ARTICLE

Variation Among Neonatal Intensive Care Units in Narcotic Administration

Doron J. Kahn; Douglas K. Richardson, MD, MBA; James E. Gray, MD, MS; Francis Bednarek, MD; Lewis P. Rubin, MD; Bhavesh Shah, MD; Ivan D. Frantz III, MD; DeWayne M. Pursley, MD

Objectives: To compare rates of narcotic administration for medically treated neonates in different neonatal intensive care units (NICUs) and to compare treated and untreated neonates to assess whether narcotics provided advantages or disadvantages for short-term outcomes, such as cardiovascular stability (ie, blood pressure and heart rate), hyperbilirubinemia, duration of respiratory support, growth, and the incidence of intraventricular hemorrhage.

Study Design: The medical charts of neonates weighing less than 1500 g, admitted to 6 NICUs (A-F), were abstracted. Neonates who had a chest tube or who had undergone surgery were excluded from the study, leaving the records of 1171 neonates. We modeled outcomes by linear or logistic regression, controlling for birth weight (<750, 750-999, and 1000-1499 g) and illness severity (low, 0-9; medium, 10-19; high, ≥20) using the Score for Neonatal Acute Physiology (SNAP), and adjusted for NICU.

Results: Narcotic use varied by birth weight (<750 g, 21%; 750-999 g, 13%; and 1000-1499 g, 8%), illness severity (low, 9%; medium, 19%; and high, 37%), day (1, 11%; 3, 6%; and 14, 2%), and NICU. We restricted analyses to the 1018 neonates who received mechanical ventilation on day 1. Logistic regression, adjusting for birth weight and SNAP, confirmed a 28.6-fold variation in narcotic administration (odds ratios, 4.1-28.6 vs NICU A). Several short-term outcomes also were associated with narcotic use, including more than 33 g of fluid retention on day 3 and a higher direct bilirubin level (6.8 µmol/L higher [0.4 mg/dL higher], $P = .03$). There were no differences in weight gain at 14 and 28 days or mechanical ventilatory support on days 14 and 28. Narcotic use was not associated with differences in worst blood pressure or heart rate or with increased length of hospital stay.

Conclusions: Our study found a 28.6-fold variation among NICUs in narcotic administration in very low-birth-weight neonates. We were unable to detect any major advantages or disadvantages of narcotic use. We did not assess iatrogenic abstinence syndrome or long-term outcomes. These results indicate the need for randomized trials to rationalize these widely differing practices.

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Editor's Note: When a 28.6-fold variation is found in the use of any treatment with no noted major advantages or disadvantages, it's time to raise the white flag and call in the controlled clinical trial cops.

Catherine D. DeAngelis, MD

THE BENEFITS of narcotic analgesia for relief of perioperative pain are well demonstrated, resulting in a clinical consensus and consistency of practice.[1-4] However, there is little agreement about the administration of narcotics to neonates in the neonatal intensive care unit (NICU) who are not undergoing surgical procedures. Despite the absence of clearly defined benefits and risks, strong opinions about the use of narcotics prevail.

Proposed benefits include reductions in the catecholamine stress response,[1] improved synchrony with the ventilator,[5] lower rates of pneumothoraces, fewer days with a need for supplemental oxygen, and diminished fluctuations in pulsatile blood flow.[6] This last effect has been associated with decreases in intraventricular hemorrhage (IVH).[7] However, narcotic administration also has been associated with substantial risks including drops in blood pressure and heart rate,[5,8,9] decreased oxygenation and respiratory drive,[5] and depression in the baroreflex control of heart rate.[5,10] Other metabolic responses, such as increased bilirubin levels,[11,12] also have been documented in association with the administration of narcotics. Moreover, reductions in pneumothoraces and chronic lung disease have not been found consistently.[9,13]

The affiliations of the authors appear in the acknowledgment section at the end of the article.

