Pilot Study Comparing Adverse Cardiorespiratory Events among Pharmacologically and Nonpharmacologically Treated Infants Undergoing Monitoring for Neonatal Abstinence Syndrome

Spoorthi Davala, BA[1], Aaron Hansbury, MPH[2], Melissa Miller, MPH[2], Jeffery Boateng, MPH[2], Hira Shrestha, MA[3], and Elisha M. Wachman, MD[3]

There is variation in cardiorespiratory monitoring practices for neonatal abstinence syndrome. We examined the incidence of cardiorespiratory adverse events in infants with neonatal abstinence syndrome who were treated or nontreated pharmacologically. Eight (10%) in the nontreated and 23 (19%) in the treated group experienced adverse events. This warrants further investigation in a larger cohort. *(J Pediatr: X 2020;3:100027).*

Neonatal abstinence syndrome (NAS), also known as neonatal opioid withdrawal syndrome, is an opioid withdrawal syndrome that develops after in-utero opioid exposure.[1,2] The incidence of NAS has increased by 5-fold between 2000 and 2012, with current estimates as high as 20 per 1000 live births in the US.[3,4] Nonpharmacologic interventions such as rooming-in and breastfeeding are first-line treatment; these have been associated with a decreased need for pharmacologic agents and shortened hospitalizations.[1,5,6] Approximately 50% of infants with prenatal exposure to opioids at risk for NAS require pharmacologic treatment with an average hospitalization length of 22 days.[1,2,7,8]

Morphine and methadone are the most common medications used to treat NAS.[1,9-11] Studies have indicated that methadone-treated adults can experience prolonged QTc intervals, putting them at risk for the rare occurrence of Torsade de Pointes, a polymorphic ventricular tachycardia in individuals with prolonged QTc which can cause significant hemodynamic compromise.[12]

Methadone is routinely used in pediatric patients weaning from prolonged sedation in intensive care settings.[13] In this setting, there have been reported episodes of bradycardia and respiratory depression, however, these doses are higher than those used for NAS.[13] Morphine is also commonly used in the newborn intensive care unit for sedation, typically at higher doses intravenously, with associated risk for sinus bradycardia and respiratory depression.[14,15]

Given the absence of data regarding side effects on infants treated pharmacologically for NAS, there is lack of a universally accepted treatment protocol with significant variation between hospital care practices.[1,9,10] One aspect of care with no national standard is the use of cardiorespiratory monitoring.

The objective of this retrospective pilot study was to estimate the incidence and severity of adverse cardiorespiratory events for opioid-exposed infants receiving pharmacologic treatment with morphine or methadone for NAS, in comparison with a cohort of opioid-exposed infants who were monitored for NAS but did not receive medication treatment.

NAS	Neonatal abstinence syndrome
AE	Adverse event
RR	Respiratory rate

Methods

This study took place in a tertiary care urban academic medical center. Over 90% of the infants at our center are born to mothers seen in a specialized prenatal program for women with opioid use disorders. Our institution practices a rooming-in model of care on the postpartum unit and inpatient pediatric unit. Mothers are encouraged to room-in throughout the inpatient hospitalization, with average of 80% presence during the study time period, and volunteer cuddlers present when parents are not present.[16]

NAS Treatment Protocol

Given the predominance of long-acting opioid exposures, all opioid-exposed infants were admitted in the inpatient setting for 5-7 days, sometimes with prolonged hospital stays because of social concerns or feeding difficulties. Infants are assessed with either the Finnegan scale (2015-November 2016) or the Eat, Sleep, Console NAS Assessment Tool (December 2016-December 2017).[16,17] Criteria for initiating pharmacologic treatment with the Finnegan scale were 2 consecutive scores greater than or equal to 8 or 1 score greater than or equal to 12.[7] Criteria for initiating pharmacologic treatment with the Eat, Sleep, Console protocol were the infant getting "yes" responses for not eating, sleeping, or consoling well due to NAS despite optimal nonpharmacologic measures.[16] First

