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ARTICLE

Treating infants with neonatal abstinence syndrome: an examination of three protocols

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Abstract

Objective Describe the characteristics of infants with NAS and determine if treatment outcomes varied between three protocols.

Study design Based on medical record data, infant treatment for NAS-related withdrawal reflected one of three protocols: (1) No rescue dose ($n = 836$, 52.7%): Prescriber ordered initiation and escalation doses and determined when infants were eligible for weaning, (2) Rescue dose ($n = 233$, 14.7%): No rescue dose with the addition of a prescriber-ordered rescue dose, (3) Rescue dose by order set ($n = 516$, 32.6%): Rescue dose with addition of nurse-assisted order of morphine during escalation.

Results The no rescue dose group had longer length of stay, days to wean, and inpatient days, and greater initial morphine dose than the two rescue dose groups ($p < 0.001$). Treatment outcomes between the two rescue dose protocols did not differ.

Conclusions The benefits related to rescue dosing further inform the development of a standardized NAS treatment protocol.

Introduction

Opioid use has dramatically increased in the US [1, 2], with Tennessee having the highest number of opioid prescriptions per capita [3]. Opioid use during pregnancy can cause low birth weight, preterm labor, poor fetal growth, stillbirth, and neonatal abstinence syndrome (NAS) [4, 5]. NAS is an infant withdrawal syndrome associated with prenatal exposure to opioids that typically manifests in the first few days of the infant's life, as hypertonia, autonomic instability, irritability, poor sucking reflex, impaired weight gain, and seizures [6]. Based on 28 states, the incidence of NAS has increased 400%, from 1.5 per 1000 hospital births in 1999, to 6.0 per 1000 hospital births in 2013 [7].

The hospital costs for newborns with NAS are $66,700 on average compared to $3500 for those without NAS—approximately a 20-fold difference. This increased cost is associated with a longer length of stay and more extensive treatment for both mother and infant, compared to infants without NAS. In 2012, NAS accounted for nearly $1.5 billion in hospital charges nationally, with Medicaid programs paying 80.7% of these costs [8].

Despite the health and economic toll of NAS, to date, there is no standard, recommended protocol to treat the symptoms associated with infant opioid withdrawal [9, 10]. To better determine which protocols are most effective in enhancing treatment outcomes, this study utilizes a natural experiment to systematically examine three NAS treatment protocols.

NAS and opioid withdrawal treatment

In the short term, prenatal opioid exposure can cause withdrawal symptoms and interfere with fetal growth and the neonate's neurobehavior. The long-term outcomes of infants diagnosed with NAS include behavioral issues such as hyperactivity, attention deficit, and memory and perceptual challenges [11].

For infants with NAS, pharmacological treatment typically follows a pattern of phases: initiation, escalation, capture, weaning, observation, and discharge (see Fig. 1). After

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hospital admission, an infant with NAS enters the initiation phase where withdrawal symptoms are evaluated and pharmacotherapy is started. The infant's symptoms are continuously monitored, typically using a standardized scoring tool such as the Finnegan system [12]. Symptom monitoring occurs throughout the duration of treatment and withdrawal symptoms are most often controlled with morphine [6, 13].

With the initiation of treatment, the infant enters escalation. During this phase, the medication dose may be increased or escalated to control the infant's symptoms. If the infant's symptoms are controlled for 48 h, the infant has completed the capture phase, and weaning begins. During weaning, adjunct medications and/or acetaminophen may be added to the administration of morphine. Morphine may be administered on escalating or deescalating increments, or the dosage can be significantly increased to reduce withdrawal symptoms. This latter dose has been referred to as rescue dose. The infant remains in the weaning phase until their symptoms subside completely without further pharmacotherapy. Once weaned, the infant enters an observation phase to ensure that symptoms do not recur. Weaning and associated observation typically cease if the infant remains symptom free for 72 h. If there are no other issues that need to be addressed beyond withdrawal, the infant may be discharged.

