ARTICLE

Analgesia and Sedation in Preterm Neonates Who Require Ventilatory Support

Results From the NOPAIN Trial

K. J. S. Anand, MBBS, DPhil; Neil McIntosh, MBBS, FRCPCH; Hugo Lagercrantz, MD, PhD; Thomas E. Young, MD; Rohitkumar Vasa, MD; Bruce A. Barton, PhD

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.

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Editor's Note: This pilot study provides some thought-provoking information. It seems logical that pain is not good at any age, and it's nice to have some (if only preliminary) data to support this logic for neonates.

Catherine D. DeAngelis, MD

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.

DESPITE IMPROVEMENTS in clinical outcomes resulting from potent anesthesia and postoperative analgesia in neonates undergoing cardiac and noncardiac surgical operations,[1,2] substantial variability exists in the routine clinical use of analgesia and sedation for newborns.[3] Accumulating evidence indicates that exposure of preterm neonates to repetitive pain and stress in the neonatal intensive care unit (NICU) leads to clinical instability[4,5] 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

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, 57 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.

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Parental consent refused or withdrawn	57*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

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[7-9] 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.[10-12] Doses used in this trial were based on the clearance and metabolism of morphine and midazolam in preterm neonates of 24 to 32 weeks' gestation.

prolonged analgesia may be associated with tolerance, withdrawal, and other adverse effects are cited as reasons against the routine use of these drugs.

Preterm neonates experience perinatal stress from difficulties during labor and delivery, adaptation to the extrauterine environment, associated diseases of prematurity, and the multiple painful or stressful procedures required for treatment just after birth.[6] Acute physiological effects of pain and the temporal association of early intraventricular hemorrhage (IVH) occurring within 72 hours after birth suggest a role of pain and stress in the multifactorial causation or extension of early IVH and/or development of ischemic lesions leading to periventricular leukomalacia (PVL).

We hypothesized that the incidence of poor neurologic outcomes in preterm neonates who require ventilatory support (defined as neonatal death, severe IVH [grade III or grade IV], or PVL) would be decreased in neonates given morphine analgesia or midazolam hydrochloride sedation compared with a control group receiving placebo therapy. This pilot trial was designed 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.

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 ($P = .72$)in the morphine group or antepartum hemorrhage ($P = .15$) 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,[13,14] which uses clinical data from the day of birth and predicts the long-term clinical outcomes of preterm neonates,[15,16] and the Neonatal Medical Index , which assesses a few clinically salient items at the time of hospital discharge,[17] and was also found to be predictive of neurobehavioral status and subsequent developmental outcome.[18] Level of sedation was assessed by the COMFORT score,[19] and responses to pain were measured by the Premature Infant Pain Profile (PIPP) score.[20] 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[20] and has proven reliability for routine NICU monitoring.[21]

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 χ^2 procedure.[22] Logistic regression techniques were used to investigate the effects of treatment group allocation and other clinical variables on binary outcomes,[23] 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.[24] 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.

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**).

SECONDARY CLINICAL OUTCOMES

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

Table 1. Loading and Maintenance Doses for the Study Drugs

Gestation, wk	Loading Dose (>1 h)			Maintenance Dose (Continuous Infusion), per Hour		
	Volume Infused, mL/kg	Morphine Sulfate Dose, µg/kg	Midazolam Dose, µg/kg	Volume Infused, mL/kg	Morphine Sulfate Dose, µg/kg	Midazolam Dose, µg/kg
24-26	2	100	200	0.2	10	20
27-29	2	100	200	0.4	20	40
30-33	2	100	200	0.6	30	60

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

**No spontaneous respiration noted at ventilator rates of 15/min or less, measured tidal volumes of 8 to 12 mL/kg, and $Paco_2$ 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 3. Demographic and Clinical Variables for Neonates and Mothers*

