BRIEF RESEARCH REPORT

Neonatal Abstinence Syndrome: A Review of Treatment in the Neonatal Intensive Care Unit

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ABSTRACT

Background: Neonatal abstinence syndrome (NAS) is a collection of symptoms that neonates may experience following antenatal exposure to substances that induce withdrawal. Optimal management remains unknown, and there is variation in management and outcomes.

Objectives: To describe the management, length of hospitalization, and adverse events in near-term and full-term neonates with NAS for whom treatment (pharmacotherapy and/or supportive care) was initiated in the neonatal intensive care unit (NICU).

Methods: A chart review was conducted of neonates admitted to the NICU of Surrey Memorial Hospital, Surrey, British Columbia, who received treatment for NAS between September 1, 2016, and September 1, 2021.

Results: A total of 48 neonates met the inclusion criteria. Opioids represented the most frequent type of antenatal exposure. Polysubstance exposures occurred in 45 (94%) of the neonates. Morphine was given to 29 (60%) of the neonates, and phenobarbital to 6 (13%); 5 of these neonates received both medications. The average duration of morphine treatment was 14 days, and the average length of hospitalization (all patients) was 16 days. All of the neonates experienced adverse events; in particular, 9 (30%) of the 30 who received pharmacotherapy were too sedated to feed, compared with 0% of the 18 with no pharmacotherapy.

Conclusions: The common finding of polysubstance antenatal exposure, involving predominantly opioids, was associated with scheduled morphine pharmacotherapy for the majority of patients, prolonged hospitalization, and frequent adverse events. Pharmacotherapy for NAS was associated with levels of sedation that interfered with feeding in neonates.

Keywords: neonatal abstinence syndrome, withdrawal, morphine, phenobarbital, neonatal intensive care

RÉSUMÉ

Contexte : Le syndrome d'abstinence néonatale (SAN) est un ensemble de symptômes que les nouveau-nés peuvent ressentir après une exposition prénatale à des substances qui induisent le sevrage. La prise en charge optimale reste inconnue et il existe des variations quant à la prise en charge et les résultats.

Objectifs : Décrire la prise en charge, la durée de l'hospitalisation et les événements indésirables chez les nouveau-nés prématurés et nés à terme atteints d'un SAN pour lesquels un traitement (pharmacothérapie et/ou soins de soutien) a été initié dans l'unité de soins intensifs néonatals (USIN).

Méthodes : Un examen des dossiers a été effectué sur les nouveau-nés admis à l'USIN de Surrey Memorial Hospital, en Surrey (Colombie-Britannique) qui ont reçu un traitement pour le SAN entre le 1er septembre 2016 et le 1er septembre 2021.

Résultats : Au total, 48 nouveau-nés répondaient aux critères d'inclusion. Les opioïdes représentaient le type d'exposition prénatale le plus fréquent. Des polyexpositions étaient présentes chez 45 (94 %) des nouveau-nés. De la morphine a été administrée à 29 (60 %) nouveau-nés et du phénobarbital à 6 (13 %) nouveau-nés, 5 ayant reçu les deux médicaments. La durée moyenne du traitement morphinique était de 14 jours et la durée moyenne d'hospitalisation (tous patients confondus) était de 16 jours. Tous les nouveau-nés ont présenté des événements indésirables; en particulier, 9 (30 %) des 30 qui avaient reçu une pharmacothérapie n'étaient pas capables de se nourrir à cause de la sédation, contre 0 % des 18 n'ayant pas reçu de pharmacothérapie.

Conclusions : La découverte commune d'une exposition prénatale à plusieurs substances, impliquant principalement des opioïdes, était associée à une pharmacothérapie programmée à base de morphine pour la majorité des patients, à une hospitalisation prolongée et à des événements indésirables fréquents. La pharmacothérapie était associée à des niveaux de sédation empêchant l'alimentation.

