

Weaning with Morphine Only Versus Weaning with Morphine and Phenobarbital for Infants with Neonatal Abstinence Syndrome

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Abstract

Purpose: To compare infant and family demographics and weaning and discharge outcomes of infants with Neonatal Abstinence Syndrome (NAS) treated with morphine only versus treatment with morphine and phenobarbital in a post-acute care hospital setting.

Design: Electronic medical record review of 76 infants with NAS admitted to a pediatric post-acute hospital from local tertiary-care neonatal intensive care units. Descriptive statistics were calculated for the total group and compared for two weaning medication subgroups (morphine only (n=25) and morphine and phenobarbital (n=51)).

Result: Thirty-nine (51%) infants were male and 49 (65%) were White, non-Hispanic. Average admission age was 17.31 days. Average length of stay (LOS) in the post-acute care hospital was 35 days. All infants began treatment before admission to the post-acute care hospital and 92% weaned from all medications before discharge. Group differences were found for admission age ($p=0.04$), discharge age ($p=0.005$), LOS ($p=0.033$), days to wean morphine ($p=0.004$) and referring acute care hospital ($p=0.01$).

Conclusion: A greater number of infants in post-acute care required phenobarbital as well as morphine than morphine alone. These infants were older at admission,

took longer to wean and stayed in the hospital longer, indicating a more difficult course.

Keywords: Hospital; Neonatal Abstinence Syndrome (NAS); Weaning

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Introduction

Neonatal Abstinence Syndrome (NAS) is a withdrawal syndrome in infants caused by the exposure to narcotic medications or other addictive substances during gestation. NAS symptoms typically appear within hours after birth [1, 2] and the diagnosis of NAS is based on a positive maternal history; identification of a drug or its metabolites in either a maternal or neonatal urine specimen; and/or observation of a group of neurological symptoms indicative of in-utero exposure to opioids. These neurobehavioral features of the withdrawal response of NAS include: irritability, tremors, hypertonicity, sleeplessness, feeding intolerance, seizures and tachypnea [2, 3].

Weaning infants from the offending agent(s) post-birth is critical and presents clinicians with the challenge of determining the correct pharmacologic treatment agents [4, 5]. Treatment drug selection is often based on the drug type during in utero

exposure as well as the post-birth clinical presentation of the infant [3, 4, 6, 7]. Morphine, an opiate derivative, is the current front line treatment, [7] along with methadone and buprenorphine, [3] while phenobarbital and clonidine act as adjunctive therapies [4, 7].

The purpose of this study was to compare the infant and maternal/family demographics and weaning and discharge outcomes for infants with NAS treated solely with neonatal morphine with those infants treated with neonatal morphine and phenobarbital in a post-acute hospital setting.

Methods

Setting and Subjects

This study was conducted at Franciscan Hospital for Children (FHC), Boston, MA, USA, a pediatric post-acute rehabilitation hospital. Infants with NAS are referred to the post-acute hospital from acute care neonatal intensive care units. Upon transfer, the infants have already started weaning with neonatal morphine and a weaning protocol is followed. Infants are weaned from morphine 10% each day based on their scoring on The Modified Finnegan Neonatal Abstinence Scoring System [8] and clinical presentation. The Finnegan is scored by nursing staff members who are trained in its administration upon orientation to the medical unit(s). A Finnegan score higher than eight is typically clinically significant for withdrawal from narcotics [9]. If an infant is unable to tolerate a 10% decrease in their treatment medication as evidenced by an increase in Finnegan score and/or based on the clinical judgment of the medical team, then a 5% decrease is used.

Often, infants are transferred to post-acute care on both morphine and phenobarbital. If the decision is made to add phenobarbital to the infants' weaning program after admission to post-acute care, this decision is made in conjunction with the program's pediatric neurologist and is typically due to the infant's inability to wean from morphine or because the infant is weaning very slowly. Phenobarbital is then weaned 20% per

day as tolerated, or 10% if the infant is having difficulty with the wean.

Nonpharmacologic approaches to NAS management include daily assessment of withdrawal, sleeping habits, feeding patterns and weight gain; and provision of a calm and soothing physical environment to meet the infant's physical and emotional needs and to promote growth and bonding. The program also provides caregiver education and training, including understanding of the weaning process, feeding issues and techniques to facilitate development. Infants are continuously monitored using cardio-respiratory monitors as per hospital protocol.

A total of 76 infants (79 admission-discharge episodes) with an admitting diagnosis of NAS were discharged from the post-acute care hospital during the study timeframe. Three infants were discharged to an acute care hospital for an emergent medical condition (e.g. sepsis evaluation) and readmitted to the post-acute care hospital to complete the weaning process. For these cases, information across admissions was combined as the weaning protocol was continued despite the transfer. No infants were excluded from the study based on medical complexity which would have potentially prolonged their hospital stay.

Study Procedures

Following approval by the hospital's Institutional Review Board, demographic (e.g. gender) and clinical (e.g. treatment medication) information for all admissions between 5/1/2010 and 5/31/2014 for infants with an admitting diagnosis of NAS was collected via retrospective review of electronic medical records. A project-specific database was created to combine the data variables used in this study. Statistical analyses were completed using the Statistical Package for the Social Sciences (SPSS).