Variable	Midazolam (n = 22)	Morphine Sulfate (n = 24)	Dextrose (n = 21)	P
Neonatal Data				
Gestation, mean (SD), wk	28.6 (2.5)	29.2 (2.2)	28.1 (2.2)	.33
Male, %	54.5	46.2	57.1	.73
Birth weight, mean (SD), g	1245 (445)	1230 (475)	1049 (419)	.36
Entry weight, mean (SD), g	1224 (491)	1265 (501)	1188 (524)	.91
Duration of study drug, mean (SD), hours of infusion	122.2 (122.1)	81.0 (94.1)	121.1 (120.8)	.37
CRIB score, mean (SD)	5.7 (3.5)	4.5 (3.1)	6.6 (4.0)	.24
Maternal Data				
Age, mean (SD), y	28.0 (5.9)	26.7 (5.3)	25.2 (4.8)	.25
Education, %				
≤High school	44.4	42.1	44.4	.86
College	38.9	47.4	50.0	
Postgraduate	16.7	10.5	5.6	
Income, $, %				
<20 000	52.6	28.5	35.3	.21
20 000-39 999	36.8	28.5	35.3	
≥40 000	10.5	42.9	29.4	
Drug use, %				
Prescription	63.6	65.4	71.4	.85
Nonprescription	13.6	19.2	28.6	.47

**P values based on analysis of variance. Obstetric diagnoses and the maternal use of prenatal medications were similar in all groups. CRIB indicates Clinical Risk Index for Babies.*

the 3 randomized groups for any of these outcomes. Pneumothorax occurred in 1 neonate from each of the midazolam and dextrose groups but not in the morphine group (Table 4). No differences occurred in daily weight gain (normalized by birth weight) or neurobehavioral outcomes of the neonates at 36 weeks (Neurobehavioral Assessment of the Premature Infant examination cluster scores) after adjusting for differences in Neonatal Medical Index and gestational age among the 3 groups (Table 4).

COMMENT

This pilot study was designed to demonstrate the feasibility of recruiting and randomizing eligible neonates, administering the masked therapies, and collecting pilot data on behavioral responses and clinical outcomes. These data support the short-term benefits of analgesia and sedation in preterm neonates who require ventilatory support; demonstrate the safety of the drugs, doses, and administration techniques used in this study; and suggest that morphine analgesia administered prophylactically may improve the defined neurologic outcomes. These data provide support for the design and analysis of a large multicenter trial.[3-6]

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 Neonatal Medical Index risk categories resulted from neonatal complications during hospitalization (Table 4) and may be related to the effects of therapy. Differences in maternal exposure to nonprescription drugs was not significantly different between the randomized groups (Table 3), although a greater proportion of mothers in the dextrose group reported drug abuse during pregnancy. The impact 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,[25-27] reduced risks with opiate abuse[28]), duration and degree of exposure (ie, doses used, route of administration), and

Table 4. Clinical Outcomes*

Variable	Treatment		
	Midazolam	Morphine Sulfate	Dextrose
Parameters Measuring the Severity of Illness in Neonates			
Neonatal Medical Index Grade†			
I	5	3	4
II	4	1	1
III	5	17	9
IV	5	0	3
V	3	3	4
Frequency of Neurologic Outcomes by Treatment Group, No. (%)			
Mortality	1 (4.6)	0	2 (9.5)
Pneumothorax	1 (4.6)	0	1 (4.8)
PVL	4 (18.2)	1 (4.2)	1 (4.8)
IVH grade†			
1	4 (18.2)	2 (8.3)	1 (4.8)
2	1 (4.6)	1 (4.2)	0
3	3 (13.6)	0	2 (9.5)
4	2 (9.1)	0	1 (4.8)
Preterm Infant Pain Profile (PIPP) and COMFORT Scores, Mean (SD)			
COMFORT			
Before drug	15.9 (3.8)	17.3 (4.6)	15.6 (3.2)
During drug	14.9 (4.6)	14.7 (3.2)	17.5 (4.2)
After drug	15.8 (4.7)	18.9 (4.0)‡	16.2 (4.1)
PIPP			
Before drug	10.5 (4.1)	11.5 (4.0)	11.4 (3.8)
During drug	8.9 (3.3)§	7.9 (2.3)§	12.7 (3.8)
After drug	8.9 (4.4)	10.2 (2.9)	9.9 (3.7)
Secondary Clinical Outcomes, Mean (SD)‖			
Ventilatory support	14.2 (11.1)	7.5 (8.3)	12.2 (12.7)
Continuous positive airway pressure	12.1 (18.8)	7.1 (8.8)	9.8 (12.9)
Oxygen	35.0 (33.0)	27.6 (29.1)	32.3 (30.2)
Neonatal intensive care unit stay	48.6 (31.1)	32.2 (30.4)	37.5 (31.4)
Hospital stay	78.0 (46.5)	56.1 (23.9)	57.5 (33.1)
Outcomes Related to Enteral Feeding, Mean (SD)‖			
Full strength	11.0 (7.1)	10.9 (7.8)	12.8 (17.4)
Full-volume NG	21.7 (14.0)	23.4 (16.4)	18.6 (15.5)
Full-volume PO	46.1 (20.7)	43.6 (18.2)	39.2 (28.4)
Daily Weight Gain Normalized by Birth Weight Treatment, Mean (SD), g/kg per Day¶			
Day			
7	0.91 (0.072)	0.97 (0.085)	0.92 (0.082)
14	0.97 (0.075)	1.00 (0.080)	0.98 (0.094)
21	1.08 (0.098)	1.12 (0.127)	1.08 (0.092)
28	1.17 (0.135)	1.26 (0.152)	1.15 (0.146)
Hospital discharge	1.97 (0.889)	1.78 (0.716)	1.96 (0.837)
NAPI Scores Adjusted for Neonatal Medical Index and Gestational Age, Mean (SEM)#			
Motor development	54.9 (3.9)	57.4 (4.1)	55.6 (4.9)
Alertness and orientation	52.2 (5.4)	52.6 (5.7)	58.7 (6.7)
Irritability and crying	56.6 (7.3)	64.2 (7.7)	60.5 (9.2)
Scarf sign	59.9 (6.9)	62.8 (7.3)	52.1 (8.6)
Popliteal angle	44.6 (8.6)	56.9 (9.1)	51.6 (10.8)
Average NAPI score	53.6 (3.9)	58.8 (4.1)	55.7 (4.9)