Mots-clés : syndrome d'abstinence néonatale, sevrage, morphine, phénobarbital, réanimation néonatale

INTRODUCTION

The incidence of perinatal opioid use disorder has increased 3-fold in the past decade, paralleling the magnitude of the opioid crisis in the general population.[1] Consequently, the incidence of neonatal abstinence syndrome (NAS) has nearly doubled, from 2.6 per 1000 live births in 2010 to 4.7 per 1000 live births in 2018.[2] NAS is a constellation of symptoms that a neonate may experience following antenatal exposure to substances that induce withdrawal. Symptoms vary in severity and include neurologic, gastrointestinal, and musculoskeletal effects. Substances implicated in NAS include opioids, stimulants, and other psychotropics.[3] The goal of NAS management is to use supportive care and

pharmacologic interventions to promote physiologic stability, including adequate nutrition, sleep, weight gain, and ocialization.[4]

A scoring tool is generally used to quantify symptom burden and guide pharmacotherapy in patients with NAS.[5] The Finnegan Neonatal Abstinence Scoring System (FNASS)[6] has been adopted and subsequently modified by many groups around the world since its introduction in 1975.[3,5,7] Subsequent variants, including the tool used in the NICU of Surrey Memorial Hospital (SMH), have modified the original criteria and overall score in attempts to quantify NAS symptoms and to reflect changes in practice. However, the criteria remain subjective, and the recommended score of 8 or more to initiate pharmacotherapy remains unchanged, despite changes to the total possible score.[1,7,8] These scoring systems may therefore overestimate symptom severity, which can lead to inappropriate introduction, escalation, and duration of pharmacotherapy. A simplified tool introduced in 2017 by Grossman and others[9] emphasizes caregiver involvement and supportive care through assessment of symptoms of withdrawal according to 3 items: the infant's ability to eat, sleep, and be consoled. Use of this tool reduced the length of hospitalization, the number of NICU admissions, and the provision of pharmacotherapy relative to the use of FNASS in the pre-intervention period.[9]

To date, no standard assessment or optimal treatment strategy for NAS has been described in the literature. In the NICU, pharmacologic therapies often prevail, including morphine for opioid exposures and phenobarbital or clonidine for non-opioid or polysubstance exposures.[10] Because NAS is a self-limiting withdrawal process, many perinatal units across North America, including the NICU at SMH, have begun to shift the focus of management from pharmacotherapy to supportive care. Therefore, the purpose of this study was to describe management, length of hospitalization, and adverse events in near-term and full-term neonates with NAS in the NICU.

METHODS

Ethics approval for this review was obtained from the Fraser Health Research Ethics Board.

Neonates who received treatment for NAS in the 36-bed NICU of SMH between September 1, 2016, and September 1, 2021, were identified from a list of inpatient neonatal prescriptions for morphine, phenobarbital, and zidovudine. In this NICU, clonidine was not used as a treatment for NAS during the study period. Historically, the majority of neonates with NAS presenting to the SMH NICU have been born to mothers with ongoing use of illicit substances and high-risk behaviours. Therefore, zidovudine treatment in the NICU was used to identify neonates from high-risk pregnancies where the neonate might have received supportive care alone for management of NAS.

The inclusion criteria for the study required that neonates have a diagnosis of NAS documented by the medical team, with receipt of treatment for NAS (including pharmacotherapy and/or supportive care) in the SMH NICU during the study period. Neonates who needed only supportive care for management of NAS were included to determine the proportion of patients requiring pharmacologic treatment, as well as to determine adverse effects associated with pharmacologic treatment. Neonates for whom pharmacotherapy for NAS was initiated outside the SMH NICU did not meet the inclusion criteria, as treatment strategies vary among sites. Neonates of gestational age less than 35 weeks were excluded, because preterm neonates have different behaviours, as well as different needs for pharmacotherapy, and the scoring systems have not been validated in this population. Neonates were also excluded if they had significant comorbidity compromising interpretation of NAS scoring or if the child died before 7 days of age.

Confirmation of NAS was based on documented symptoms consistent with NAS, along with maternal history of medication and substance use near the time of delivery or, if such maternal history was suspected but not available, a positive result on neonatal drug screening. Management of NAS was at the discretion of the clinical team providing care, based on neonatal withdrawal symptoms, including but not limited to their FNASS scores. The team provided supportive care or supportive care plus regular and/or as-needed medications. Assessment of each neonate by the clinical team occurred at least twice daily, nursing observations occurred at least hourly, and FNASS scores were documented every 2 to 4 hours.