Although this pattern of phases is typical, NAS weaning strategies can vary. Few centers treat NAS consistently within and between hospitals [14], so little is known about the best practice for treatment protocols, and no conclusion has been made about which treatment protocol or outcome is most favorable for treating NAS [15]. Protocol variability can include, but is not limited to: type of withdrawal drug, drug dosage [9], inclusion of adjunct medication [9], use of rescue dose, persons responsible for ordering and/or administering the treatment, and the standardized symptom scoring system [16, 17].

The quality of treatment has been assessed via outcomes such as the duration of postnatal opioid exposure, days to wean, length of stay, and use of adjunct medications [18]. Given that infants are typically weaned prior to discharge, days to wean and length of stay are related. A prolonged length of stay for patients with NAS can lead to adverse patient harm, impaired maternal–infant attachment, and significant health care costs [19]. Lower levels of maximum morphine dose, initial morphine dose, and number of rescue doses administered, are also indicators of treatment quality, as the potential consequences associated with postnatal opioid exposure are unknown [18].

East Tennessee Children's Hospital and NAS Treatment Protocols

From 2010 to 2017, East Tennessee Children's Hospital (ETCH) implemented three distinct NAS treatment protocols. All three protocols applied symptom-based dosing contingent on Finnegan scores and the primary medication was morphine. The ETCH treatment and pharmacological therapy for infants with NAS, includes six phases: initiation, escalation, capture, weaning, observation, and discharge. The series of six phases was consistent across the three ETCH protocols: (1) No rescue dose—The prescriber ordered the initiation and escalation doses and determined when the infant was captured in order to begin weaning phase. ($n = 836$, 52.7%), (2) Rescue dose—This group was similar to the no rescue dose, with the addition of a prescriber-ordered rescue dose when necessary ($n = 233$, 14.7%), (3) Rescue dose by order set. This protocol utilized a standardized order set for rescue dosing, eliminating the need to obtain a one-time order for each rescue dose when required during the weaning phase ($n = 516$, 32.6%). This order set allowed for greater immediacy of treatment administration and symptom relief.

Several approaches were consistent across the three protocol groups. Monitoring was recorded with Finnegan scores across all phases, except discharge. Non-pharmacological comfort measures, including swaddling and rooming in as possible, were employed throughout all stages of treatment [16]. The first three phases followed the general pattern highlighted earlier. During the weaning phase, in addition to morphine, acetaminophen [20] and adjunct medications (i.e., phenobarbital and/or clonidine) were administered based on symptom severity. The capture phase was completed after symptoms were controlled for 48 h.

For the two rescue dose groups (rescue dose and rescue dose by order set), if infants received three consecutive Finnegan scores of 8 or higher during the weaning phase, they were eligible for a rescue dose. The ETCH rescue dose, calibrated based on the highest of the three consecutive Finnegan scores, was given in addition to the scheduled dose. Given its relation to the Finnegan score, the rescue dose reflected 50% of the escalation dose associated with that particular Finnegan score. If the infant required more than one rescue dose in a 24-h period, then the prescriber considered re-escalation or re-entering the escalation phase.

The weaning stage concluded when the infant's symptoms subside completely. Observation concluded when the infant remains symptom free for 72 h. Discharge from ETCH would occur only after weaning and observation were complete. Formerly ETCH prescribers (i.e., doctors and nurse practitioners) were responsible for prescribing and administering medications. As of June 2015, nurses took on a greater role in supporting the administration of the protocol. Specifically, in the weaning phase of the third protocol (rescue dose by order set), nurses administer the prescribed rescue doses per the standardized order set.

