Sedation, Analgesia, and Paralysis during Mechanical Ventilation of Premature Infants

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Objective To characterize administration of sedatives, analgesics, and paralytics in a large cohort of mechanically ventilated premature infants.

Study design Retrospective cohort study including all infants <1500 g birth weight and <32 weeks gestational age (GA) mechanically ventilated at 348 Pediatrix Medical Group neonatal intensive care units from 1997 to 2012. The primary outcome is the proportion of mechanically ventilated days in which infants were administered drugs of interest. Multivariable logistic regression was used to evaluate the predictors of administration of drugs of interest.

Results We identified 85 911 mechanically ventilated infants. Infants received a drug of interest (opioids, benzodiazepines, other sedatives, and paralytics) on 433 587/1 305 413 (33%) of mechanically ventilated infant days. The administration of opioids increased during the study period from 5% of infant days in 1997 to 32% in 2012. The administration of benzodiazepines increased during the study period from 5% of infant days in 1997 to 24% in 2012. Use of paralytics and other drugs remained ≤1% throughout the study period. Predictors of drug administration included younger GA, small for GA status, male sex, presence of a major congenital anomaly, older postnatal age at intubation, exposure to high-frequency ventilation, exposure to inotropes, more recent year of discharge, and neonatal intensive care unit site.

Conclusions Administration of opioids and benzodiazepines in mechanically ventilated premature infants increased over time. Because infant characteristics were unchanged, site-specific differences in practice likely explain our observations. Increased administration over time is concerning given limited evidence of benefit and potential for harm. *(J Pediatr 2017;180:99-104).*

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Premature infants admitted to neonatal intensive care units (NICUs) frequently receive mechanical ventilation through an endotracheal tube.[1] Mechanical ventilation has been associated with pain, distress, and feelings of breathlessness in older children and adults.[2,3] To alleviate these discomforts and facilitate gas exchange during mechanical ventilation, children and adults routinely receive sedatives and analgesics.[4,5] However, routine administration of analgesics in premature infants receiving mechanical ventilation may be associated with harm.[6-11]

Randomized controlled trials of routine morphine administration demonstrate an increased incidence of hypotension, drug dependence, air leaks, prolonged duration of mechanical ventilation, and prolonged time to full enteral feeds.[6-11] Opioids also are associated with apoptosis in the developing brains of animals, and although it is unknown how extensively this occurs in humans, concerns about adverse neurocognitive outcomes associated with opioid use during infancy exist.[12-17] Based on available evidence, guidelines in 2006 recommended against routine use of sedatives and analgesics in premature infants receiving mechanical ventilation.[18,19] Guidelines regarding use of paralytics in preterm infants do not currently exist. Even though some studies suggested possible benefits in infants with ventilator dyssynchrony, routine use of paralytics in preterm infants may be associated with sustained paralysis, joint contractures, and hearing loss.[20-23]

The frequency and determinants of sedative and analgesic use in premature infants receiving mechanical ventilation are not well described. Information regarding determinants of sedative and analgesic use in this population will help identify infants

GA	Gestational age
NICU	Neonatal intensive care unit
SGA	Small for gestational age

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at risk for associated adverse neurocognitive outcomes and will allow more efficient design of future trials investigating the risks and benefits of sedative and analgesic administration. Here, we seek to characterize the use of sedatives, analgesics, and paralytics over time in a large cohort of mechanically ventilated premature infants and to identify factors associated with use.

Methods

We obtained data from the Pediatrix Medical Group Data Warehouse, which prospectively captures information from an electronic medical record of daily progress notes and other documentation prepared by clinicians involved in the care of infants. Information is collected regarding maternal history and demographics, drugs, laboratory results, culture results, mechanical ventilation and respiratory support, and diagnoses. Details of administered drug dose were not recorded during this study period.

We identified all infants <1500 g birth weight and <32 weeks gestational age (GA) who received ≥1 day of mechanical ventilation (high frequency or conventional) in the first 120 days of life during their initial admission to one of 348 NICUs from 1997 to 2012. We followed infants during mechanically ventilated days, excluding days of a major surgical intervention and 6 days following the surgical intervention, from NICU admission until one of the following events occurred: death, discharge, or day 120 of admission. We evaluated the use of sedatives, analgesics, and paralytics measured in infant days of administration of drug during the study period.