The following demographic data were collected: gestational age, birth weight, Apgar score, assigned sex, prenatal care, hypoglycemia, respiratory support at birth, other neonatal medications, substance exposures in utero, year of admission, length of hospitalization, and duration of NICU admission. The following data concerning treatment regimen were also collected: daily dosing information for morphine and phenobarbital and breast milk exposure in the first 3 days of life. The modified FNASS used in the SMH NICU assesses 21 criteria, with the maximum possible score being 46. It is identical with the 2012 modified FNASS of the American Academy of Pediatrics,[3] with the addition of a score for "excoriation" as its own category at SMH. Data collected for assessment of efficacy included highest total daily FNASS score and neurologic and gastrointestinal scores from the same time point. Safety was assessed in terms of the following events, as documented by the nurse or physician caring for the patient: respiratory rate less than 30/min, systolic blood pressure less than 60 mm Hg, heart rate less than 100/min, requirement for respiratory support, being too sedated to feed, and other adverse reactions. Neonates were described as being too sedated to feed when nursing notes documented that feeding was attempted by

nursing staff or caregivers and oversedation resulted in ineffective or unsafe feeding.

Descriptive statistics were used to analyze the data. All treatment regimens were converted to milligrams per kilogram (mg/kg) according to birth weight. Safety data were analyzed for the duration of pharmacotherapy (or 14 days for untreated neonates). The Fisher exact test was used to determine the statistical significance of different rates of adverse events between treated and untreated groups.

RESULTS

A total of 103 patients were identified for review. Nineteen of these patients did not meet the inclusion criteria (because there was no NAS diagnosis or because the neonate received treatment at another site), which left 84 patients treated for NAS in the NICU at SMH over the 5-year period, or 3.5 per 1000 live births. This group did not include neonates with NAS managed outside the SMH NICU. Thirty-six additional patients were then excluded for the following reasons: gestational age less than 35 weeks (n = 31), significant comorbidity (n = 3), and death before 7 days of age (n = 2). Thus, a total of 48 patients were included for data collection and analysis.

The average gestational age was 37 weeks, and the average birth weight was 2886 g (Table 1). The most common antenatal substance exposure was opioids (n = 41, 85%) (Table 1), and 45 (94%) of the neonates had polysubstance exposures. Twenty-nine neonates (60%) received morphine therapy (5 of whom also received phenobarbital), 1 (2%) received phenobarbital monotherapy, and 18 (38%) received no pharmacotherapy for NAS.

For the 29 neonates who received morphine, this drug was initiated on day 1 to 3 of life; the dosage was from 0.03 to 0.05 mg/kg every 3 hours for 25 (86%) of these neonates and from 0.01 to 0.04 mg/kg as needed for 4 neonates (14%). The average cumulative morphine dose (total morphine exposure within the treatment period) was 2.6 (range 0.3–6.1) mg/kg. The average number of scheduled morphine doses per patient was 93 (range 0–222), and the average number of as-needed doses was 3 (range 0–17). The average duration of morphine pharmacotherapy was 14 (range 6–28) days, including an average of 8 days for scheduled morphine taper to discontinuation. Neonates transferred out of the NICU before morphine discontinuation had a longer duration of therapy (20 days) than those not transferred out (12 days). Average cumulative and peak morphine doses decreased in the years 2017 and 2020 (Figure 1).

Six (13%) of the neonates received phenobarbital as needed, initiated on day 2 to 7 of life, with cumulative doses ranging from 10 to 62 mg/kg. The average duration of therapy was 5 (range 2–11) days. Of these 6 neonates, 4 had known polysubstance exposure in addition to concurrent morphine therapy, whereas the other 2 had either polysubstance exposure or concurrent morphine therapy.