From the [1]Boston University School of Medicine; [2]Boston University School of Public Health; and [3]Department of Pediatrics, Boston Medical Center, Boston, MA

Supported by the Boston University School of Medicine Student Summer Research Program (to S.D.). The authors declare no conflicts of interest.

https://doi.org/10.1016/j.ympdx.2020.100027

line medication was morphine from 2015 to June 2016, then methadone from July 2016 to December 2017. During the study time period, infants were placed on standing morphine (dosed every 4 hours, dose range 0.3-0.9 mg per kg per day) or methadone (dosed every 8 hours, dose range 0.2-0.8 mg per kg per day). Opioids were weaned by 10% of the maximum dose daily down to 20% of the maximum dose, and then infants were monitored for 24-48 hours off medication prior to discharge. Second line adjunctive medication treatment consisted of phenobarbital or clonidine, initiated if the infant was unable to consistently wean from their first-line opioid medication, or if the infant had reached maximum dosing on their opioid medication with persistent symptoms. Clonidine was weaned as an inpatient after weaning off the opioid, and phenobarbital was weaned as an outpatient.

The standard of care at the time was for all infants treated pharmacologically to be placed on continuous cardiorespiratory and oximetry monitoring. In addition, once infants were transferred to the inpatient pediatrics unit after maternal discharge, they were routinely placed on continuous monitoring as part of unit protocol, irrespective of need for pharmacotherapy. The typical limits for the monitor to trigger an alarm were an oxygen saturation <85%, heart rate <80 or >220, respiratory rate <10, or apnea >20 seconds.[18]

Data Abstraction

This study was approved by Institutional Review Board as part of an exempt quality improvement study. We included infants born between May 2015 and December 2017 who had in-utero opioid exposure and gestational age of ≥36 weeks who were monitored for NAS. Subjects were identified through the use of an existing research database. Infants with major medical comorbidities impacting vital signs and requiring sedation or intravenous morphine or fentanyl, and those enrolled in a blinded clinical trial were excluded from this study (NCT 01958476).

All vital sign data was abstracted from the medical record flowsheet, as well as all documented apnea/bradycardia/desaturation events from the electronic medical record flowsheets. Nursing staff hand enters vital signs and adverse events (AEs) on dedicated flow sheets; events are entered when the monitors trigger alarms meeting unit criteria for nursing documentation. Then, study staff performed chart reviews for all infants with AEs to determine details surrounding each event. Because of the retrospective nature of this pilot project, monitor tracings were not available for review and were not routinely analyzed as part of routine care.

Identified subjects were divided into 2 groups: a nontreated group that was not pharmacologically treated, and a treated group (morphine or methadone). For infants, birth measures, details of pharmacologic treatment, and length of hospital stay were collected. For mothers, prenatal characteristics were collected including demographics, pregnancy outcomes, type of opioid pharmacotherapy at delivery, and co-exposures.

Outcome measures included the incidence of AEs (defined as documented events in the nursing flow sheet per institutional guidelines of bradycardia with heart rate <80, desaturation with oxygen saturation <85%, and/or apnea), and severity of the AEs (level of bradycardia and desaturation, transfer to higher level of care because of the AE). Respiratory rates and blood pressure readings were also evaluated and compared.

Statistical Analyses

Baseline demographics and infant in-utero exposures were compared between the 2 groups using t tests and the χ^2 test of independence. We then compared the incidence and severity of AEs for the 2 groups using the χ^2 test for categorical variables, t tests for means, and the Mann-Whitney test for medians. Results were stratified where indicated based on type of opioid used to treat NAS, morphine, or methadone. Lastly, we performed tests of association with maternal and infant variables with the risk for having an AE. No multivariate modeling was performed because of small sample size and lack of associations identified with potential covariates. All analyses were performed in SAS v 9.4.

