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ORIGINAL ARTICLE

The effect of standardizing treatment when managing neonatal abstinence syndrome*

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ABSTRACT

Objective: Standardizing treatment of neonatal abstinence syndrome (NAS) is currently recommended; however, single institution prospective studies are lacking regarding the success of this approach. The study objective was to evaluate overall newborn response and length of stay (LOS) of neonates treated for NAS following the institution of a strict standardized treatment protocol.

Methods: From 1 January 2014 to 30 June 2016, a prospective cohort study was performed collecting neonatal outcomes before and after the standardization of a strict NAS morphine weaning treatment protocol. The primary outcome measure was length of stay. The standardized protocol was fully instituted in June 2015.

Results: A total of 395 neonates were treated for NAS during the study. The LOS for the 17 months prior to the initiation of this protocol was 23.31 (±6.2) days (233 neonates). The LOS in the 13 months after protocol initiation was 18.17 (±5.1) days (162 neonates). This was a difference of 5.14 days (95%CI 4.0–6.3 days) less in LOS ($p < .0001$).

Conclusions: These data demonstrate that the initiation of a standardized NAS treatment protocol can significantly improve neonatal response and decrease LOS. It is recommended that institutions with nurseries that treat infants with NAS develop standardized treatment protocols to improve care for this complicated patient population.

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KEYWORDS
Neonatal abstinence syndrome; neonatal treatment protocols; opiate use disorder in pregnancy; substance abuse in pregnancy

Introduction

Opiate addiction is epidemic in Appalachia resulting in a large increase in the number of newborns requiring treatment for neonatal abstinence syndrome (NAS) [1–3]. The American Academy of Pediatrics currently recommends standardization of treatment of NAS; however, single institution prospective studies are lacking regarding the success of this approach [4]. In the State of Tennessee, NAS became a reportable condition starting January 2013.

Since 1 January 2014, all neonatal and maternal data has been prospectively collected at our institution on mothers treated for opiate use disorder and all newborns that are treated for NAS. At our institution, quality improvement work was performed that demonstrated a high reliability around inter-rater assessment of infant Finnegan scoring, a nurse-driven morphine escalation protocol was developed, and guidelines were created regarding adjunctive therapy with phenobarbital and clonidine. Initially, the management approach for treating a newborn with NAS in our neonatal intensive care unit (NICU) was based on the attending neonatologist in charge at the time. However, a new protocol that standardized oral morphine for weaning was developed and fully implemented by June of 2015.

The study objective was to evaluate overall newborn response and length of stay (LOS) of neonates treated for NAS prior to and after the institution of this strict standardized NAS treatment protocol.

Methods

We performed a prospective cohort study regarding the response to neonatal treatment in relation to LOS before and after instituting a strict NAS management protocol. As NAS is a reportable condition in the state of Tennessee, starting 1 January 2014, we developed an ongoing prospective database of all neonates and mothers for the purpose of evaluating numerous study questions. A standardized NAS treatment protocol was introduced June of 2015 and this study reports the

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newborn response before and after the protocol was instituted. Therefore, the study duration was from 1 January 2014 through 30 June 2016. The study was reviewed and approved by the institutional review board at University of Tennessee Medical Center, Knoxville.

Neonatal data collection included gestational age at delivery, birthweight, gender, Apgar score, and length of newborn stay. Maternal data collection included age, race, parity, mode of delivery, drugs used during the pregnancy, comorbidities (diabetes, hypertension, and other chronic illnesses, etc.), and tobacco usage. All mothers had a urine drug screen on admission and periodically throughout the pregnancy and because this was a prospective database, no data points were missing. All neonates had urine and meconium drug screens obtained at delivery.

The newborns were initially observed and managed with nonpharmacologic measures while rooming-in with their mothers on the postpartum unit. If symptoms of NAS escalated, the infant was transferred to the NICU. The criteria for starting pharmacologic treatment of NAS had previously been standardized and consisted of two Finnegan scores $\geq$10 consecutively or a single Finnegan score $>$12. All newborns were included at our institution if a diagnosis of NAS was made. The strict standardized treatment protocol for managing NAS involved pharmacologic treatment with an oral morphine solution (0.4 mg/mL) at a dose of 0.05 mL/kg q 3 hours if there were two Finnegan scores $\geq$10 consecutively or a single Finnegan score $>$12. Nurses increased the morphine solution 0.05 mL (0.02 mg) every 6 hours if the Finnegan score was $\geq$10 consecutively to a maximum dose of 0.5 mL (0.2 mg) every 3 hours. After a 48-hour period with Finnegan scores $\leq$8 without dose escalation, tapering began. The new weaning protocol more strictly identified candidates for weaning based on the Finnegan score: if the average Finnegan score for 24 hours was $\leq$8, the morphine solution was weaned by 0.05 mL (0.02 mg) to a minimum dose of 0.05 mL, then discontinued. This new protocol also added the institution of "prn" morphine doses of 0.05 mL (0.02 mg) every 6 hours (in addition to the scheduled dose) if the Finnegan score escalated $>$10 for two consecutive scores. If two or more "prn" doses were required in a 24-hour time period, the dose was increased to the previously tolerated dose and tapering started again after 24 hours of average Finnegan scores $\leq$8. The baby was observed for 48 hours off morphine prior to discharge. No infants were treated with any type of opiate medication as an outpatient. Adjunctive therapy with phenobarbital was instituted if NAS symptoms were not controlled with an oral morphine dose of 0.5 mL (0.2 mg) q 3 hours, OR if the infant failed morphine weaning twice after the initial stabilization period. Adjunctive therapy with clonidine (1.5 μg/kg every 6 hours) was added if the withdrawal symptoms were not controlled on morphine 0.5 mL (0.2 mg) q 3 hours plus phenobarbital with a level between 25 and 30 μg/mL.