For the 29 neonates who received morphine, the average FNASS score at morphine initiation for each year from 2016 to 2021 was 16, 13, 16, 14, 18, and 16, respectively (Figure 1). The average score at initiation of morphine tapering

TABLE 1. Characteristics of Patients and Substance Exposure

Characteristic	Mean (Range) or No. (%) of Patients (n = 48)
Patient	
Gestational age (weeks)	37 (35–42)
Birth weight (g)	2886 (1620–3825)
Apgar score at 5 minutes	9 (6–10)
Sex, female	33 (69)
Parent received prenatal care	8 (17)
Experienced hypoglycemic event	10 (21)
Received any feeds with parent's own milk	10 (21)
Required respiratory support at birth	20 (42)
Received HIV prophylaxis	38 (79)
Received antibiotics	25 (52)
Substance exposure in utero	
Opioids	41 (85)
Fentanyl	25 (52)
Heroin	26 (54)
Methadone	24 (50)
Other (oxycodone, hydromorphone, or buprenorphine)	3 (6)
Amphetamines	35 (73)
Nicotine	24 (50)
Cocaine	15 (31)
Cannabis	10 (21)
Benzodiazepines	6 (13)
SSRI or SNRI	5 (10)
Alcohol	4 (8)
Gabapentin	1 (2)
Barbiturates	0 (0)
Tricyclic antidepressants	0 (0)

SNRI = serotonin–norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

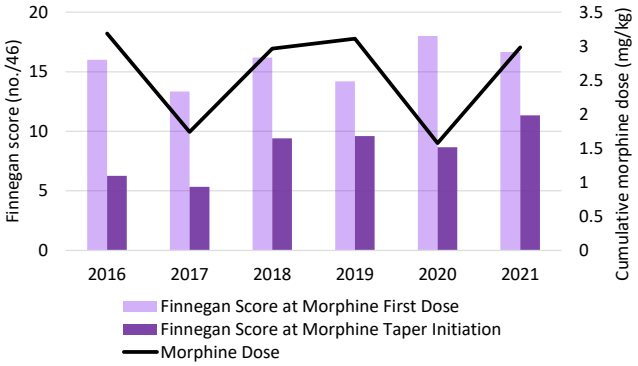

FIGURE 1. Mean score with the Finnegan Neonatal Abstinence Scoring System (FNASS) and morphine use (as cumulative dose per patient), by year (n = 29 neonates who received morphine). The modified FNASS used in the Surrey Memorial Hospital neonatal intensive care unit assesses 21 criteria, and the maximum possible score is 46.

increased over the study period, from 6 in 2016 to 11 in 2021 (Figure 1). Of the 18 neonates who received no pharmacotherapy, 14 were assessed using FNASS, with an average score of 7 (range 0–17) on day 2 of life.

The average length of hospitalization for each year from 2016 to 2021 was 22, 13, 17, 14, 11, and 19 days, respectively. The overall average for the entire study period was 16 days.

All 48 neonates experienced a minimum of 1 adverse event. The rate of bradypnea was 93% (28/30) among those who received pharmacotherapy and 100% (18/18) among those with no pharmacotherapy (p = 0.52); no neonates in either group required respiratory support. The rate of hypotension was 10% (3/30) and 22% (4/18), respectively (p = 0.40), and the rate of bradycardia was 10% (3/30) and 6% (1/18), respectively (p > 0.99). Nine (30%) of the neonates who received pharmacotherapy were too sedated to feed, compared with none (0%) of those not receiving pharmacotherapy (p = 0.018). The average number of adverse events per patient was 1 among those who received no morphine (0 mg/kg), 6 among those with cumulative morphine dose between 0.1 and 2 mg/kg, and 15 among those with cumulative morphine dose between 3.6 and 6.1 mg/kg. The average number of adverse events per patient was 3 among those with cumulative phenobarbital dose between 10 and 17 mg/kg and 7 among those with cumulative phenobarbital dose between 31 and 62 mg/kg.

DISCUSSION

In this study, management of NAS with pharmacotherapy (especially regularly scheduled morphine, 0.03 to 0.05 mg/kg orally every 3 hours), led to unanticipated sedation, whereby 30% of neonates who received pharmacotherapy, compared with 0% who received no pharmacotherapy, were too compromised to feed. Oversedation may be related to a prolonged half-life in neonates and accumulation of morphine when administered routinely every 3 hours.

