; therefore, the mean (SEM) values are presented in this table.
duration of 120 hours in 20 preterm neonates 36 in-
toxication. Trends for the reduced durations of ventilation
term neonates received the study drug only as long as it
was considered clinically necessary, resulting in a variable duration of therapy for each preterm neonate. Clinical
criteria were standardized for weaning and stopping the study drug infusions
(Table 2). No significant differences occurred in the number of doses
required by the 3 groups on day 1, day 2, day 3, or days 4 through 14.
Numbers at the top of the bars indicate the total cumulative doses in
milligrams per kilogram.

![Figure 1. Neurologic clinical outcomes in the midazolam hydrochloride,
morphine sulfate, and dextrose groups.](image)

![Figure 2. Number of neonates requiring additional doses of morphine sulfate
analgesia on day 1, day 2, day 3, or days 4 through 14 after starting the
study drug infusion. Study drug infusions were masked from the clinical staff
and were administered for only as long as considered clinically necessary.
Numbers at the top of the bars indicate the total cumulative doses in
milligrams per kilogram.](image)

trimesters of pregnancy associated with drug abuse. It is
unclear whether drug abuse during pregnancy had any
impact on the neurologic outcomes of neonates included in
this study.

Physiological effects of intravenous opioid therapy
from clinical trials in preterm neonates have noted
decreases in stress hormones, 25–32 stabilization of blood pressure, 32,33 increased ventilator synchrony, 30,33,34 and improved oxygenation. 34,35 Fentanyl infusions for a fixed duration of 120 hours in 20 preterm neonates 36 increased sedation and decreased plasma stress hor-
mones, but also increased ventilatory requirements on
the third and fourth days compared with a placebo group. 36

A placebo-controlled trial 37 of midazolam infusion in
46 preterm neonates noted midazolam’s sedative effects
on neonatal behavior and maintenance of hemodynamic
stability, although no differences occurred in clinical outcomes
of the midazolam and placebo groups. Intravenous

doses of midazolam were noted to have variable effects on
the blood pressure and cerebral blood flow velocity of pre-
term neonates who required ventilatory support. 10,12

Our study design was based on the experience gained
in these previous studies. Loading dose and infusion rates
of morphine and midazolam were defined by pharma-

cokinetic data from preterm neonates. 7–12 Loading dose was
 injected slowly to prevent hypotension, and standard guid-
elines were developed for weaning and stopping the study
drug (Table 2). As occurs in routine clinical practice, pre-
term neonates received the study drug only as long as it
was deemed clinically necessary for analgesia or seda-
tion. Trends for the reduced durations of ventilation
(\( P = .13 \)), continuous positive airway pressure (\( P = .54 \)),
oxygen therapy (\( P = .77 \)), NICU (\( P = .24 \)) and hospital stay
(\( P = .11 \)), and reduced requirements for additional anal-
gesia in the morphine group (\( P = .80 \), all days; \( P = .06 \), days 4–14) were not statistically significant. Differences of such
magnitude must be investigated in a larger clinical trial.

Endotracheal suctioning causes substantial discom-
fort and is associated with acute cardiovascular changes,
hyoxemia, 35 release of catecholamines, 36,39 and atrial natriuretic peptide 39 in preterm neonates. This was the only
invasive procedure that occurred routinely, was ethi-
cally justified, and could be performed repetitively in pre-
term neonates who required ventilatory support. Anal-
geic effects were suggested by the decreased PIPP scores
during morphine and midazolam infusion compared with
the placebo group. Whether the decreased PIPP scores in
both the morphine and midazolam groups reflect the
sedative effects of both drugs or analgesic effect of mor-
phine in preterm neonates is open to question. A lack of
significant differences between groups in the COMFORT
scores assessed during active drug infusion may be due to
the psychometric properties of this method, which was
not developed or validated for preterm neonates. 19
However, the increase in COMFORT scores in the morphine
group at 10 to 12 hours after stopping the drug infusion
(Table 4) may indicate agitation associated with opioid
withdrawal.

Although the study drugs were infused for variable
periods and were carefully weaned before discontinua-
tion, it is likely that some neonates who received mor-
phine for prolonged periods may have developed mild opio-
id withdrawal. All neonates were assessed with the
Finnegan Neonatal Abstinence Scale at 12 and 24 hours
(and then daily) after discontinuation of treatment with
the study drug. Two neonates from the morphine group
developed mild opioid withdrawal with Neonatal Abstinen-
cence Scale scores of less than 8 at 12 and 24 hours after
stopping the drug infusion. In addition to tolerance and
withdrawal, the routine clinical use of opioids is not without
significant risks or adverse effects. Historically, opioids
were avoided in neonates and children because of po-
tential respiratory depression. Other central effects include
sedation, dysphoria, nausea and vomiting, and rarely, sei-
zures. Anticholinergic effects include urinary retention,
decreased intestinal motility, and biliary sludge syndrome.
Histamine release by morphine and its congeners may cause
pruritus, vasodilation, hypotension, and bronchospasm in
some neonates. Acute adverse effects can be reversed with
naloxone, whereas other adverse effects can be treated with
laxatives or prokinetic agents, antihistaminics, antiemet-
ic, and urinary catheterization as required.
Although the severity of illness and neurobehavioral outcomes were similar in the 3 groups, neonates in the morphine group showed a decreased incidence of poor neurologic outcomes compared with the midazolam and placebo groups. The incidence of poor neurologic outcomes in the dextrose group (24%) corresponds to the reported incidence of IVH and PVL in preterm neonates of this gestational age. However, because of a small sample size, we do not endorse changes in clinical practice based on these results.