MATERIALS AND METHODS

STUDY DESIGN

We performed a secondary analysis of data collected as part of an ongoing study of NICU outcomes (see acknowledgments for a list of sites). For that study, we prospectively abstracted medical charts of all neonates with birth weights less than 1500 g admitted to 6 major regional NICUs during 21 months (October 1, 1994, to June 30, 1996). The charts of neonates who were readmitted and neonates born outside the study sites who were admitted after 24 hours of life were excluded from the study. Neonates born in a study site constituted 87% to 100% of the very low-birthweight admissions to the 6 NICUs. Our intention was to study narcotic sedation in medically treated neonates, rather than pain control in surgical patients. We therefore excluded from analysis the charts of neonates who had a chest tube or pericardial tube in place or who had undergone major or minor surgery at any time. Since many of these surgical treatments occurred after day 1, we retained a larger data set for day 1 analyses, but still excluded day 1 surgically treated neonates. Since all but 3 neonates receiving narcotics on day 1 were receiving mechanical ventilation, we controlled for the 1018 neonates who received mechanical ventilation on day 1. Narcotic use data were collected on days 1, 3, and 14 of hospitalization. Narcotic use was defined as any narcotic administered during the 24-hour period. We did not collect information about the dosage or the type of narcotic. The methods of narcotic administration (intravenous bolus or constant infusion) were recorded but were combined for most analyses. On study days 1, 3, and 14, we collected data by using a checklist of other therapies included on the Neonatal Therapeutic Intervention Scoring System[22] (eg, modes of respiratory support, medications, invasive and noninvasive monitoring, operations or procedures, feedings, use of intravascular catheters, and administration of transfusions) and calculated the Score for Neonatal Acute Physiology (SNAP),[23] a neonatal illness severity index. The SNAP assesses the worst status of a neonate during a 24-hour period (12 hours for day 1) for a variety of physiologic measures (including vital signs, laboratory values, and the occurrence of seizures and apnea). The SNAP is the sum of points given for the physiologic derangements of each organ system. A higher SNAP indicates a sicker neonate. The SNAP has been shown to be a highly significant predictor of morbidity and mortality risk.[24] We used several of the individual components of SNAP (eg, blood pressure measurement, heart rate, and bilirubin level) as measures of specific organ-system effects. Data about important outcomes, including respiratory distress syndrome, bronchopulmonary dysplasia, IVH, and length of stay also were collected.

DATA COLLECTION

Data abstraction was performed prospectively using laptop computers equipped with a customized data entry program and explicit definitions. This process allowed for immediate error checking and minimized the problem of missing medical charts. Extensive training and supervision ensured uniformity at all sites. Medical chart review was approved by the institutional review boards at all 6 participating institutions. To preserve the confidentiality of the sites, they are labeled as A through F.

STATISTICAL ANALYSIS

All data management was performed using the Statistical Analysis System (Version 6.09; SAS Corporation, Cary, NC). Univariate analyses were performed using *t* tests and χ^2 tests. Multivariate methods included linear and logistic regression, for which we used dummy variables for the site. Our principal models used linear regressions predicting short-term physiologic responses (eg, blood pressure measurement, serum bilirubin level, and weight gain) as a function of narcotic administration, adjusted for illness severity and birth weight. For outcomes with significantly skewed distributions, such as duration of mechanical ventilation or oxygen treatment, we used log-linear regression. Short-term outcomes (eg, IVH and respiratory support at 28 days) were modeled using logistic regression. We repeated the intersite regression analyses using SUDAAN (Research Triangle Institute, Research Triangle Park, NC), which controls for clustering, in computing site-specific SEs. Results are stated as the mean ± SD or as odds ratios (ORs) with 95% confidence intervals (CIs).

Narcotic tolerance develops rapidly, requiring steadily higher doses, and is compounded by the relatively slow metabolism of opiates by premature neonates.[14] Iatrogenic narcotic dependence has been reported to occur in 50% to 60% of patients in 2 pediatric intensive care units[15,16] and 1 NICU.[17] Reports of long-term adverse behavioral effects in children of narcotic-addicted mothers and in animal studies are disturbing.[18-21]

Despite the frequent use of narcotic sedation in the NICU, only 3 small randomized trials of narcotic sedation in nonsurgical neonates have been reported.[5,9,13] Quinn et al[9] demonstrated a significant reduction in catecholamine levels in 41 neonates randomized to morphine infusion or placebo. There were no other differences in measured outcomes. Dyke et al[5] showed improved synchrony with mechanical ventilation, decreased heart rate, and fewer days with a need for supplemental oxygen in 26 neonates. Orsini et al[13] randomized 20 preterm neonates receiving mechanical ventilation to fentanyl citrate infusion or placebo and showed reduced heart rate, more sedated behavior, and lower serum 11-deoxycortisol levels. However, the fentanyl-treated neonates required higher ventilatory pressures and rates and remained catabolic as measured by 3-methylhistidine–creatinine ratios. None of the studies addressed long-term outcomes. Considered together, these studies demonstrated limited short-term benefits but were too small to identify clinically significant adverse effects, and they did not address long-term outcomes.