We included the following drugs of interest: opioids (fentanyl, morphine, meperidine, methadone), benzodiazepines (midazolam, diazepam, clonazepam, lorazepam), paralytics (atracurium, mivacurium, pancuronium, rocuronium, vecuronium), and "other" drugs (chloral hydrate, dexmedetomidine, ketamine, clonidine). We measured drug use as the number of mechanically ventilated infant days of administration for each drug of interest.

We defined the duration of mechanical ventilation as the total number of days of mechanical ventilation during the hospitalization of each infant, excluding the day of major surgery and 6 days thereafter. We defined surgical intervention as any surgical or catheter-based intervention (ie, cardiac catheterization) documented in the chart for which the administration of general anesthesia was likely. An infant was considered to have a major congenital anomaly if an anomaly presenting at birth had 1 or more of the following characteristics: (1) lethal; (2) life shortening; (3) life threatening; (4) requiring major surgery; or (5) significantly affecting the infant's quality of life. We grouped sites into quartiles of average annual site volume of mechanically ventilated infants during the study period.

Statistical Analyses

The primary unit of observation for this study was an infant day of mechanical ventilation. We used standard summary statistics, including counts, percentages, medians, and 25th and 75th percentiles to describe the study variables. We compared the distribution of infants with any drug use across infant characteristics using Wilcoxon rank-sum tests. We evaluated trends over time using the Cochran-Armitage test for trend. To evaluate the independent associations between infant characteristics and daily exposure to sedatives, analgesics, or paralytics of interest, we used multivariable logistic regression with a robust variance estimator to account for the clustered nature of the data by infant. The final multivariable model included the following predictors: GA (categorical) status, small for gestational age (SGA, binary) status, postnatal age at the time of intubation (categorical), race (categorical), sex (binary), exposure to inotropic support (binary), exposure to high-frequency ventilation (binary), discharge year (categorical), and a binary indicator variable for each site. To investigate the potential effect on our results of outliers in mechanical ventilation duration, we conducted a sensitivity analysis limited to the first 7 days of mechanical ventilation for each infant.

To characterize differences in drug administration by site, we used the final model without the indicator for site to calculate predicted probability of daily drug administration for each site.

We used STATA 13.1 (StataCorp, College Station, Texas) to perform all statistical analyses. A 2-sided P value of $<.05$ was considered statistically significant for all tests. The study was approved by the Duke University Institutional Review Board without the need for written informed consent because the data were collected without identifiers.

Results

We identified 85 911 infants who received mechanical ventilation for a total of 1 305 413 days at 329 sites. The median GA and postnatal age at initial intubation were 27 weeks (IQR; 25, 29) and 0 days (0, 0), respectively. Infants were ventilated for a median of 6 days (2, 22). A total of 31 078 (36%) infants received high-frequency ventilation on 297 751 (23%) days (**Table I**).

Over time, the median birth weight among infants in our cohort decreased, the median GA remained stable, and the proportion of infants born with a major congenital anomaly increased (957 g in 1997 and 890 g in 2012, $P = .001$; 27 weeks in 1997 and 2012; and 6% in 1997 and 8% of infants in 2012, $P = .027$). After 1998, the proportion of infants who received high-frequency ventilation declined (38% in 1999 and 36% in 2012, $P = .003$), as did the proportion receiving inotropes during ventilation (37% in 1999 and 33% in 2012, $P = .008$).

Among infants in our cohort, 32 058 (37%) received ≥1 drug of interest during 433 587 (33%) ventilated days. Fentanyl, midazolam, and morphine were the most frequently administered drugs of interest: 215 663 (17%), 180 791 (14%), and 112 612 (9%) ventilated days, respectively. Chloral hydrate was the most frequently administered "other" drug on 7410 (<1%) ventilated days, and vecuronium was the most frequently administered paralytic on 9312 (<1%) days.

Administration of 2 or 3 drugs of interest occurred on 175 437 (13%) and 16 121 (1%) days, and 4, 5, or 6 drugs of interest were administered on 1693, 126, and 22 (all <1%) days, respectively. Infants who received a drug of interest were less