Descriptive statistics were generated to characterize the study population. Two weaning medication subgroups (morphine only, n=25 and morphine and phenobarbital, n=51) were created

and compared for infant demographics (gender, gestational age, birth weight, race/ethnicity, Apgar Scores, age at admission, payer, referring hospital) and maternal/family characteristics (maternal age at infant birth, parental marital status, maternal drug use-mono or polysubstance illicit substances and/or prescription medications).

Groups were also compared for the following weaning and discharge outcomes: age at start of morphine, days to wean morphine, days to wean phenobarbital, percent weaned at discharge, age at discharge, length of stay in post-acute care hospital, discharge disposition (home, home with extended family, foster home, transfer to acute care hospital) and Department of Child and Family (DCF) Services Involvement (case closed, ongoing involvement with family, DCF custody). Demographic and outcome variables were compared using an Independent Samples *t*-test, a Median Test or a Chi-Square Test for group proportions.

Results

Infant Demographics and Maternal/Family Characteristics

Of the total sample, 39 (51%) infants were male and 49 (65%) infants were White, non-Hispanic. Mean gestational age was 38 weeks (SD=1.86; range=34 – 41 weeks) and mean birth weight was 3019 grams (SD=408; range=2090–3885 grams). Median Apgar score at 1 minute was 8 (range=1 – 9) and median Apgar score at 5 minutes was 9 (range = 1 – 9). Average age at admission to the post-acute care hospital was 17.31 days (SD=12.89, range=3–70 days). Infants were referred to the post-acute care hospital from 8 different acute care hospitals in Massachusetts.

Average maternal age at infant birth was 29.62 years (SD= 4.74, range= 21 – 42 years) and 47 (62%) mothers were single at the time of the infant's birth. Seventy percent of all mothers were polysubstance users and 67 (88%) of the infants in the total sample had a public payer. Demographics of the infants and

maternal/family characteristics by medication subgroup can be found in Table 1.

Weaning and Discharge Outcomes

Treatment medications for the infants included: morphine only (n=25, 33%) or morphine and phenobarbital (n=51, 67%). All infants began on morphine prior to admission to the post-acute care hospital. Mean age at start of morphine was 1.53 days (SD=1.51, range=0–7 days) while the mean age at the initiation of phenobarbital use was 6.92 days (SD=8.19, range= 0-40 days). Only five of the 51 infants who were treated with phenobarbital were started on phenobarbital after admission to post-acute care. Ninety-two percent of the total sample weaned from all medications prior to discharge.

For the total group, the average time to wean morphine was 38.08 days (SD=14.69, range=14–78 days), regardless if the infant was also on phenobarbital. Six infants were discharged home on phenobarbital. Mean age at discharge from the post-acute care hospital for the total sample was 51.80 days (SD=27.26, range=20–154 days) and average length of stay was 34.72 (SD=23.26, range = 8-138 days). At discharge, 59 (78%) of the infants went home with their mother/immediate family, while eight (11%) went home with extended family and nine (12%) were discharged to foster care. Within the total sample, the Massachusetts Department of Child and Family Services had discontinued involvement prior to transfer to post-acute care for seven (9%) of the infants while 53 (70%), had ongoing involvement with the family and for 16 infants (21%) had custody. One hundred percent of the infants were referred to an Early Intervention Program that services the geographic area to which they were discharged. (Table 2)

Differences between the two weaning subgroups were found for age at admission ($p = 0.044$), age at discharge ($p = 0.005$), hospital length of stay ($p = 0.033$), and days to wean morphine ($p = 0.004$). In addition, drug weaning group was related to the referring acute care hospital ($p=0.01$) (Tables 1 and 2)

Table 1: Infant Demographics and Maternal/Family Characteristics by Subgroup

	Morphine Only (n=25)	Morphine and Phenobarbital (n=51)	<i>p</i>
Gender (n, % Male)	14 (56%)	25 (49%)	NS
Gestational Age (weeks)*	38.5 (1.77) 35-41	38.3 (1.92) 34-41	NS
Birth Weight (grams)*	2979 (405.79) 2405-3572	3040 (412.84) 2090 -3885	NS
Race/Ethnicity (n, % White/Caucasian)	20 (80%)	29 (57%)	NS
Apgar Score at 1 minute (median, range)	8 7 - 9	8 1 - 9	NS
Apgar Score at 5 minutes (median, range)	9 7 - 9	9 5 - 9	NS
Age at Admission (days)*	12.92 (7.60) 3.0 – 37.0	19.12 (14.1) 4.0 – 70.0	0.044
Payer (% public)	21 (84%)	46 (90%)	NS
Maternal Age at Infant Birth (years)*	28.8 (3.90) 24 - 36	30.07 (5.17) 21 - 42	NS
Parental Marital Status (n, % single mother)	16 (64%)	31 (61%)	NS
Maternal Drug Use (n, % polysubstance use)	15 (60%)	38 (75%)	NS

*Mean (Standard Deviation)