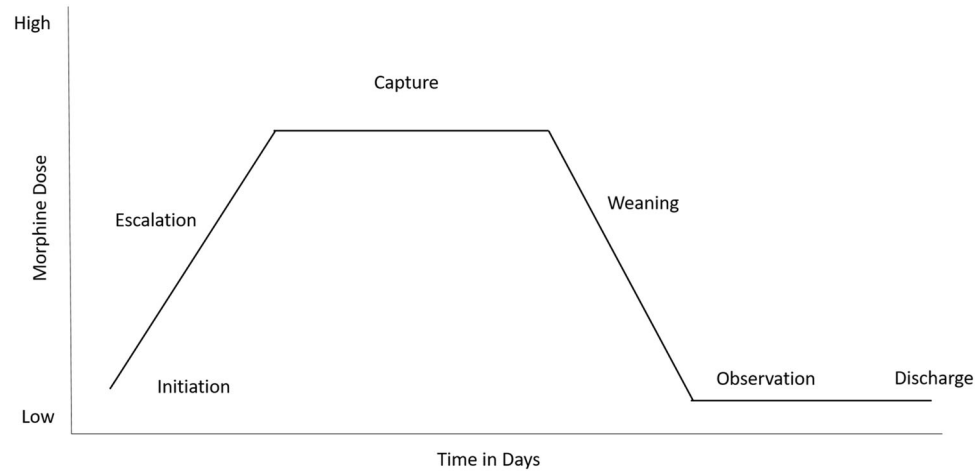

Fig. 1 Phases of treatment for opioid withdrawal

Contextualizing NAS in East Tennessee

Geographic disparities in the incidence and prevalence of NAS escalate the importance of Appalachian studies [21]. The Appalachian region contains three of the top five prescribing states of short-acting opioids Alabama, Tennessee, and Kentucky [3]. Tennessee has a particularly high rate of NAS [22] (12.9 per 1,000 in 2015) [23]—especially in the Appalachian region of East Tennessee, where 2014 county NAS rates were as high as 80.2 per 1,000 live births [24]. Infants with NAS from across East Tennessee are referred to ETCH for treatment. ETCH medical records and Tennessee Department of Health data [24] infer that ETCH treats over 25% of Tennessee infants with NAS [25].

During the data collection period, state laws were enacted that may have impacted the occurrence and/or reporting of NAS. In 2013, Tennessee passed the Safe Harbor Act; this allows pregnant women who misuse or abuse of prescription drugs to seek treatment without risking loss of custody [26]. In 2014, the Tennessee General Assembly passed SB 1391, intending to prevent NAS by criminalizing maternal narcotic abuse. In response, several doctors testified that the law deterred pregnant women from seeking care, endangering the lives of mothers. SB 1391 was allowed to sunset in 2016 [27].

East Tennessee's high rate of NAS and ETCH's systemic treatment protocols provide a natural experiment by which to investigate whether treatment and associated outcomes varied by protocol. We examine the three mutually exclusive protocols that ETCH administered from 21 November 2010 to 7 March 2017. Two questions are addressed: (1) What are the infant and treatment characteristics for the overall sample? and (2) Do length of stay, days to wean, inpatient post-wean days, initial morphine dose, maximum morphine dose, and number of adjunct medications differ by treatment protocol?

Methods

To address quality improvement initiatives, pharmacy staff extracted data from ETCH medical records of all NAS diagnosed infants admitted to the neonatal intensive care unit from 21 November 2010 to 7 March 2017 ($n = 1597$). These data were de-identified for the purpose of our analysis. Study data excluded 12 cases where NAS was ruled out or the days of weaning exceeded days of hospitalization. The final sample included 1585 cases. Initial Internal Review Board (IRB) approval was granted to the hospital pharmacist for data extraction. Subsequent IRB approval was granted for this study from ETCH and the University of Tennessee, Knoxville.

Measures

NAS status reflected infant's NAS diagnosis at discharge. Three mutually exclusive categories of treatment protocol were created based on dates of treatment: (1) No rescue dose (21 November 2010 to 19 July 2014): Prescribers ordered the initiation and escalation doses and determined when the infant was captured in order to begin weaning phase ($n = 836$, 52.7%), (2) Rescue dose (21 July 2014 to 31 May 2015): Similar to group one, with the addition of a prescriber-ordered rescue dose ($n = 233$, 14.7%); (3) Rescue dose by order set (2 June 2015 to 7 March 2017; $n = 516$, 32.6%): This rescue dose protocol added nurse-assisted administration of morphine during the escalation phase per the standardized order set.