Results

The demographics of the study cohort are shown in Table I. There were 204 opioid-exposed infants monitored for NAS who were included in the study, 81 in the nontreated group and 123 in the treated group (69 morphine and 54 methadone). There were no significant differences in demographics between the treated and nontreated groups. The mean maternal age at delivery was 29 years, with average infant gestational age at birth of 38-39 weeks, and mean infant birth weight of 3.0 kg. The primary opioid exposures at delivery were methadone and buprenorphine, with less than 5% taking un-prescribed opioids. The most common co-exposures included nicotine, selective serotonin re-uptake inhibitors, benzodiazepines, and illicit drugs (Table I). The mean length of hospital stay was 7.3 (SD 2.3) days for infants receiving no pharmacologic treatment and 21.0 (SD 8.9) in the treated group ($P < .001$). Thirty-six (18%) of all of the infants also received an adjunctive agent to treat their NAS.

A summary of AEs by treatment group is shown in Table II. There was no statistically significant difference in the incidence of AEs between groups (8 [10%] in the nontreated vs 23 [19%] in the treated group, $P = .09$). Bradycardia was primarily heart rates in the 70s and desaturations events to oxygen saturations in the 70s. Per documentation in the nursing flowsheets, no infant had an event that qualified as apnea, received positive pressure ventilation or other intensive intervention, or were transferred to higher levels of care because of the AEs. No doses of morphine or methadone were weaned or held as a result of the AEs. The average number of events per infant was 1 per hospitalization for those who had an adverse event.

The average respiratory rate (RR) did not differ between the nontreated (47.8 [SD 4.2]) and treated (48.7 [SD 3.5]) groups. There were 7 (8.6%) infants in the nontreated and

Table I. Summary demographics of nontreated vs treated infants

Demographics	Mean (SD) or n (%) Nontreated N = 81	Mean (SD) or n (%) Treated N = 123	*P* value
Maternal age (y)	29.0 (5.1)	29.6 (4.5)	.21
Infant gestational age (wk)	38.8 (1.5)	38.9 (1.5)	.80
Infant birth weight (g)	3099 (554)	3056 (552)	.58
Cesarean delivery	35/81 (43%)	46/123 (37%)	.41
Infant sex = male	36/81 (44%)	53/123 (43%)	.08
Maternal opioid agonist treatment at delivery			.08
Methadone	37/81 (46%)	75/123 (61%)	
Buprenorphine	41/81 (51%)	43/123 (35%)	
None/other	3/81 (4%)	5/123 (4%)	
Dose at delivery (mg/d)			
Methadone	94.7 (42.1)	104.5 (48.5)	.30
Buprenorphine	14.1 (6.9)	13.8 (5.5)	.83
Breastfed to any extent	41/81 (51%)	50/123 (41%)	.20
Co-exposures in third trimester			
Nicotine	51/81 (63%)	88/123 (72%)	.18
SSRIs	8/81 (10%)	9/123 (7%)	.56
Benzodiazepines	10/81 (12%)	32/123 (26%)	**.03**
Illicit drugs*	25/81 (31%)	44/69 (64%)	**<.001**
NAS outcomes			
Primary agent	N/A		N/A
Morphine		69/123 (56%)	
Methadone		54/123 (44%)	
Secondary agent	N/A	36/123 (29%)	N/A
Phenobarbital		32/123 (26%)	
Clonidine		11/123 (9%)	
Length of hospital stay (d)	7.3 (2.3)	21.0 (8.9)	**<.001**
Opioid treatment d	N/A	16.3 (9.2)	N/A
Total mg of opioids	N/A		N/A
Morphine		20.4 (17.0)	
Methadone		7.9 (8.8)	

N/A, not applicable; *SSRIs*, selective serotonin reuptake inhibitors.
Bold values *P* values < .05 indicating statistical significance with alpha level set at 0.05.
*Illicit drugs = cocaine, fentanyl, heroin, other unprescribed opioids, unprescribed benzodiazepines.