Table 2: Weaning and Discharge Outcomes by Subgroup

	Morphine Only (n=25)	Morphine and Phenobarbital (n=51)	<i>p</i>
Age at start of Morphine (days)	1.96 (1.34) 0 - 5	1.31 (1.56) 0 – 7	NS
Age at Start of Phenobarbital (days)	N/A	6.92 (8.19) 0 – 40	N/A
Days to wean Morphine*	31.0 (9.85) 14 - 60	41.41 (15.47) 18 -78	.004
Days to wean Phenobarbital*(n=45)	N/A	44.89 (18.82) (20-92)	N/A
Weaned at Discharge from medication (%)	100%	100% Morphine 87% Phenobarbital	N/A
Age at Discharge (days)*	39.56 (25.23) 22 - 154	57.80 (26.42) 20 - 135	.005

Length of Stay in Post-Acute Hospital (days)*	26.64 (24.6) 9 - 138	38.69 (21.74) 8 - 92	.033
Discharge Disposition (n, % home with Mother)	21 (84%)	37 (73%)	NS
Department of Child and Family Services Involvement (n, % ongoing involvement with family)	19 (76%)	34 (67%)	NS

*Mean (Standard Deviation)

Discussion

The purpose of this study was to compare infant and maternal/family demographics and weaning and discharge outcomes for infants with NAS treated with neonatal morphine and infants treated with neonatal morphine and phenobarbital in a post-acute care hospital setting. A greater number of infants transferred to post-acute care from the NICU for ongoing medication wean due to NAS required phenobarbital as an adjunct to morphine as opposed to morphine alone.

Infants, children and youth are transferred to a post-acute care hospital from an acute care hospital because they need additional time, medical care and therapeutic services before going home [10]. Infants with NAS are typically cared for in a NICU with the average length of stay about 25 days [9, 11]. While there is no standard process or protocol for determining which infants are transferred to post-acute care, generally, the referring institution has determined that weaning will be prolonged either because the infant has required a high dose of medication(s) initially, or the infant begins a wean and then develops difficulty with weaning indicating the likelihood of a prolonged hospital stay. A transfer to post-acute care following a NICU stay would thus, generally indicate that an infant has more complex needs and thus, it is not surprising that two-thirds of the study sample required phenobarbital as an adjunct to morphine. Also, the group of infants on both medications was older at admission, allowing speculation that they stayed in the NICU longer to be weaned, and that weaning could not be accomplished within a reasonable time frame for a NICU stay.

When an infant is transferred to the post-acute care hospital, limited information is available about the mother's history as the infant is the patient. Limited information is available about

maternal prenatal care, smoking history, breastfeeding, maternal marital status, type and duration of drug use (psychiatric medications versus illicit substances), and maternal opioid substitute use, all potential contributors to the need for adjunctive therapy [12-18]. The severity of the infant's withdrawal however, has not always been linked to number and type of maternal drug dose [13], yet in a study by Irner et al. [14] infants exposed to more than one substance in utero were more vulnerable to the development of NAS after birth. In this study, 70% of all mothers of infants in this study were polysubstance users, however, limited details were available about the types of substances (prescribed psychiatric medications versus illicit substances) and the duration of the mothers' use.

All infants were weaned from morphine before hospital discharge with 31 days being the average for the total sample and the "morphine only" group weaning significantly faster than the "morphine + phenobarbital group". These findings are in line with previous work indicating that the treatment time for morphine administration has been reported to last 8-79 days [19] and the duration of treatment was significantly shorter for infants who received morphine compared with infants who were treated with Phenobarbital [20].

Infants treated with both morphine and phenobarbital were discharged older and thus, had a longer length of stay in the post-acute care hospital. Patrick et al. [21] also reported that when phenobarbital is used as an adjunctive therapy, there was an increase in length of treatment. A longer overall therapy time has also been reported for infants treated with phenobarbital when compared to infants treated with clonidine [22]. In this study, there was a small group of infants discharged

home on phenobarbital, similar to a sample described by Isemann et al. [18] who reported that once off methadone for 48 hours, infants were being discharged on phenobarbital based on appropriate Finnegan scores and supportive social settings.

While the majority of infants in this study were discharged to the care of their mother, this includes many mother-infant dyads that were discharged to residential housing and treatment programs designed to provide support for their specific needs. Follow-up of infants with NAS has indicated deficits in development [23, 24] and provides evidence to support the referrals to early intervention in this study cohort. Additional medical and developmental follow-up studies are needed to determine the long-term effects of NAS, exposure to pharmacological treatment and prolonged hospitalization.

While this is the first known study detailing the weaning of infants with NAS in a post-acute care hospital, this study has limitations. The group comparison is limited by the infants' initial care being provided at multiple acute care hospitals with potentially varied NAS protocols. In addition, we are unable to fully explore the implications of the maternal history and exposures, important covariates of NAS severity. Also, reliability testing was not completed for Finnegan scoring within or between clinical providers.

In conclusion, a greater number of infants with NAS referred to a post-acute care hospital required phenobarbital as well as morphine. These infants were older at admission, took longer to wean and stayed in the hospital longer, indicating a more difficult course.

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