Narcotics and Sedative Use in Preterm Neonates

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Objectives To evaluate patterns of narcotic and sedative use in neonatal intensive care units (NICUs) across Canada using data collected by the Canadian Neonatal Network.

Study design We conducted a retrospective observational cohort study of preterm neonates at <33 weeks' gestation and admitted to a participating Canadian Neonatal Network NICU. The proportion of all neonates who received sedative(s), narcotic(s), or either sedative(s), narcotic(s), or both during their NICU stay was calculated for each year. Because opioids are used for premedication before intubation, only continuous infusions of a narcotic drug were included. Variation in narcotics and sedative usage between sites in 2014 was determined using logistic regression analysis, with adjustment for gestational age, surgery, and mechanical ventilation.

Results Of 20 744 neonates, 29% of neonates received a narcotic, a sedative, or both; 23% received a narcotic and 17% a sedative. Although no clinically significant changes in drug exposure were documented during the 5-year period, there were statistically significant differences in narcotic and sedative use between sites, ranging from 3% to 41% for narcotic and 2% to 48% for sedative use (aORs 0.2-5.7 and 0.1-15, respectively, $P < .05$).

Conclusions Exposure to narcotic or sedative agents is highly variable in preterm neonates across Canada despite concerns of adverse outcomes associated with these drugs. The tremendous variation in practice suggests that further research on their current usage, as well as identifying optimal practice procedures is warranted. *(J Pediatr 2017;180:92-8).*

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The neonatal intensive care unit (NICU) is a stressful environment where preterm neonates are typically exposed to 10-14 painful procedures daily.[1] Prior to the late 1980s, pain in the preterm neonate was poorly understood and often unrecognized and untreated[2]; however, since then, the adverse effects of untreated pain in very preterm neonates have become clear. In the short term, unmanaged pain has an immediate impact on hemodynamic and physiologic stability and altered stress hormone expression.[3,4] Meanwhile, greater exposure to procedural stress and pain in the NICU is associated with long-term adverse effects on brain growth and development,[5-8] as well as cognitive and motor functions[8,9] As a result, the importance of measuring and managing pain for acute procedures has become well-recognized in recent years,[10] as national and international evidence-based guidelines and initiatives have been implemented to address this issue. These guidelines emphasize the need for continuous evaluation of stress and pain experienced by neonates in the NICU and the use of appropriate environmental, nonpharmacologic, and pharmacologic interventions to prevent, reduce, or eliminate stress and pain.[10] Currently, several multidimensional pain assessment tools with demonstrated validity, reliability, and clinical utility for acute and postoperative pain are used in the NICU,[11-13] however, defining and managing chronic pain remains a challenge.

The use of sedatives and analgesics to treat pain and agitation has increased in the NICU, but the optimal use of these drugs and their long-term effects remain unknown. The use of sedation or analgesia in neonatal NICUs in European countries was recently investigated in a prospective cohort study containing 243 NICUs across 18 European countries.[14] The frequency of sedation or analgesia use varied widely from 0% to 100% between the different centers.

CNN	Canadian Neonatal Network
GA	Gestational age
IVH	Intraventricular hemorrhage
NICU	Neonatal intensive care unit
PVL	Periventricular leukomalacia

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In light of the uncertainty of the benefits and harms of sedatives and narcotics in the preterm population, our aim was to evaluate variations in the rate of use of narcotic and sedative agents in NICUs across Canada using data collected by the Canadian Neonatal Network (CNN).

Methods

This retrospective observational study cohort included preterm neonates born between January 1, 2010, and December 31, 2014, at less than 33 weeks' gestational age (GA) and admitted to 1 or more of the 30 participating level III NICUs in the CNN. All CNN sites have research ethics board or quality improvement committee approval for data collection. This study protocol was approved by the Clinical Research Ethics Board at the University of British Columbia and Children's and Women's Hospitals of British Columbia.

CNN sites gather data on all level III NICU admissions born at less than 33 weeks' GA. Data were collected by trained data abstractors using a data definition manual and standardized procedures as previously described.[15] Data collection was revised in January 2010 to include information on the use of narcotics and sedatives as continuous infusion during a neonate's NICU stay. Because opioids are used for premedication before intubation only, a continuous infusion of a narcotic drug was considered. Data and information regarding medications given during surgery in the operating room was not collected.

