Sedatives and Analgesics Given to Infants in Neonatal Intensive Care Units at the End of Life

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Objective To describe the administration of sedatives and analgesics at the end of life in a large cohort of infants in North American neonatal intensive care units.

Study design Data on mortality and sedative and analgesic administration were from infants who died from 1997-2012 in 348 neonatal intensive care units managed by the Pediatrix Medical Group. Sedatives and analgesics of interest included opioids (fentanyl, methadone, morphine), benzodiazepines (clonazepam, diazepam, lorazepam, midazolam), central alpha-2 agonists (clonidine, dexmedetomidine), ketamine, and pentobarbital. We used multivariable logistic regression to evaluate the association between administration of these drugs on the day of death and infant demographics and illness severity.

Results We identified 19 726 infants who died. Of these, 6188 (31%) received a sedative or analgesic on the day of death; opioids were most frequently administered, 5366/19 726 (27%). Administration of opioids and benzodiazepines increased during the study period, from 16/283 (6%) for both in 1997 to 523/1465 (36%) and 295/1465 (20%) in 2012, respectively. Increasing gestational age, increasing postnatal age, invasive procedure within 2 days of death, more recent year of death, mechanical ventilation, inotropic support, and antibiotics on the day of death were associated with exposure to sedatives or analgesics.

Conclusions Administration of sedatives and analgesics increased over time. Infants of older gestational age and those more critically ill were more likely to receive these drugs on the day of death. These findings suggest that drug administration may be driven by severity of illness. *(J Pediatr 2015;167:299-304)*.

End-of-life care for dying patients is central to the provision of quality health care.[1] Research efforts have sought to understand current management and identify best practices of end-of-life care.[1] Although most of these efforts focus on critically ill adults, systematic data are urgently needed to guide end-of-life care for children and their families.[1-4] Existing data suggest that high-quality end-of-life care for children includes interventions for relief of pain and other symptoms, most often by pharmacotherapy.[2,3,5,6] Increasing recognition of pain in the neonatal period, historical evidence of limited administration of analgesia to infants undergoing painful procedures, and the high incidence of infant deaths compared with pediatric deaths outside this period offer unique opportunities to evaluate drug administration to infants at the end of life.[7-9]

Data on drug administration at the end of life in North American neonatal intensive care units (NICUs) are few.[9-14] In a 4-center study (2 in the US and 1 each in Canada and The Netherlands), providers most frequently administered opioids, 116/151 (77%), and benzodiazepines, 61/151 (41%), to dying infants.[11] At each center, providers increased doses of opioids or benzodiazepines as the time of death approached; however, there was great variability among the centers in the doses given to achieve infant comfort.[11] In 4 US studies, providers also variably administered opioids or benzodiazepines during the process of ventilator withdrawal or withholding in infants.[9,12-14] Variable drug administration may be due to patient- or provider-level characteristics.[15-20] Here, we describe the administration of sedatives and analgesics at the end of life to a large cohort of infants in NICUs in North America and seek to determine the patient characteristics that influence this drug administration.

Methods

We identified all infants who died from 1997-2012 in 348 NICUs managed by the Pediatrix Medical Group. Data were from the Pediatrix Medical Group Clinical Data Warehouse. The Pediatrix Clinical Data Warehouse prospectively captures data entered from history and physicals, daily

NICU Neonatal intensive care unit

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notes, and discharge notes. These data include maternal history and demographics, administered drugs, laboratory results, culture results, and diagnoses. Drug dosing, intervals, and indications were not recorded. The study was approved by the Duke University Institutional Review Board without the need for written informed consent as the data were collected without identifiers.

Sedatives and analgesics of interest included opioids (fentanyl, methadone, morphine), benzodiazepines (clonazepam, diazepam, lorazepam, midazolam), central alpha-2 agonists (clonidine, dexmedetomidine), ketamine, and pentobarbital. Infants were classified as exposed to a drug of interest if there was documentation of drug administration on the day of death or on either of the last 2 days of life. Infants who had a documented drug start date within 7 days of death but no documented end date were also presumed to be exposed to drugs of interest on the day of death. We evaluated infant severity of illness by exposure to antibiotics, inotropes, and mechanical ventilation on the day of death, and exposure to an invasive procedure within 2 days of death. We categorized NICUs based on average annual discharges (low volume, <300 infants; medium volume, 301-600 infants; high volume, >600 infants).