Wide differences in clinician attitudes about narcotic sedation lead to marked differences in administration. We made use of these arbitrary (quasi-random) differences in clinical practice patterns to compare out-

Table 1. Population Characteristics*

	NICU						
	A	B	C	D	E	F	*P*
Birth weight, g	1047 ± 294	1050 ± 289	1086 ± 263	996 ± 295	1080 ± 287	1082 ± 254	<.01
Gestational age, wk	28.2 ± 2.9	28.3 ± 2.7	28.3 ± 2.7	27.7 ± 2.8	28.5 ± 2.8	28.2 ± 2.8	<.01
Boys	49.7	50.0	58.8	53.3	49.1	53.0	.75
Apgar score <7 at 5 min	42.7	20.5	17.5	29.9	20.7	22.6	<.001
SGA	12.6	12.2	8.1	7.2	12.8	8.3	.19
Day 1 SNAP	11.8 ± 6.7	9.9 ± 6.7	8.6 ± 6.6	11.7 ± 7.8	9.0 ± 5.7	12.0 ± 7.2	<.01

**All neonatal intensive care unit (NICU) admissions (N = 1422) after day 1 exclusions. Values represent mean ± SD or percentage. The letters for the NICUs represent 6 NICUs that participated in the study. SGA indicates small for gestational age, less than the fifth percentile for birth weight; SNAP, Score for Neonatal Acute Physiology.*

Table 2. Comparison of Patients Receiving and Not Receiving Narcotics on Day 1*

	Narcotics	No Narcotics	*P*
Population characteristics			
n	199	1223	<.001
Birth weight, g	929 ± 284	1080 ± 279	<.001
Gestational age, wk	27.5 ± 2.6	28.5 ± 2.8	<.001
Boys	58.8	50.2	.07
White	64.3	61.3	.14
Apgar score <7 at 5 min	43.7	23.5	<.001
SGA	5.6	11.8	<.01
Day 1 SNAP	16.0 ± 8.0	9.5 ± 6.1	<.001
Treatment			
Pressor support	55.8	16.5	<.001
Volume support	46.7	16.5	<.001
Mechanical ventilation	98.4	67.2	<.001
Treatment of acidosis	27.6	6.6	<.001
Arterial catheter	92.0	49.4	<.001
Ventilator use, d	33.5 ± 27.4	21.5 ± 26.5	<.001
Oxygen use, d	55.3 ± 39.8	31.9 ± 38.3	<.001

**All neonatal intensive care unit admissions (N = 1422) after day 1 exclusions. Values represent mean ± SD or percentage. SGA indicates small for gestational age, less than the fifth percentile for birth weight; SNAP, Score for Neonatal Acute Physiology.*

comes of a large cohort of neonates treated in different NICUs, in which narcotic treatment reflected local practices, not simply a sicker neonate. Fair comparisons were achieved by adjustment for individual risk factors, including birth weight and illness severity. The goals of the present study were to compare rates of narcotic administration for medically treated neonates in different NICUs and to compare treated and untreated neonates to assess whether narcotics provided advantages or disadvantages for short-term outcomes, such as cardiovascular stability (ie, blood pressure and heart rate), hyperbilirubinemia, duration of respiratory support, growth, and the incidence of IVH.

RESULTS

POPULATION

The demographic data for the patient population on day 1 are listed in **Table 1** according to site. The NICUs are designated A through F and ranked by increasing day 1 narcotic use. The mean birth weight at the 6 sites ranged from 996 g to 1086 g ($P<.01$), and the mean gestational age at birth ranged from 27.7 weeks to 28.5 weeks ($P<.01$). The significant variation in average day 1 SNAP scores among the sites (8.6-12.0) indicates differences in illness severity at admission. We therefore adjusted for SNAP, as well as birth weight and mechanical ventilation, in each analysis. A comparison of the rates of low Apgar scores (<7) at 5 minutes also showed significant inter-NICU differences. The proportion of neonates born outside the study sites ranged from 0% to 10% (data not given to preserve the identity of sites). The lower birth weights, gestational ages, and Apgar scores, and higher SNAP scores at NICUs A, D, and F indicate a population at higher risk in these NICUs.