Table II. AE summary in nontreated vs treated Infants

Demographics	Nontreated n = 81	Treated n = 123	*P* value
Incidence of any AE – n (%)	8/81 (10%)	23/123 (19%)	.09
Number of AEs per infant who had an AE – Mean (SD)	1.1 (0.4)	1.3 (0.5)	.63
AE type bradycardia – n (%)	5/81 (6%)	16/123 (13%)	.12
Heart rate during bradycardic AEs			
Mean (SD)	75.3 (3.4)	73.6 (4.8)	.09
Median (IQR)	75.0 (4.0)	75.0 (7.0)	.17
AE type oxygen desaturation – n (%)	4/81 (5%)	11/123 (9%)	.28
Oxygen saturation during desaturation AEs			
Mean (SD)	78.1% (6.4)	76.6% (9.0)	.63
Median (IQR)	79.0% (5.5)	80.0% (11.0)	.95
AE type apnea – n (%)	0 (0%)	0 (0%)	N/A
Duration of morphine treatment at time of first AE (h)	N/A		N/A
Mean (SD)		19.2 (8.3)	
Median (IQR)		20.0 (29.8)	
Amount of morphine at time of the first AE (mg/kg/d)	N/A		N/A
Mean (SD)		0.5 (0.2)	
Median (IQR)		0.4 (0.7)	
Duration of methadone treatment at time of first AE (h)	N/A		N/A
Mean (SD)		155.6 (273.1)	
Median (IQR)		51.4 (765.5)	
Amount of methadone at time of the first AE (mg/kg/d)	N/A		N/A
Mean (SD)		0.3 (0.2)	
Median (IQR)		0.2 (0.6)	

N/A, not applicable; *NICU*, newborn intensive care unit.

6 (4.9%) infants in the treated group with a documented RR of <20 breaths per minute, all with 1 low RR recording per infant in the range of 14-19 breaths per minute.

Factors associated with the incidence of AEs are seen in Table III. There was no association between the incidence of AEs between the morphine and methadone treated infants. There were also no differences with the amount of pharmacologic treatment received, gestational age, birth weight, or dose of maternal opioid medication. The only significant association was maternal buprenorphine exposure, associated with a higher incidence of AEs, and combined infant treatment with morphine and clonidine. There were no episodes of documented hypotension.

Discussion

This pilot study found no statistically significant differences in the incidence of cardiorespiratory AEs in untreated vs pharmacologically treated infants, however, there was a 10% higher rate in those pharmacologically treated. This difference would be clinically significance if found to be true in a larger, appropriately powered study. The severity of events was mild, occurred on average once per hospitalization, and did not require intervention based on documentation available in the electronic health record. There were no documented episodes of hypoventilation, apnea, or hypotension. Given this was a pilot study that was underpowered to detect rare severe AEs, these results should be interpreted with caution.

Currently, there is significant variation among hospital care practices in terms of the use of cardiorespiratory monitoring for NAS.[19] The perceived necessity of monitoring often means that infants are transferred to more intensive care settings. Previous studies have found that these settings are associated with a significant reduction in the receipt of pharmacologic treatment and shortened hospitalizations.[5] Therefore, determining the necessity of cardiac monitoring could impact the location of care for these infants and significantly impact the short-term NAS outcomes of inpatient hospitalization outcomes. As state perinatal quality improvement collaboratives begin to examine cardiorespiratory practices across various hospital settings, data should be collected systemically to understand the full range of inpatient outcomes as changes in practice evolve.