Statistical Analyses

We used standard summary statistics including counts, percentages, and medians with IQRs to describe the study variables. We determined the number of infants exposed to sedatives and analgesics on the day of death, on either of the last 2 days of life, and at any time during their hospitalization. We compared the proportion of infants exposed to sedatives and analgesics on the day of death, on either of the last 2 days of life, and at any time during their hospitalization by gestational age, NICU volume, and year of death using χ^2 tests of association. We performed univariable logistic regressions to evaluate the association between: (1) sedative and analgesic exposure on the day of death, on either of the last 2 days of life, and at any time during their hospitalization; and (2) the following variables: gestational age, postnatal age, race/ethnicity, sex, invasive procedure within 2 days of death, and inotrope, antibiotic, and ventilator exposure on the day of death. For multivariable modeling, we included all covariates that might be clinically associated with sedative and analgesic exposure on the day of death. The final model included random effects for NICU site and the following covariates: race/ethnicity, gestational age, postnatal age, invasive procedure within 2 days of death, year of death, and inotropic support, antibiotic exposure, and ventilator status on the day of death.

We performed a sensitivity analysis, limiting our cohort to infants admitted to the NICU for at least 2 days. STATA 12 (StataCorp, College Station, Texas) was used to perform the statistical analysis. A P value of <.05 was considered statistically significant for all tests.

Results

We identified 19 726 infants who died during their NICU admission from 1997-2012. The median gestational age at birth, birth weight, and postnatal age on the day of death were 26 weeks (IQR 24, 32), 820 g (615, 1641), and 8 days (2, 21), respectively. Of the 19 726 infants, 6188 (31%) received a sedative or analgesic on the day of death, 6601 infants (33%) received a sedative or analgesic within the last 2 days of life, and 9538 (48%) received a sedative or analgesic at any point during their hospitalization. The median gestational age and birth weight were higher in infants who received sedatives and analgesics on the day of death compared with those who did not: 27 weeks (24, 33) vs 26 weeks (24, 32) ($P < .001$), and 861 g (633, 1790) vs 800 g (605, 1570) ($P < .001$), respectively (**Table I**). Of the 19 726 infants, 5366 (27%) received an opioid on the day of death, and 3142 (16%) received a benzodiazepine on the day of death (**Table II**; available at www.jpeds.com).

The use of sedatives or analgesics varied widely across centers and over time. The proportion of infants exposed to a sedative or analgesic on the day of death varied across NICUs (median 18%, IQR 0, 34) (**Figure 1**). Centers with the highest use administered sedatives and analgesics to approximately

Table I. Demographics

	No sedative or analgesic exposure on day of death (N = 13 538)	Sedative or analgesic exposure on day of death (N = 6188)	Sedative or analgesic exposure during hospitalization (N = 9538)
Gestational age (wk)			
<28	7868 (58)	3391 (55)	5488 (58)
28-33	2661 (20)	1319 (21)	1936 (20)
>33	2988 (22)	1469 (24)	2103 (22)
Male	7562 (56)	3558 (57)	5443 (57)
Birth weight (g)			
<750	5863 (43)	2402 (39)	3965 (42)
750-999	2140 (16)	1014 (17)	1608 (17)
1000-1499	1655 (12)	812 (14)	1180 (12)
≥1500	3786 (28)	1947 (31)	2768 (29)
Postnatal age (d)			
1	2551 (19)	565 (9)	1558 (16)
2-7	5051 (37)	2719 (44)	2410 (25)
8-28	3740 (28)	1877 (30)	3181 (33)
>28	2092 (15)	1027 (17)	2365 (25)
Postmenstrual age (wk)			
<28	5960 (44)	2476 (38)	3530 (37)
28-33	3507 (26)	1748 (29)	2752 (29)
≥33	3946 (29)	1955 (33)	3221 (34)
Race/ethnicity			
White	5753 (42)	2684 (40)	4116 (43)
Black	3237 (24)	1391 (22)	2239 (23)
Hispanic	3225 (24)	1588 (26)	2349 (25)
Other	674 (5)	317 (5)	486 (5)
Antibiotic support*	4612 (34)	2881 (47)	
Inotropic support*	3703 (27)	2605 (42)	
Procedure†	266 (2)	320 (5)	
Ventilation support*	11 492 (85)	5800 (94)	

Values are expressed as n (%).
*On the day of death.
†Within 2 days of death.