Narcotic drugs were classified as 1 or more of the following opiates: morphine, fentanyl, sufentanil, alfentanil, meperidine, codeine, and opium solutions. Sedative drugs included benzodiazepines (midazolam, lorazepam, diazepam), chloral hydrate, ketamine, phenobarbital, and propofol. The specific drug(s) that were used, the indication for administration, and the length of treatment were not captured in the CNN database. Characteristics of newborns who received analgesics and sedatives were also collected and stored within the CNN database.

GA was determined by the best estimate based on obstetric history, obstetric examination, and first prenatal ultrasonography examination. Bronchopulmonary dysplasia was defined as the need for supplemental oxygen at 36 weeks' corrected GA or at the time of discharge to level II NICUs.[16] Intraventricular hemorrhage (IVH) was classified according to the criteria of Papile et al[17] and based on the most severe findings on head ultrasound during the neonate's stay in the NICU. Periventricular echogenicity or periventricular leukomalacia (PVL) was detected using cranial ultrasound or magnetic resonance imaging findings. Necrotizing enterocolitis was defined according to Bell criteria (stage 2 or higher).[18] Small for GA was specified as birth weight smaller than the 10th percentile for the given GA. Retinopathy of prematurity was defined by the International Committee on Retinopathy of Prematurity.[19] Duration of mechanical ventilation was described as the total number of days a neonate received invasive mechanical ventilation. Late-onset sepsis was defined as the presence of a pathogenic organism in either a blood or cerebrospinal fluid culture in a symptomatic neonate after the third day of life.

Statistical Analyses

The proportion of all neonates who received sedative(s), narcotic(s), or either sedative(s) or narcotic(s) or both during their NICU stay was calculated for each year. A Cochran-Armitage analysis was used to address whether the exposure in these 3 groups has changed significantly over the 5-year study period. Univariate analyses (χ^2 test for categorical variables and Student *t* test for continuous variables) were performed to compare the characteristics of the following groups: (1) neonates who received narcotic(s); (2) neonates who received sedative(s); (3) neonates who received either sedative(s) or narcotic(s) or both; and (4) neonates who did not receive a narcotic or a sedative. A *P* value of <.05 was considered significant.

ORs and aORs with 95% CIs were computed for the use of narcotics and sedatives in different NICUs in 2014 and were adjusted for GA, surgery, and mechanical ventilation. The site with the median rate of narcotics (or sedatives) usage was chosen to be the reference site.

Results

A total of 20 744 neonates born less than 33 weeks' GA were admitted to participating level III units during the study period. Overall, 29% of neonates received a narcotic, a sedative, or both, 23% received a narcotic, and 17% a sedative (**Table I**). Over the 5-year period, there was a significant decrease in the use of either one or both from 31% to 27% ($P < .001$), narcotic exposure from 24% to 22% ($P = .0027$), and no statistically significant change in sedative use over the 5-year period. The demographic and clinical characteristics of preterm neonates by exposure to narcotics and/or sedatives are presented in **Table II**. Except for hypothermia, neonates not exposed to either drug differed from those who received either one or both medications, with a higher mean GA and birth weight, lower severity of illness score, less exposure to invasive ventilation and postnatal corticosteroids, fewer surgeries including ligations of a patent ductus arteriosus, fewer proven sepsis events, and lower rates of neonatal complications.

Unadjusted comparisons of narcotic usage revealed significant variations among participating NICUs. Logistic regression analyses adjusted for GA, surgery, and mechanical ventilation showed statistically significant differences in narcotic use between sites, as 7 and 8 sites used narcotics

Table I. The incidence of narcotic and/ or sedative use in preterm neonates

Years	Received narcotics (%)	Received sedatives (%)	Received narcotic or sedative or both (%)
2010 (N = 4105)	24	17	31
2011 (N = 3937)	25	17	30
2012 (N = 4250)	22	16	28
2013 (N = 4239)	22	18	29
2014 (N = 4213)	22	17	27
Total (N = 20744)	23	17	29
P value	.0027	.6556	<.0001