The neonatal management prior to institution of the strict protocol was primarily different regarding when and how to wean and the addition of "prn" dosing. Prior to protocol initiation, when to start weaning was up to the neonatologist and this decision could vary from day to day based on the clinical impression of the physician in charge. The strict protocol changed this by tying when to start weaning and the rate of weaning to the Finnegan score. This assured that all clinicians used the same indicators for when to start weaning and the procedure for the weaning process. The second change involved the ability to use "prn" dosing. Prior to the strict protocol, if the newborn did not appear to be tolerating the current morphine dosing rate, the rate would often be increased. The "prn" dosing option would decrease the number of episodes where morphine rates were fully increased.

Adherence to this protocol was continually monitored by the first author of this manuscript once the protocol was put into place in June 2015. Statistical analysis involved chi-square, Fisher's exact, and Student *t*-test where applicable and $p < .05$ was considered as significant. All tests were considered against a two-sided alternative hypothesis. Poisson's binomial 95% confidence intervals were calculated on proportions.

Results

During the 30-month study period, 395 neonates were treated for NAS at our institution. The mean LOS for the 17 months prior to the initiation of this protocol was 23.3 (±6.2) days (233 neonates). The mean LOS in the 13 months after protocol initiation was 18.2 (±5.1) days (162 neonates). This was a difference of 5.1 days (95%CI 4.0–6.3 days) less in LOS and was highly significant ($p < .0001$). The median number of days for the preprotocol time period was 21 days (IQR 14–30). The median number of days for the postprotocol time period was 16 days (IQR 11–24), a difference of 5 days.

No statistical differences were found between the groups regarding the demographic data (Table 1). As depicted, 377 (95%) of the neonates were Caucasian and 225 (57%) were male gender. A total of 316 (80%) of the mothers were multiparous.

Table 1. Demographics of the neonatal abstinence syndrome (NAS) study groups before and after the standardization of the treatment of NAS in the neonatal intensive care unit (total *n* of 395 neonates).

Category	NAS study group prior to treatment standardization (1 January 2014 through 31 May 2015)	NAS study group after treatment standardization (1 June 2015 through 30 June 2016)	Significance
Total number of neonates	233	162	
Maternal age (years)	27.9 (±5.7)	28.6 (±5.9)	0.24
Maternal age range (years)	19–42	17–43	
Race (Caucasian)	220 (94%)	157 (97%)	0.33
Multiparity	188 (81%)	128 (79%)	0.78
Delivery GA (weeks)	38.3 (±1.6)	38.1 (±1.4)	0.20
Delivery GA range (weeks)	$34^{0/7}$–$42^{4/7}$	$34^{2/7}$–$41^{4/7}$	
GA <35 weeks	8 (3.4%)	6 (3.7%)	0.89
Mode of delivery (vaginal)	161 (69%)	120 (74%)	0.34
Birthweight (grams)	2896 (±471)	2905 (±442)	0.85
Newborn gender (male)	126 (54%)	99 (61%)	0.20
5-minutes Apgar score <7	5 (2.1%)	4 (2.5%)	1.00

NAS: neonatal abstinence syndrome; GA: gestational age.

Table 2. Primary opiate used at the time of delivery and other substances used during the course of the pregnancy in the NAS study groups before and after the standardization of the treatment of NAS in the neonatal intensive care unit (total *n* of 395 neonates).