A physiological rationale to explain these differences may be based on decreased stress, blood pressure stability, ventilator synchrony, and improved oxygenation. These effects of opioid therapy have been correlated with decreased neonatal mortality in one study and prolonged ventilatory support in another. Preterm neonates receiving opioid therapy for the prevention of opioid withdrawal were also noted to have a lower incidence of IVH than matched controls. The acute physiological effects of pain and stress and the temporal association of early IVH with the multiple invasive procedures required just after birth suggest a role for pain and stress in the multifactorial causation of early neurologic injury.

Painful procedures in neonates are generally associated with diaphragmatic splinting, forced expiratory movements (crying), tachycardia, and hypertension secondary to sympathetic activation. These changes will cause marked fluctuations in intracranial pressure and cerebral blood volume, leading to venous hemorrhage in the germinal matrix or brain parenchyma or extension of a small previous IVH. Effective opioid analgesia before or soon after intubation may prevent these physiologic changes in some neonates. Antenal factors other than chorioamnionitis play a limited role in the causation of early neurologic injury. These clinical data suggest the need for a large, randomized, placebo-controlled clinical trial to evaluate the effects of opioid analgesia on the incidence of poor neurologic outcomes in preterm neonates who require ventilatory support.

Our primary outcome measure was based on cranial ultrasonographic examinations performed routinely in the participating NICUs. The technique and equipment used for these ultrasonograms were not standardized, and the interpretation of each cranial ultrasonogram was performed locally. Standard criteria were used for the diagnosis of PVL and for grading the severity of IVH. However, a centralized reading of the ultrasonograms could not be obtained because of a lack of funding for this research.

This pilot study showed that it is feasible to recruit patients from participating centers, to perform randomization and therapeutic procedures, and to collect the data in a blinded fashion. Clinical outcomes important for testing our primary hypothesis were identified and their incidence was determined in the target population—allowing precise sample size calculations for a definitive study. Sample size calculations showed that the inclusion of 470 neonates in each group would allow the detection of a 30% decrease in incidence of poor neurologic outcomes with 80% power. In addition to differences in neurologic outcome, we report important trends for altering the duration of respiratory support and NICU and hospital stay in preterm neonates given morphine therapy. The drugs and doses used in this study were well tolerated, with no clinical or physiological changes during the loading dose or maintenance infusion, although much larger numbers will be required to adequately demonstrate the safety of these treatment regimens. We propose that preemptive analgesia in large numbers of preterm neonates must be investigated before the indiscriminate use of these drugs becomes widespread.

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REFERENCES

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likely to inhibit communication or to mislead us with extraneous information. She may save time but she also focuses thinking.

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Sleep Terrors

Owens et al found that night terrors in a 5-year-old girl characterized by agitation, unresponsiveness, violent shaking, flailing, screaming, crying, a “choking” sensation at sleep onset, and extreme autonomic arousal were exacerbated by sleep deprivation and environmental noise. They also noted that the periods of exacerbation immediately preceded or coincided with linear growth spurts, and a recent move and the father’s frequent absences on business travel were identified as potential stressors. She had had a recent onset of severe, unilateral headaches accompanied by photophobia, which were subsequently diagnosed as migraine headaches by a pediatric neurologist. Neurobiological features are suggested by reports linking noise stress, wakefulness, subclinical impairment of lung airways, disruption of brainstem cardiovascular control, and dysregulation of cortical silent periods, growth hormone, the microvasculature, and mood with dopamine abnormalities lateralized to the right hemisphere for which the metabolic rate is higher in females. This hypothesis is supported by optimal response organization and working memory at intermediate dopamine tone in a mediofrontostriatal activation system and deactivation of the right hemisphere, a state marker of depression, that promotes dominance of the left hemisphere associated with cardiac dysrhythmia, vasoconstriction, and aggressive response. It is also supported by the correlation of periodic leg movements in sleep with microarousals lasting more than 3 seconds and a more marked shortening of the R-R interval in the electrocardiographic signal. Therefore, the reemergence of an abnormally increased percentage of slow-wave sleep after discontinuation of treatment with benzodiazepines in this patient prompts cognitive-behavioral and/or pharmacological strategies that balance asymmetrical brain functions and promote a primary rhythm in the central nervous system that entrains heart rate, blood pressure, and respiratory rate, to prevent the arousal response going from autonomic activation to bursts of Δ activity to α activity to a full awakening.

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Correction

Coauthor’s Name Missing in Byline. The article by Anand et al titled “Analgesia and Sedation in Preterm Neonates Who Require Ventilatory Support: Results From the NOPAIN Trial,” published in the April issue of the ARCHIVES (1999;153:331-338), should have listed Bruce A. Barton, PhD, as a primary coauthor in the byline on page 331. The ARCHIVES regrets the error.