Gestational age was measured in weeks and birth weight in grams; both were recorded by clinicians at the hospital of birth and served as controls. These measures were also dichotomized to reflect premature birth (<37 weeks) and low birth weight (<2500 g). Length of stay was measured as the number of days the infant was hospitalized after birth. Days to wean is the number of days the infant received

pharmacotherapy to wean from opioids. Inpatient days post wean is the number of days the infant was hospitalized after weaning was complete.

Initial morphine dose and maximum morphine dose were recorded in micrograms (μg). Adjunct medications reflected the use of morphine alone (no adjunct medications) or morphine with phenobarbital and/or clonidine. This measure was also recoded to reflect the number of adjunct medications recorded (0 = none; 1 = phenobarbital or clonidine; 2 = phenobarbital and clonidine).

Analysis

Analyses were conducted using SPSS version 25. Descriptive analyses to describe the infant and treatment characteristics included frequencies and percentages (categorical measures) and means and standard deviations (continuous measures). ANOVA was used to test for mean-level differences in birth weight and gestational age by treatment group. Following correlational analysis to test for multicollinearity between the continuous measures, ANCOVAs, controlling for birth weight and gestational age, were conducted to assess adjusted mean level differences of infant and treatment characteristics. If the model was significant, post hoc Least Significant Difference (LSD) tests were used to assess significant contrasts.

Table 1 Characteristics of Infants with NAS ($n = 1585$)

Measure	Frequency (%) or mean ± standard deviation	Minimum	Maximum
Treatment groups			
No rescue dose	836 (52.7)		
Rescue dose	233 (14.7)		
Rescue dose by order set	516 (32.6)		
Gestational age (weeks)	38.20 ± 1.86	27	45
Premature (<37 weeks)	245 (15.5%)	27	36
	34.81 ± 1.59		
Birth weight (grams)	2952.45 ± 517.78	980	4726
Low birth weight (<2500 g)	278 (17.5%)	980	2498
	278 ± 17.5		
Length of stay (days)	27.89 ± 15.32	5	155
Days to wean	21.49 ± 12.194	2	129
Inpatient days post wean	5.79 ± 5.15	0	52
Initial morphine Dose (μg)	62.92 ± 32.69	10	500
Max morphine dose (μg)	136.27 ± 103.25	10	1990
Adjunct medication			
None	1064 (67.1)		
Phenobarbital	175 (11.0)		
Clonidine	164 (10.3)		
Phenobarbital and clonidine	181 (11.4)		
Missing	1 (0.1)		
Number of adjunct medications	0.44 ± 0.69	0	2

Results

Infant and treatment characteristics

Across the three treatment protocols, 839 (52.7%) infants were in the no rescue dose group, 234 (14.7%) infants were in the rescue dose group, and 518 infants (32.6%) were in the rescue dose with nurse assistance group. Most infants were born near full term (Mean = 38.2 weeks; SD = 1.86), with 15.5% ($n = 245$) being premature. The majority of the NAS diagnosed infants were born within normal weight ranges (Mean = 2952.45 g; SD = 517.78), but 17.5% ($n = 278$) were characterized as low birth weight babies Table 1.

On average an infant with NAS was hospitalized for 27.9 days; with an average of 21.5 days to wean. The initial morphine dose ranged from 10 to 500 mcg (Mean = 62.92; SD = 32.69). The mean maximum morphine dose was 136.3 mcg, ranging from 10 to 1990 mcg. In addition to morphine, a third of the infants (33.2%, $n = 526$) received one or more adjunct medication.

Infant and treatment characteristics by protocol

ANOVA revealed no mean level differences for gestational age and birth weight by treatment group. The correlation matrix of the continuous measures included in the ANCOVA models revealed that no correlations exceeded 0.60, indicating a low threat of multicollinearity. A series of ANCOVAs showed that after controlling for gestational weight and age, significant adjusted mean level differences by treatment group emerged for four of the six treatment characteristics. The model was significant for length of stay with neither covariate being significant. A post hoc LSD test revealed that the no rescue dose group had a significantly longer mean length of stay than the two rescue dose groups. The days to wean model was significant with gestational age as a significant covariate ($p = 0.001$). LSD revealed that the no rescue dose group had a significantly longer weaning period than either of the rescue dose groups. Gestational age was a significant covariate ($p = 0.000$) for the inpatient days post weaning model. The no rescue dose group again had a significantly greater mean number of inpatient days than the two rescue dose groups Table 2.