During the study period, 1572 very low-birthweight neonates were admitted (primary admission) to 1 of the 6 NICUs. We excluded 150 cases (9.5%) from day 1 analyses for the following reasons: the neonate had undergone surgery or had a chest tube in place (n = 33, 2.1%); the neonate was not born at one of the study sites and was admitted after 24 hours of life (n = 18, 1.1%); the neonate died within 24 hours of admission (n = 37, 2.4%); the neonate was transferred out of the NICU within 24 hours of admission (n = 18, 1.1%); and the medical chart was incomplete (n = 74, 4.7%). These exclusions resulted in 1422 charts included for day 1 analysis. An additional 251 medical charts of neonates were excluded from day 3, day 14, and short-term outcome analyses because of subsequent surgery or placement of chest tubes or surgically placed central lines, resulting in use of the charts of 1171 neonates for day 3, day 14, and short-term outcome analyses (a total of 401 were excluded, 25.5%). The 199 neonates who received narcotics on day 1 were more premature, sicker, and had lower Apgar scores. Virtually all of these neonates received mechanical ventilation and a greater number of critical care treatments (**Table 2**).

NARCOTIC ADMINISTRATION BY BIRTH WEIGHT, ILLNESS SEVERITY, AND DAY

The administration of narcotics was more frequent for the smallest neonates and declined with increasing birth weight category (<750 g, 22%; 750-999 g, 13%; and 1000-1499 g, 8%; $P<.001$) among the total nonsurgical cohort eligible for study after day 1. Use rates declined sig-

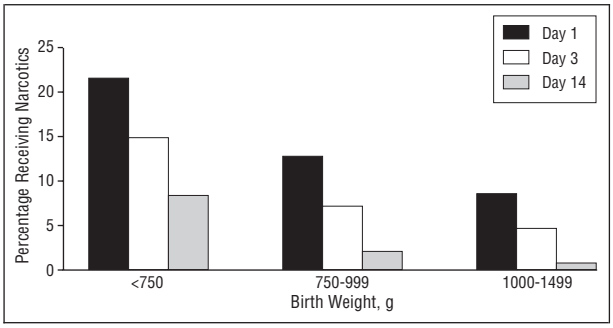

Figure 1. *Narcotic use by birth weight and by day of life for all neonates weighing less than 1500 g at birth admitted to 1 of 6 neonatal intensive care units. Lesser use by increasing birth weight group was significant on days 1, 3, and 14 (all P<.001). Declining rates of use from day 1 to day 3 and day 14 were significant within each birth weight group (P<.001).*

Table 3. Odds of Day 1 Narcotic Treatment by Birth Weight, Illness Severity, and Mechanical Ventilation*

Risk Factor	Odds Ratio (95% Confidence Interval)
Birth weight, g	
<750	1.0 (0.6-1.6)
750-999	1.2 (0.6-1.6)
1000-1499	1.0 (Reference)
SNAP	
0-9	1.0 (Reference)
10-19	2.3 (1.5-3.6)
≥20	8.3 (4.5-15.2)

**All neonates receiving mechanical ventilation (N = 1018) after day 1 exclusions. SNAP indicates Score for Neonatal Acute Physiology.*

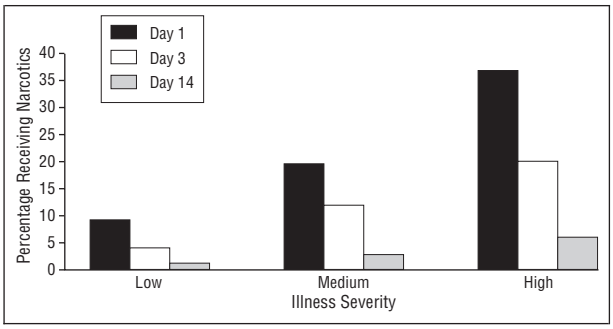

Figure 2. *Narcotic use by illness severity on days 1, 3, and 14 for neonates weighing less than 1500 g at birth who were receiving mechanical ventilation on day 1 and eligible for the study during days 1 to 14 (see text). Illness severity was measured using the Score for Neonatal Acute Physiology, categorized as low (0-9), medium (10-19), or high (≥20). Declining use by day was significant in each illness severity group (all P<.01). Differences between severity groups were significant on days 1 (P<.001) and 3 (P<.01).*