Strengths of this study are that it systematically examined the incidence and severity of bradycardia, desaturation and apneic events in a cohort of infants being monitored for

Table III. Association of demographic and treatment factors with AEs

Demographics	Mean (SD) or n (%) No AEs n = 173	Mean (SD) or n (%) AEs n = 31	*P* value
First-line medication for NAS			.38
Morphine (n = 69)	58/173 (34%)	11/31 (35%)	
Methadone (n = 54)	42/173 (24%)	12/31 (39%)	
Length of opioid treatment (d) (n = 123)	16.5 (9.0)	15.2 (10.3)	.54
Total mg of morphine over hospitalization (n = 69)	19.4 (15.7)	23.9 (19.7)	.38
Total mg of methadone over hospitalization (n = 54)	8.0 (9.4)	7.5 (6.8)	.88
Adjunct pharmacologic therapy (n = 43)	35/173 (20%)	8/31 (26%)	.48
Phenobarbital (n = 32)	28/173 (16%)	4/31 (13%)	.25
Phenobarbital + methadone (n = 6)	6/173 (3%)	0/31 (0%)	N/A
Phenobarbital + morphine (n = 26)	22/173 (13%)	4/31 (13%)	.98
Clonidine (n = 11)	7/173 (4%)	4/31 (13%)	.13
Clonidine + methadone (n = 4)	3/173 (2%)	1/31 (3%)	.58
Clonidine + morphine (n = 7)	4/173 (2%)	4/31 (13%)	**.02**
Gestational age at delivery (wk)	38.8 (1.4)	39.0 (1.8)	.52
Birth weight (g)	3036 (517)	3127 (726)	.71
Maternal opioid medication*			
Methadone (n = 112)	101/173 (58%)	11/31 (35%)	**.01**
Buprenorphine (n = 84)	64/173 (37%)	20/31 (65%)	
Mean dose of maternal opioid medication (mg/d at delivery)*			
Methadone (n = 112)	101.3 (47.0)	100.4 (40.2)	.95
Buprenorphine (n = 84)	13.7 (6.8)	13.6 (5.7)	.95

Bold values *P* values < .05 indicating statistical significance with alpha level set at 0.05.
*The 8 infants exposed to unprescribed opioids were not included given unknown/fluctuating dose and confirmed type of opioid exposures in these cases.

NAS. In addition, this study includes a comparable group of infants with NAS who did not receive pharmacologic treatment but were placed on continuous cardiac monitoring.

This study has several limitations. First, as a retrospective pilot study, we could not take into account any events that were not documented in the medical record. Future studies should use data taken directly from the monitors to more accurately detect subtle changes and apnea. Because of the small sample size, we were not able to perform any multivariate modeling to look for associated risk factors for AEs. For instance, it is possible that late preterm infants have a higher incidence of AEs at baseline and, therefore, require a different monitoring algorithm. In addition, given that the untreated infants were discharged earlier, it could be that the treated group had a higher incidence of AEs given they were monitored longer in the inpatient setting. We were underpowered to detect rare severe AEs to make any definite statements about the incidence of AEs in this population. Lastly, EKGs were not obtained routinely, thus, we could not evaluate for the potential risk of prolonged QTc.

In conclusion, there was no statistically significant difference in AEs between the infants receiving pharmacologic treatment and controls in our small cohort, however, a 10% difference would represent a meaningful clinical difference if found to be significant in a larger, appropriately powered study. The incidence of adverse cardiorespiratory events in this population requires further study in a large prospective cohort so that best practice recommendations can be made about the necessity of monitoring and appropriate care locations for these infants. ■

We thank the Boston Medical Center Neonatal Abstinence Syndrome quality improvement and research teams.

Submitted for publication Feb 25, 2020; last revision received May 6, 2020; accepted May 11, 2020.