Finally, the model for initial morphine dose was significant ($p = 0.000$), with both covariates being significant. The post hoc LSD revealed that the no rescue dose group had significantly higher adjusted mean level of initial

Table 2 ANCOVA results: protocol status effects on outcome after partialing out covariates

Measure	No rescue dose ($n = 836$)	Rescue dose ($n = 233$)	Rescue dose by order set ($n = 516$)	*F* Value	*P*-Value	Contrasts
Length of stay	33.44 ± (1.04)	21.83 ± (1.82)	21.47 ± (1.24)	136.74	0.000	1 > 2,3
Days to wean	26.28 ± (0.75)	16.57 ± (1.42)	15.96 ± (0.95)	166.22	0.000	1 > 2,3
Inpatient days post wean	6.69 ± (0.34)	4.89 ± (0.64)	4.74 ± (0.43)	28.74	0.000	1 > 2,3
Initial morphine dose	66.77 ± (2.19)	57.83 ± (4.15)	58.98 ± (2.79)	12.67	0.000	1 > 2,3
Max morphine dose	138.00 ± (6.89)	138.54 ± (13.03)	132.43 ± (8.76)	0.55	0.578	
Number of adjunct meds (0–3)	0.44 ± (0.02)	0.46 ± (0.05)	0.43 (0.03)	0.18	0.848	

Covariate adjusted means ± SD

Gestational weeks and birth weight as covariates

morphine dose than the two rescue dose groups. The two final ANCOVA models, maximum morphine dose and number of adjunct medications by treatment group, were not significant.

Discussion

East Tennessee has some of the highest rates of NAS in the nation [21]. This study of retrospective hospital record data provides a regional snapshot of infants diagnosed with NAS and their treatment. Most infants were born full term and not considered low birth weight. Protocols that included the rescue dosing option were related to more desirable outcomes (e.g., shorter length of stay and lower initial morphine dose). There was no significant difference in the use of adjunct medication by treatment protocol. The findings are discussed in relation to previous research and potential applications. In closing, we review the data limitations and their implications for future studies.

Most infants of this study were born near full term and within normal weight ranges, yet the risk of low birth weight (17.5%) and prematurity (15.5%) for the East Tennessee infants with NAS exceeded the 2016 rates for the state (9.3% low birth weight; 11.3% prematurity) and nation (8.2% low birth weight; 9.9% prematurity) [28]. The increased risk of low birth weight and prematurity are consistent with previous research on infants with NAS [29], where the percent of NAS infants with birth weight has ranged from 16.2 to 19.4% [21, 29, 30]. Interestingly, the lowest figure of 16.2% is reported in a 2017 study of East Tennessee infants with NAS, however this study included only NAS infants on Medicaid. Our study reflects all infants with NAS treated at ETCH, regardless of type of insurance coverage.

Compared to birth weight, less is understood about the identified increased risk of prematurity for the NAS infants. For the East Tennessee Medicaid population, the risk of prematurity did not differ between infants with NAS and their non-NAS counterparts, with both groups reporting a median gestational age of the 39.0 weeks [21]. However, consistent with our finding (15.5% premature), a Florida study that reported 18.2% of the infants with NAS were also premature [29]. These figures are higher than the overall prematurity rate in the U.S. (9.5%) [31]. Tobacco use may be confounded with risk of low birth weight and premature birth, given the higher prenatal tobacco use rates of Tennessee [32], particularly among women who give birth to babies with NAS [21]. Maternal tobacco use was not available in our data, however, an East Tennessee study revealed greater risk of prenatal smoking exposure for infants with NAS born to mothers on Medicaid than their counterparts without NAS [21].