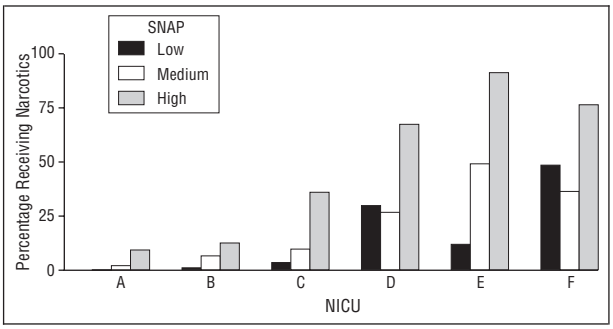

Figure 3. *Day 1 narcotic use for neonates receiving mechanical ventilation by level of illness severity and by neonatal intensive care unit (NICU). The neonates weighed less than 1500 g at birth. Illness severity was measured using the Score for Neonatal Acute Physiology (SNAP), categorized as low (0-9), medium (10-19), and high (≥20). There was substantial inter-NICU variation in overall rates of narcotic use, as well as inter-NICU differences in use according to each level of severity (P<.001).*

nificantly from day 1 to day 14 across all birth weight groups (**Figure 1**).

For the 1018 neonates who received mechanical ventilation on day 1, narcotics were used most frequently for the sickest patients (ie, SNAP ≥20) and less frequently for moderately and mildly ill neonates (**Figure 2**). Narcotic administration declined rapidly by day 3 and day 14. However, initial severity of illness remained associated with high rates of use on day 3 ($P<.001$) and day 14 ($P=.03$). The independent contributions of birth weight and illness severity as predisposing factors for narcotic use on day 1 among the 1018 neonates who received mechanical ventilation are given in **Table 3**. This logistic model indicates that lower birth weight exerts its effect entirely through its association with higher illness severity. In this population, moderately ill neonates were 2.3 times more likely and severely ill neonates were more than 8 times more likely to receive narcotics.

On day 1, 38 (19.1%) of 199 narcotics treatments were by infusion, the rest by intermittent boluses. Preference for constant infusion ranged from 0% at site C to 100% at site B. This mode of treatment was used for slightly sicker neonates (SNAP, 19.2 vs 15.2; $P<.05$) and for those with lower Apgar scores (65% of infusions vs 35% of bolus; $P<.01$). There were no differences between neonates receiving bolus vs infusion in birth weight, gestational age, presence of an arterial line, or volume support, and no differences were noted based on weights considered small for gestational age. However, pressor infusions were significantly more likely to be used for neonates receiving narcotic infusions (73% of infusions vs 52% of bolus; $P<.02$), suggesting a physician preference effect.

VARIATIONS AMONG NICUs

Since illness severity and mechanical ventilation were the 2 major factors associated with narcotic administration, we compared rates of day 1 narcotic use, stratified by SNAP, for neonates receiving mechanical ventilation, by NICU (**Figure 3**). NICUs D, E, and F showed significantly higher overall narcotic use and, moreover, had significantly higher rates of use for each level of illness severity. The marked differences in narcotic use may be driven by the additive risks of birth weight and illness severity. To control for these combined effects, we used a maximum likelihood estimate model for the 1018 neonates who received mechanical ventilation included in day 1 analysis, with sites B through F as dummy variables and site A as the reference. The adjusted ORs for day 1 narcotic use, given in the following tabulation, indicate that the likelihood of treatment in sites B through

Table 4. Association of Day 1 and Day 3 Narcotic Treatment With Specific Short-term Outcomes*

Outcome	Attributable Effect	*P*	Model
Cardiovascular (day 1 only)			
Mean blood pressure, mm Hg			
Lowest	. . .	.13	Linear†
Highest	. . .	.11	Linear†
Sustained heart rate, beats/min			
Lowest	. . .	.07	Linear†
Highest	. . .	.09	Linear†
Respiratory, OR			
Receiving ventilation at day 14	. . .	.52	Logistic†
Receiving ventilation at day 28	. . .	.32	Logistic†
Duration of positive-pressure ventilation, d	. . .	.12	Log-linear‡
Duration of supplemental oxygen	. . .	.43	Log-linear‡
Illness severity, day 3 SNAP points	+1.8	.001	Linear†
Growth, weight, g			
Day 3	+33	.001	Linear†§
Day 14	. . .	.60	Linear‡℠§
Day 28	. . .	.31	Linear‡§
Nutrition support, OR			
Gavage feedings, day 14	. . .	.07	Logistic‡
Parenteral nutrition, day 14	. . .	.38	Logistic‡
Central vascular line	. . .	.21	Logistic‡
Serum bilirubin level, μmol/L (mg/dL)			
Highest			
Direct	+6.8 (+0.4)	.03	Linear‡
Indirect	. . .	.06	Linear‡
Day 14			
Direct	+17.1 (+1.0)	.01	Linear‡
Indirect	. . .	.10	Linear‡
Intraventricular hemorrhage, any, OR	2.6	.04	Logistic†
Length of stay, gestational age in weeks at discharge	. . .	.40	Linear§

**OR indicates odds ratio; SNAP, Score for Neonatal Acute Physiology; and ellipses, no significant effect.*

†*Adjusted for day 1 SNAP.*

‡*Adjusted for day 1 and day 3 SNAP. Effects attributable to day 3 narcotic use.*

§*Includes small for gestational age.*

F ranged from 2.0- to 28.6-fold greater compared with the lowest-use NICU.