	NAS study group prior to treatment standardization (1 January 2014 through 31 May 2015)	NAS study group after treatment standardization (I June 2015 through 30 June 2016)	Significance
Total number of neonates	233	162	
Buprenorphine at delivery	182 (78.1%)	127 (78.4%)	0.95
Methadone at delivery	16 (6.9%)	13 (8.0%)	0.81
Heroin at delivery	3 (1.3%)	2 (1.2%)	0.99
Other opiates at delivery[a]	32 (13.7%)	20 (12.3%)	0.80
Polysubstance use during pregnancy	169 (72.5%)	115 (71.0%)	0.82
Oxycodone use anytime during the pregnancy	105 (45.1%)	66 (40.7%)	0.45
Benzodiazepine use during the pregnancy	59 (25.3%)	40 (24.7%)	0.98
SSRI use during the pregnancy	32 (13.7%)	25 (15.4%)	0.74
Cigarette use during the pregnancy	181 (77.7%)	118 (72.8%)	0.32
Marijuana use during the pregnancy	112 (48.1%)	73 (45.1%)	0.63
Maternal comorbidity during the pregnancy[b]	39 (16.7%)	28 (17.3%)	0.99

NAS: neonatal abstinence syndrome; SSRI: selective serotonin reuptake inhibitor.
[a]Oxycodone, oxymorphone, hydrocodone.
[b]Hypertension, diabetes, and other chronic maternal illnesses.

Additionally, there were no differences found in the types of drugs used by both groups during the pregnancy or the primary opiate in use at the time of delivery (Table 2). At our institution, the primary opiate in use at delivery was buprenorphine with 309 total cases or 78% of the study population. Very few were on methadone or heroin at the time of delivery. The other opiates found at delivery were mostly oxycodone followed by oxymorphone and then hydrocodone. About 25% (99 of 395) of the study population also used a benzodiazepine; about 76% (299 of 395) smoked cigarettes; and about 14% (57 of 395) used a selective serotonin reuptake inhibitor (SSRI). Marijuana usage was also high at 47% (185 of 395) of the study population. There were no differences in comorbidities between the two groups.

Discussion

These prospective data verify that the initiation of a standardized NAS treatment protocol can significantly improve neonatal response and decrease LOS. These findings are consistent with a few large retrospective studies. Asti et al. evaluated mean LOS in 92 newborns and reported a reduction from 36 to 18 days by administering a standardized morphine protocol [5]. Hall et al., evaluated data on 547 neonates managed at 20 different hospitals in six Ohio regions [6]. They found that the LOS for the 417 newborns managed with an established NAS weaning protocol was 22.7 versus 32.1 days for the 130 newborns managed without an establish weaning protocol [6]. These authors expanded on this to 981 infants and reported an LOS reduction to 23.7 days in neonates treated with stringent weaning guidelines compared with 31.6 days LOS in those not treated by the guidelines [7]. Lastly, Patrick et al., conducted a prospective cohort study using serial cross-sectional audits of centers enrolled in the Vermont Oxford Network NAS Internet-Based Quality Improvement Collaborative [8]. They reported a reduction in LOS from 21 to 19 days from 199

participating centers following standardization of hospital patient care policies.

The strengths of this study are the prospective data collection of the variables that can affect length of stay and the large number of treated neonates at a single institution involving the same group of neonatologists. The study does, however, have several limitations that could affect its generalization. First, the study population was primarily Caucasian and results could vary if compared with populations that have a higher mix of African–American or Hispanic races. Second, the most frequent drug seen at the time of delivery was buprenorphine and again, differences may be seen in populations that mainly have methadone or heroin as the primary opiates that lead to NAS. Third, any study that involves the effects of drugs is hampered by truly knowing what was ingested and the actual amount used. Though drug screens were performed on all patients at delivery and were also obtained periodically throughout gestation, 72% of the population for certain (and possibly more) involved polysubstance abuse and the intermixing of drugs and their effects cannot accurately be separated. However, with the large number of neonates evaluated before and after treatment standardization, these theoretical effects would likely be found in both groups.

Another limitation is that this study does not prove that the strict morphine weaning protocol used at our institution should be adopted universally across the country. Rather, this study demonstrated that implementing a standardized protocol decreased LOS. It currently is unknown whether one specific treatment protocol or drug should be used as the standard since other options of methadone, buprenorphine, and outpatient treatment have also been reported to be successful [9–12].

It is well-known that the treatment of NAS is costly. Patrick et al., reported that the mean hospital charge for NAS in 2012 was $66,700 and that the estimated nationwide aggregate hospital charges for NAS in 2012 was $1.5 billion [1]. In addition, approximately 80% of these costs fell on the Medicaid system. In Tennessee, the average Medicaid "payment" for 1 day in the NICU is a minimum of $2100 [13]. The state of Tennessee has approximately 1000 neonates treated for NAS annually. If 80% of the neonates treated for NAS in Tennessee are covered by the Medicaid program and standardization of NAS treatment resulted in five fewer days in the NICU, the cost savings would be a minimum of $8.4 million annually. Therefore, it is recommended that institutions with nurseries that treat infants with NAS develop standardized treatment protocols to cost effectively improve care for this complicated patient population.

In conclusion, these study data demonstrate that the initiation of a standardized NAS treatment protocol, as recommended by the American Academy of Pediatrics, can significantly improve neonatal response and decrease LOS.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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