The incidence of preterm birth does not influence the odds of infants receiving treatment for NAS [33], however, preterm birth has been consistently confounded with low birth weight—another characteristic of NAS diagnosed infants [34, 35]. There is evidence that both preterm and low birth weight infants with NAS can face less hospitalization time compared to full-term infants diagnosed with NAS [36, 37]. After controlling for low birth weight and gestational age, compared to the no rescue dose group, the two rescue dosing groups had more beneficial outcomes including shorter length of stay, fewer days to wean and inpatient days, and lower initial morphine dose.

To our knowledge, there are no comparative studies that include rescue dosing. Our study relies on a natural experiment. To further test this finding, future studies could incorporate a quasi-experimental design with randomized control and treatment groups. Our study also seems to be the first to examine the association of nurse assistance during escalation with treatment outcomes. The outcomes related to the addition of nurse assistance to the rescue dose protocol did not differ significantly from those of the rescue

dose group. The lack of significance between the two rescue dosing protocols suggests that during escalation, nurses can reduce prescriber involvement in monitoring and administering of treatment without compromising treatment outcomes.

Expansion to escalation by order set may reduce prescriber time and effort in treatment, which may reduce cost and increase efficiency. Further, escalation by order set can potentially enhance physician-nurse relations (e.g., fewer late night nurse consultation calls to physicians). Finally, ETCH nurse practitioners believe nurse assistance during escalation may decrease the opportunity for medication error and increase compliance with protocol (C. Saunders, K. Cook, personal communication, 17 January 2017). Future qualitative studies on the implementation process of nurse assistance during escalation could further clarify the importance of this contribution, despite the lack of significant outcome differences between the two rescue dosing protocols (rescue dosing and the rescue dosing by order set).

Limitations and future directions

Our study data included a limited number of variables across maternal, infant, and treatment characteristics. As such, the models used to test differences between the three treatment protocols were limited. The large number of infants treated for NAS at ETCH supports the examination of more complex models. With greater resources, the data could be enhanced with additional efforts to increase data extraction and/or aggregate medical record data with other ETCH data.

The study data are also limited to quantitative data, which are ideal for testing models, but fail to provide a more nuanced examination of the various protocols and the experiences of the persons responsible for administration. Future qualitative investigations could focus on the quality of the relationship between prescribers and nurses, perceived impact of shorter hospitalization on family and infant outcomes, and a greater understanding of contextual factors that may influence protocol administration.

Further, replication studies that focus on NAS weaning protocol, especially those that examine the efficacy of rescue dosing in geographic regions beyond East Tennessee, will be informative. As aforementioned, this study is a natural experiment. The examination of health and social outcomes associated with different treatment protocols is warranted.

Finally, the study data reflects infants with NAS, who were born across 7 years, 2010 to 2017. Across these 7 years, factors related to opioid use disorder and NAS changed. For example, in 2015 the Tennessee General Assembly passed SB 1391, which intended to prevent NAS by criminalizing maternal narcotic abuse. This bill deterred mothers form seeking prenatal treatment; however, little is known on how this affected NAS before the law was allowed to sunset in July 2016. Also during this time, the Tennessee General Assembly strove to reduce access to opioids. The Prescription Safety Act was designed to reduce the likelihood of patients and obtaining prescriptions from multiple prescribers and requires that all pain management clinics are licensed [38]. Prior to this law, there were over 300 pain management clinics in Tennessee; now there are 182 [38]. However, as access to prescription opioids is reduced, there is concern about increased illicit opioid use, including less controlled substances such as heroin [39]. Legislation may have impacted the severity of NAS—and hence the treatment efficacy—across time.

Conclusion

The continued improvement of NAS treatment protocol remains a compelling issue as a definitive, most recommended protocol to treat withdrawal symptoms has not been determined. The prevalence of NAS in Appalachia comes with great social and economic cost; however, this geographic area provides statistical power ideal for more sophisticated studies. The consistent use of a standardized NAS treatment protocol provided the opportunity to contrast three treatment protocols, with rescue dosing significantly enhancing treatment outcomes. These informative findings assist in developing more standardized guidance for the treatment of NAS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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