NICU	OR (95% CI)
A	1.0 (Reference)
B	2.0 (0.7-5.1)
C	4.1 (1.5-11.0)
D	13.6 (5.9-31.6)
E	22.3 (10.3-48.5)
F	28.6 (12.5-65.3)

SHORT-TERM OUTCOMES ANALYSIS

Next we compared several short-term outcomes for the neonates who received narcotics on day 1, 3, or 14 with the remainder of the population who did not receive narcotics. In all models, we controlled for birth weight, SNAP, mechanical ventilation, and site. For items that are included in SNAP (specifically, highest and lowest day 1 heart rate and mean blood pressure measurements), we reduced SNAP by the corresponding variable in the respective models. The 20 neonates receiving narcotics on day 14 were too few to permit multivariate analysis. Results are given in **Table 4** and discussed in the following sections.

Cardiovascular Stability

Narcotic treatment was not associated with significant alterations in highest and lowest blood pressure measurements and heart rates on day 1, independent of birth weight, illness severity, and mechanical ventilation.

Respiratory Outcomes

Narcotic administration on days 1 and 3 was not associated with the need for mechanical respiratory support on day 14 or on day 28. However, in this very low-birthweight population, the median duration of mechanical support was 23 days, so such short-term analyses may underestimate the effects. A more complete picture comes from the analyses of duration of mechanical ventilation and duration of supplemental oxygen treatment. We used log-linear models for handling the skewed distribution in respiratory support. A log-linear model tests for the proportionate increase (or decrease) rather than the absolute increase (or decrease). We found a 63% relative increase (95% CI, 34-101; $P<.002$) in days on which ventilatory support was required for narcotic-treated neonates on day 3. Similarly, the relative increase in oxygen support for narcotic-treated vs untreated neonates was 103% higher (95% CI, 60-160; $P<.001$). However, neonates still receiving narcotics on day 3 were significantly sicker than those who received narcotics on day 1 only (SNAP, 11.5 vs 6.6; $P<.01$). We therefore adjusted for day 3 illness severity. The revised results indicated no independent effect of narcotics on duration of mechanical ventilation or duration of supplemental oxygen.

Illness Severity

Our findings of higher severity of illness for neonates still receiving narcotics by day 3 could result from 2 causes: (1) self-selection or bias of indication; narcotic administration was more likely to be stopped for neonates who received narcotics on day 1 when their conditions improved, while those who remained ill would be more likely to receive longer treatment with narcotics; and (2) causal; continued treatment with narcotics on days 2 and 3 might lead to a cycle of lowered blood pressure, higher volume support, and edema, resulting in higher day 3 severity. To explore these possibilities, we performed a regression predicting day 3 severity from day 1 severity, birth weight, and day 1 narcotic use. We found that day 1 narcotic use was associated with a 1.8-point increase in the day 3 SNAP ($P<.02$) relative to neonates receiving mechanical ventilation, who were of comparable size and severity of illness on day 1, who did not receive narcotic sedation. Most of this effect (1.2 points) was attributable to the respiratory subscore of SNAP ($P<.001$). While this finding of more compromised respiratory status cannot exclude bias of indication, an association with narcotics during the first 12 hours strengthens the second argument.

Weight Gain and Nutritional Support

Narcotic use on day 1 was associated with a 33-g increase in weight by day 3 ($P<.001$), likely reflecting fluid accumulation. In contrast, narcotic use on days 1 and 3 did not predict weight gain at day 14 or day 28. Similarly, the levels of nutrition support at day 14 (eg, use of parenteral nutrition and use of gavage feedings) were unaffected by day 1 or day 3 narcotic use.

Serum Bilirubin Levels

Narcotic administration was associated with significantly increased direct but not indirect serum bilirubin levels. Models predicting peak direct bilirubin as a function of birth weight, SNAP, and day 3 narcotic use indicated a 6.8-µmol/L or greater (0.4-mg/dL; $P<.03$) increase compared with neonates who did not receive narcotics and a 17.1-µmol/L (1.0-mg/dL) differential elevation on day 14 ($P<.01$). Narcotic use on days 1 or 14 was not associated with direct or indirect bilirubin levels. There were significant site-specific differences in day 3 direct and indirect serum bilirubin levels; however, controlling for site-specific differences confirmed the absence of an association with narcotic use.