**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 $\chi^2 = 16.571$, P = .01; IVH incidence likelihood ratio is $\chi^2 = 11.818$, P = .16.

‡Morphine during drug vs morphine after drug is P<.01.

§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.

‖Mean (SD) of the number of days required for each treatment or number of days required to achieve enteral feeding; no significant differences were observed on analysis of variance.

¶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.

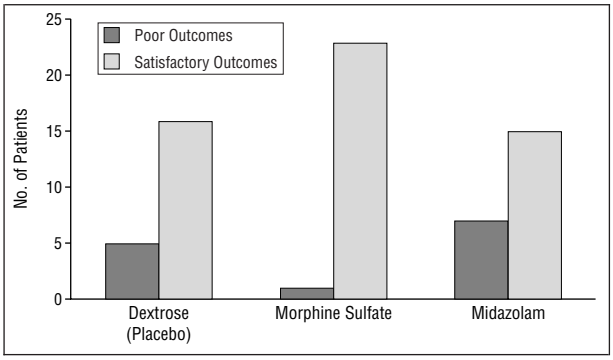

Figure 1. *Neurologic clinical outcomes in the midazolam hydrochloride, morphine sulfate, and dextrose groups. Clinical outcomes were defined as satisfactory: intraventricular hemorrhage (IVH) absent, grade I or grade II, no periventricular leukomalacia (PVL), and survival for more than 28 days; poor: IVH grade III or IV, PVL, or death at 28 days or less without discharge from the neonatal intensive care unit. Decreased incidence of poor neurologic outcomes occurred in the morphine group (likelihood ratio $\chi^2 = 7.04$, P = .03).*

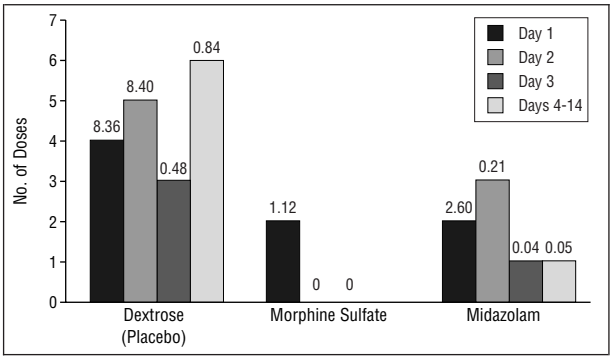

Figure 2. *Number of neonates requiring additional doses of morphine sulfate analgesia on day 1, day 2, day 3, or days 4 through 14 after starting the study drug infusion. Study drug infusions were masked from the clinical staff and were administered for only as long as considered clinically necessary, 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.*