The occurrence of other adverse events, including bradypnea and absence of respiratory support, was similar between the groups that did and did not receive pharmacotherapy. Perhaps the definitions of bradypnea, bradycardia, and hypotension used in this study were not sensitive enough to identify a difference between groups, given hemodynamic variability in the early neonatal period. Sedation also precedes respiratory depression, so it is possible that the neonates in this study did not reach an opioid level associated with respiratory depression requiring respiratory support. Additionally, Hocker and others[11] have hypothesized that neonates may develop tolerance to respiratory depression after in utero exposure to maternal opioids.

Overall, in this study, as the cumulative dose of pharmacotherapeutic agents increased, so did the incidence of adverse events associated with both morphine and phenobarbital. Similarly, DeAtley and others[12] reported that a higher initial dosing regimen of morphine (0.06 mg/kg) was linked to oversedation events, necessitating dose adjustment.

Phenobarbital is being used more conservatively at SMH than has been reported in the literature. As-needed doses were used for 13% of neonates in this study, whereas Merhar and others[4] reported adjunctive phenobarbital therapy for 32% of neonates, despite polysubstance exposures being less prevalent in their study than at SMH, ranging from 55% to 72%, compared with 94% in this study. The cumulative doses of 10 to 62 mg/kg that we observed were also significantly lower than what was reported in several other studies, which used regularly scheduled doses ranging from 2.5 to 12.5 mg/kg/day, with phenobarbital therapy often continuing after discharge for an average duration of up to 3.8 months.[4,13-15]

The length of hospitalization in our study was 16 days, much longer than the 6 days reported by Grossman and others.[9] Differences in study populations may have contributed to the prolonged hospitalization that we observed. First, substance exposures in the previous study involved primarily methadone,[9] with fewer polysubstance exposures than in the SMH population (33% versus 94%). Second, on average, the neonates described by Grossman and others[9] had older gestational age than those at SMH (38.9 weeks versus 37 weeks). Gestational age can affect the interpretation of NAS symptoms, as preterm neonates exhibit different behaviours from full-term neonates, which may influence management. Third, the population described by Grossman and others[9] included non-NICU patients, who may receive more frequent supportive care while rooming-in with parents after birth, possibly reducing the need for pharmacologic intervention.

Scheduled morphine therapy requires dose tapering before discharge; therefore, exposure and hospitalization are prolonged. In our study, the average time required to taper morphine was more than 50% of the total duration of morphine treatment. If regularly scheduled morphine is used, a faster taper, such as 10% up to 3 times daily (as suggested by Grossman and others[9]), should be considered, instead of the prolonged historical weaning process of 10% every 24 to 48 hours.

Education plays a role in supporting practice changes, and ongoing education is required as staff rosters change continually. In 2017, 2019, and 2020, presentations were delivered to SMH NICU staff to introduce and reinforce an emphasis on supportive care and limiting morphine use, which appeared to temporarily affect management. Additionally, supportive care may have been limited in 2020 and 2021 because of the burden of the COVID-19 pandemic and restricted NICU access. This situation may have contributed to a larger cumulative morphine dose and longer hospitalization in 2021.

Some limitations of this study include the small sample size and our retrospective interpretation of outcomes.

Neonates born to mothers with no recent high-risk activity and a diagnosis of NAS, who required only supportive care in the NICU, would have been missed by our selection process. On average, 8 near-term and full-term patients per year were admitted to the NICU for NAS management. Observed trends in FNASS, pharmacotherapy dosing, and length of hospitalization may have been influenced by the small sample size. The high rate of polysubstance exposures, the average gestational age, and the rates of breastfeeding are unique to SMH, and differences in these characteristics should be considered when these results are applied to other populations. Finally, the retrospective analysis made it difficult to interpret the clinical status of neonates, given our reliance on documented nursing and physician assessments.

CONCLUSION

Morphine and phenobarbital were used for pharmacologic management in 60% and 13% of neonates, respectively. The number of adverse events increased as cumulative pharmacotherapy doses increased. Current management using regularly scheduled morphine led to prolonged pharmacotherapy and a high rate of accumulation, with 30% of neonates being too sedated to feed. Opportunities exist to emphasize supportive care and use pharmacotherapy as needed, instead of on a scheduled basis, to reduce adverse events and length of hospitalization.

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