Incidence of IVH

The incidence of any IVH for neonates receiving mechanical ventilation who had received narcotics on day 1 was 26.0% (33/127), which did not differ significantly from the 21.5% incidence (142/659) for untreated neonates. Logistic models controlling for birth weight, illness severity on days 1 and 3, and mechanical ventilation confirmed this absence of association. The incidence of severe (grade III-IV) IVH was 9.4% (12/127) for narcotic-treated neonates and 3.3% (22/659) for neonates who received no narcotic treatment ($P<.01$). Because treated neonates were sicker and smaller, we performed a logistic adjustment. The OR remained elevated (OR, 2.6; 95% CI, 1.05-6.7; $P=.04$). This finding may represent residual confounding by indication.

Length of Stay

Surviving neonates who had received narcotics were discharged at ages comparable to those of the neonates who had not received narcotics.

COMMENT

Narcotic administration for very low-birth-weight neonates who do not have surgical conditions seems to be a common practice in NICUs. We found that administration of narcotics was reserved almost exclusively for neonates receiving mechanical ventilation, although the majority of these neonates did not receive narcotics. The present study also demonstrated considerable inter-NICU variation in narcotic treatment for very low-birth-weight neonates (a 28.6-fold difference between the highest-use compared with the lowest-use site) that cannot be explained by birth weight or by illness severity. These differences reflect differing clinical styles among physicians practicing in the study NICUs. These practice patterns are probably related to differing impressions about the hazards and benefits of narcotic use. It is noteworthy that this magnitude of variation exists among similar units. The 6 NICUs are major regional academic perinatal centers in 2 adjacent New England states. Our findings raise the possibility that even wider variations may exist among geographically or organizationally disparate NICUs. These observations confirm that there is no common standard of care for the administration of narcotics for high-risk neonates. One explanation for the variation in narcotic use may lie in the difficulties of recognizing pain in neonates that might lead to overprescription or underprescription of narcotics.[25-28] Another possible explanation lies in the choice of therapy for neonates breathing asynchronously against the ventilator. While some clinicians view narcotics as the treatment of choice for such sedation, others prefer benzodiazepines or phenobarbital as sedatives.[3,25,29] Other clinicians believe it is feasible to calm agitated neonates by using nonpharmacologic measures, such as soothing by talking to or stroking them or by adjusting ventilator rates. The recent introduction of synchronized ventilation also may affect sedation practices. In 5 of the 6 participating NICUs, 90% to 100% of ventilators were equipped for synchronized ventilation, and this was the mode of choice when a conventional ventilator was used. At NICU E, only 50% to 60% of the ventilators were equipped for synchronized ventilation, but at site F, a higher narcotic-use site, the percentage was 90%. This alone cannot explain the differences. We did not measure the substitution of alternative sedatives on a case-specific basis, but our general impression was that aggressive treatment was global; sites that used narcotics also used pressors, fluid boluses, and supplemental sedatives.

Such widely divergent practice styles constitute a natural experiment. Our study made use of these arbitrary differences in clinician practices to compare outcomes in a large cohort of similar neonates, adjusting for birth weight, illness severity, and mechanical ventilation. We found that narcotic treatment was associated with some clinically significant effects on short-term outcomes. Narcotic use on day 1 was associated with a 33-g greater weight on day 3. This increase could be due to associated fluid volume support, fluid retention from inactivity, or both. Regardless of the mechanism, increased weight on day 3 has been associated with a significant increase in the development of chronic lung disease.[30,31] Narcotic use also was associated with small but statistically significant increases in serum direct bilirubin levels on day 3. Roth et al[12] reported a similar finding, that neonates who received fentanyl had higher values of serum bilirubin than did neonates in the control group. The long-term clinical significance of these modest elevations in serum bilirubin is unknown, but it is likely to be inconsequential. Our finding of an association between higher day 3 illness severity and day 1 narcotic use probably represents bias of indication (ie, sicker babies were still receiving narcotics). However, it does raise the possibility that prolonged narcotic administration may delay resolution of illness, possibly through the mechanism of fluid accumulation as noted.