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,[29-32] 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 hormones, 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 preterm 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 pharmacokinetic data from preterm neonates.[7-12] Loading dose was injected slowly to prevent hypotension, and standard guidelines were developed for weaning and stopping the study drug (Table 2). As occurs in routine clinical practice, preterm neonates received the study drug only as long as it was deemed clinically necessary for analgesia or sedation. 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 analgesia 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 discomfort and is associated with acute cardiovascular changes, hypoxemia,[35] release of catecholamines,[38,39] and atrial natriuretic peptide[39] in preterm neonates. This was the only invasive procedure that occurred routinely, was ethically justified, and could be performed repetitively in preterm neonates who required ventilatory support. Analgesic 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 morphine 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 discontinuation, it is likely that some neonates who received morphine for prolonged periods may have developed mild opioid 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 Abstinence 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 potential respiratory depression. Other central effects include sedation, dysphoria, nausea and vomiting, and rarely, seizures. 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, antiemetics, 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.[40-43] 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,[4,29-32,42] blood pressure stability,[32,33] ventilator synchrony,[30,33,34] and improved oxygenation.[34,35] These effects of opioid therapy have been correlated with decreased neonatal mortality in one study[4] and prolonged ventilatory support in another.[36] Preterm neonates receiving opioid therapy for the prevention of opioid withdrawal were also noted to have a lower incidence of IVH than matched controls.[32] 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.[4-6,43]

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[44] or extension of a small previous IVH. Effective opioid analgesia before or soon after intubation may prevent these physiological changes in some neonates. Antenatal 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.[43]

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[45] and for grading the severity of IVH.[46] 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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Centers and Contributors: Crawford Long Hospital, Emory University, Atlanta, Ga: K. J. S. Anand, MBBS, DPhil; Theresa Gauthier, MD; Ann Critz, MD; Carole Reddick, RN; Royal Infirmary, University of Edinburgh, Scotland: Neil McIntosh, MBBS, FRCPCH; Gopi Menon, MBBS; Osman G. Osman, MBBS; Karolinska Institute, Stockholm, Sweden: Hugo Lagercrantz, MD, PhD; Lena Bergqvist, RN; Björn Larsson, MD, PhD; Grace Maternity Hospital, Dalhousie University, Halifax, Canada: Ermelinda Pelausa, MD; Michael J. Vincer, MD; Robin K. Whyte, MD; Wake Medical Center, Raleigh, NC: Thomas E. Young, MD; Melissa R. Johnson, PhD; Mercy Hospital and Medical Center, Chicago, Ill: Rohitkumar Vasa, MBBS; Jagjit S. Teji, MBBS; Universitat Kinderklinik, Medical University of Lübeck, Lübeck, Germany: Ludwig Gortner, MD, PhD; Jens Möller, MD; Christiane Meyer, MD; I. Reiss, MD; Children's Hospital, University of Kentucky College of Medicine, Lexington: Nirmala S. Desai, MD; Vicki Whitehead, RN; Lori A. Shook, RN; Thomas H. Pauly, MD; Medical Center of Delaware, Thomas Jefferson Medical College, Philadelphia, Pa: Deborah J. Tuttle, MD; John L. Stefano, MD; Kathleen H. Leef, RN; Maryland Medical Research Institute, Baltimore: Bruce A. Barton, PhD; Joyce Depkin; Moscoe Johnson.

Corresponding author: K. J. S. Anand, MBBS, DPhil, Division of Critical Care Medicine, Arkansas Children's Hospital, Room S-431, 800 Marshall St, Little Rock, AR 72202-3591 (e-mail: anandsunny@exchange.uams.edu).

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likely to inhibit communication or to mislead us with extraneous information.[6,7] *She may save time but she also focuses thinking.*

Allan S. Cunningham, MD
Steven D. Blatt, MD
Paul G. Fuller, Jr, MD
Howard L. Weinberger, MD
Department of Pediatrics
SUNY Health Science Center
90 Presidential Plaza
Syracuse, NY 13202

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Sleep Terrors

Owens et al[1] 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.[2-5] 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.[6] Therefore, the reemergence of an abnormally increased percentage of slow-wave sleep after of 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,[5] to prevent the arousal response going from autonomic activation to bursts of δ activity to α activity to a full awakening.[6]

Ernest H. Friedman, MD
1831 Forest Hills Blvd
Cleveland, OH 44112-4313

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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.