Reprint requests: Elisha M. Wachman, MD, Boston Department of Pediatrics, Boston Medical Center, Boston University School of Medicine, 801 Albany St, Floor 2, Boston, MA 02119. E-mail: Elisha.Wachman@bmc.org

Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Wachman EM, Schiff DM, Silverstein M. neonatal abstinence syndrome advances in diagnosis and treatment. JAMA 2018;319:1362-74.
2. Kocherlakota P. Neonatal abstinence syndrome. Pediatrics 2014;134: e547-61.
3. Milliren C, Gupta M, Graham DA, Melvin P, Jorina A, Ozonoff A. Hospital Variation in Neonatal Abstinence Syndrome Incidence, Treatment Modalities, Resource Use, and Costs Across Pediatric Hospitals in the United States, 2013 to 2016. Hosp Pediatr 2018;8:15-20.
4. Tolia VN, Patrick SW, Bennett MM, Murthy K, Sousa J, Smith PB, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. Neonatal ICUs. N Engl J Med 2015;372:2118-26.
5. MacMillan KDL, Rendon CP, Verma K, Riblet N, Washer DB, Volpe Holmes A. Association of rooming-in with outcomes for neonatal abstinence syndrome a systematic review and meta-analysis. JAMA Pediatr 2018;172:345-51.
6. Howard MB, Schiff DM, Penwill N, Si W, Rai A, Wolfgang T, et al. Impact of parental presence at infants' bedside on neonatal abstinence syndrome. Hosp Pediatr 2017;7:63-9.
7. Davis JM, Shenberger J, Terrin N, Breeze JL, Hudak M, Wachman EM, et al. Comparison of safety and efficacy of methadone vs morphine for treatment of neonatal abstinence syndrome: a randomized clinical trial. JAMA Pediatr 2018;172:741-8.
8. Patrick SW, Davis MM, Lehman CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. J Perinatol 2015;35:667.
9. Bogen DL, Whalen BL, Kair LR, Vining M, King BA. Wide variation found in care of opioid-exposed newborns. Acad Pediatr 2017;17:374-80.
10. Patrick SW, Kaplan HC, Passarella M, Davis MM, Lorch SA. Variation in treatment of neonatal abstinence syndrome in US children's hospitals, 2004-2011. J Perinatol 2014;34:867-72.
11. Brown MS, Hayes MJ, Thornton LM. Methadone versus morphine for treatment of neonatal abstinence syndrome: a prospective randomized clinical trial. J Perinatol 2015;35:278-83.
12. Alinejad S, Kazemi T, Zamani N, Hoffman RS, Mehrpour O. A systematic review of the cardiotoxicity of methadone. EXCLI J 2015;14:577-600.
13. Dervan LA, Yaghmai B, Watson RS, Wolf FM. The use of methadone to facilitate opioid weaning in pediatric critical care patients: a systematic review of the literature and meta-analysis. Paediatr Anaesth 2017;27: 228-39.
14. Ancora G, Lago P, Garetti E, Merazzi D, Savant Levet P, Bellieni CV, et al. Evidence-based clinical guidelines on analgesia and sedation in newborn

infants undergoing assisted ventilation and endotracheal intubation. Acta Paediatr 2019;108:208-17.
15. Fleishman R, Gleason CA, Myaing MT, Zhou C, Mangione-Smith R. Evaluating patterns of morphine use in a neonatal intensive care unit after NEOPAIN. J Neonatal Perinatal Med 2013;6:333-8.
16. Wachman EM, Grossman M, Schiff DM, Philipp BL, Minear S, Hutton E, et al. Quality Improvement initiative to improve inpatient outcomes for neonatal abstinence syndrome. J Perinatol 2018;38:1114-22.
17. Finnegan LP, Connaughton JF Jr, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. Addict Dis 1975;2:141-58.
18. Eichenwald EC , Committee on Fetus and Newborn, American Academy of Pediatrics. Apnea of prematurity. Pediatrics 2016:e20153757.
19. The Neonatal Quality Improvement Collaborative of Massachusetts. Improving the Care of Opioid-Exposed Newborns and their Families: A PNQIN Initiative [homepage on the Internet]. https://www.neoqicma.org/substance-exposed-newborns. Accessed April 1, 2020.