Owing to the nature of the study (medical chart abstraction), we did not measure acute cardiovascular and metabolic effects immediately after administration of narcotics. We did, however, record the highest and lowest blood pressure measurements and heart rates during the first 12 hours on day 1 and found that narcotic use had no significant effect on these extreme values. There are conflicting reports involving the effects of narcotics on cardiovascular function. Orsini et al[13] found no differences in mean arterial pressure between neonates who received fentanyl infusions and those who received placebo, but they did find that the group who received narcotics had significantly lower mean heart rates. Dyke et al[5] found a similar effect in morphine-treated neonates. In contrast, Roth et al[12] and Miall-Allen and Whitelaw[6] found no relationship between narcotic treatment and change in heart rate. Friesen and Henry[8] found a significant decrease in mean arterial pressure after administration of narcotics. A more controlled study, measuring the immediate effect of narcotic use on cardiovascular function in medically treated very low-birth-weight neonates, is warranted. The association in our study between narcotic treatment and severe IVH likely represents residual confounding by indication; no previous studies have suggested that narcotic treatment enhances the odds of IVH. Confounding by indication is present and powerful; sicker neonates are more likely to receive narcotics and to have IVH. Adjustment for SNAP may incompletely measure and control for the factors that cause IVH. At a minimum, however, the absence of a protective effect of narcotic treatment against IVH is not consistent with the hypothesis that sedation or skeletal muscle relaxation might reduce the cerebrovascular pulsatility and protect against IVH.[7,32]

There are several limitations to this study. First, it is an observational study making use of predefined variables. Second, we did not measure important long-term outcomes, including neurodevelopment and behavior. Several studies have found that prolonged in utero exposure to opiates affects behavioral development (specifically, heightened activity and brief attention spans) and motor inhibition.[19-21] The similarity between the premature neonate in the NICU and the fetus in utero supports suggestions that narcotics may affect brain development and behavior. Third, we did not ascertain occurrence of iatrogenic withdrawal. Finally, practice patterns at the study sites may covary with narcotic use; eg, clinicians at a given site may prefer a globally aggressive practice style, using narcotics and pressors. By controlling our multivariate models for site (and therefore for such copractices), we may be underestimating the effects of narcotics.

The results of the present study are reassuring and cautionary. Advocates of narcotic treatment for very low-birth-weight neonates receiving mechanical ventilation may argue that the absence of major untoward effects (on duration of respiratory support, growth, and age at discharge) and the limited clinical significance of the ill effects (cholestasis, fluid retention, and possible delay in resolution of illness) should encourage brief narcotic treatment to relieve the pain and stress of intensive care. Alternatively, it might be argued that several potential adverse effects have been demonstrated, that efficacy has not been established by clinical trials, and that serious consequences, such as iatrogenic dependence or long-term behavior disturbances, remain to be determined. This study provides the clinical equipoise to justify a randomized trial,[33] despite the blind passion of some critics.[34]

Wide differences in the administration of narcotics for very low-birth-weight, medically treated neonates exist among NICUs, and these differences cannot be explained by birth weight or illness severity. Our study found several associated short-term adverse outcomes, including elevated serum bilirubin levels, fluid retention, and delayed resolution of illness. There were no associations between narcotic treatment and cardiovascular instability, chronic lung disease, growth, or discharge timing. The association with IVH probably represents confounding. We did not measure other important outcomes, such as iatrogenic withdrawal and long-term developmental, social, and behavioral effects, related to prolonged exposure to narcotics.

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From the Joint Program in Neonatology, Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Children's Hospital, and Harvard Medical School, Boston, Mass (Mr Kahn and Drs Richardson, Gray, and Pursley); the Department of Maternal and Child Health, Harvard School of Public Health, Boston (Dr Richardson); Memorial Health Care and University of Massachusetts, Worcester (Dr Bednarek); the Department of Pediatrics, Brown University and Women and Infant's Hospital, Providence, RI (Dr Rubin); the Division of Neonatology, Baystate Medical Center, Springfield, Mass (Dr Shah); and the Division of Newborn Medicine, Floating Hospital for Children at Tufts New England Medical Center, Boston (Dr Frantz). Mr Kahn is a medical student at Albert Einstein College of Medicine, New York, NY.

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Women's Hospital, Boston; Floating Hospital for Children at Tufts New England Medical Center, Boston; University of Massachusetts–Memorial Medical Center, Worcester; and Women and Infants' Hospital, Providence, RI.

Reprints: Douglas K. Richardson, MD, MBA, Department of Neonatology, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215 (e-mail: richardson@neonatology.bidmc.harvard.edu).

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