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Morphine Versus Methadone Treatment for Neonatal Withdrawal and Impact on Early Infant Development

Sharon Burke, MD[1], and Anna Malia Beckwith, MD[2]

Abstract

Objective. Compare developmental outcomes in infants treated with morphine versus methadone. *Method*. Retrospective chart review of newborns identified through use of ICD-9 code for neonatal abstinence syndrome (NAS). Thirty-six infants were evaluated—17 treated with methadone and 19 treated with morphine. Assessment was completed following treatment using the Bayley Scales of Infant and Toddler Development–Third Edition (Bayley-III). Scores in Cognitive, Language, and Motor domains were compared. *Results*. Comparison of scores between morphine- and methadone-treated groups revealed differences in mean Cognitive Composite (91.3 vs 83.0; $P = .03410$) and mean Total Motor Composite Scores (96.3 vs 89.6; $P = .0149$). *Conclusion*. Newborns with NAS treated with morphine had significantly higher scores in Cognitive and Gross Motor domains compared to infants treated with methadone. Development screening should be pursued to determine if this difference persists throughout early childhood. Results may influence accepted treatment protocols for NAS.

Keywords

neonatal abstinence syndrome (NAS), opoid, development

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Introduction

Newborns prenatally exposed to heroin, methadone, prescribed analgesics, or other opioids are a growing population of concern for health care providers. The rate of maternal use is now 5.63/1000 live births, while the rate of newborns treated for neonatal abstinence syndrome (NAS) is 5.8/1000 live births.[1]

Current Committee Opinion of the American College of Obstetrics and Gynecology supports the use of methadone and buprenorphine as the standard of care in pregnant women who are addicted to opioids before, during, and after pregnancy. This treatment is to be dispensed by a licensed provider and/or treatment center, in coordination with addiction specialists and obstetricians.[2]

Evidence supports this treatment as it prevents perinatal complications including fetal demise, maternal relapse, and illicit opioid use. In addition, the subsequent development of NAS in prenatally exposed newborns is a recognized and expected condition, treatable in the newborn period.[2] NAS is a pattern of neurologic and behavioral features developing when the infant is abruptly deprived of opioid at time of birth.[3]

The pathophysiology of NAS begins with maternal use of opioids in the prenatal period, which readily cross the placenta into the developing fetus where they are absorbed into the fetal central nervous system (CNS) across a fetal blood-brain barrier. These opioids attach to Mu receptors in the CNS, block the action of neurotransmitters, and inhibit the release of primary excitatory neurotransmitters such as norepinephrine.[4]

Abrupt discontinuation of exogenous opioids at time of delivery results in a marked release of norepinephrine, responsible for the autonomic and behavioral signs and symptoms of newborn withdrawal. These physiologic and behavioral features of the NAS may include hypertension, diaphoresis, fever, tremors, high-pitched crying, seizures, poor feeding, vomiting, diarrhea, and poor weight gain.[5]

[1]Children's Specialized Hospital, New Brunswick, NJ, USA
[2]Children's Specialized Hospital, Mountainside, NJ, USA

Corresponding Author:
Anna Malia Beckwith, Children's Specialized Hospital, 150 New Providence Road, Mountainside, NJ 07092, USA.
Email: ABeckwith@childrens-specialized.org

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The American Academy of Pediatrics Policy Statement on Infant Withdrawal recommends that treatment of newborns with NAS who fail to respond to nonpharmacologic measures be given medical opioid replacement therapy with either morphine or methadone.[6] Reports note variability in findings when comparing length of hospital stay in morphine- versus methadone-treated newborns.

A retrospective study published in 2005 concluded that among 17 infants treated with methadone versus 29 treated with morphine, there was no significant difference in median hospital length of stay (40 vs 36 days).[7] In a later, prospective study in 2014, a shorter length of stay for methadone- versus morphine-treated newborns was revealed (14 vs 21 days).[8] Another retrospective study in 2014 showed a shorter length of stay for methadone-treated infants (21 vs 25.5 days).[9] There may exist a shorter length of stay for methadone-treated infants, even if not statistically significant. This may be important knowledge to consider in the development of optimal treatment protocols.

However, there is a paucity of literature that examines developmental outcomes for newborns treated for NAS along the continuum of care. In our previous retrospective chart review of newborns treated for withdrawal, analyses of performance on the Bayley Scales of Infant Development–Third Edition (Bayley-III) revealed statistically significant delays in the domains of cognition and language compared to a historical control group of non-NAS infants matched for chronologic age.[10]

There are no published reports to date comparing morphine versus methadone treatment for newborn withdrawal with regard to impact on developmental outcomes in the newborn period. In this study, we compare performance on the Bayley-III for infants treated with morphine versus methadone, to determine if one regimen results in improved performance in early language, motor, and cognitive skills. This knowledge may help guide future clinician choice of drug for NAS treatment.

Methods

Study Design and Population

Thirty-six Infants were enrolled over a 2-year period to an inpatient rehabilitation program for opioid replacement therapy and a therapeutic developmental program. Infants were identified via retrospective chart review; qualification for inclusion included an ICD-9 diagnosis of Neonatal Abstinence Syndrome (779.5) on admission and maternal and newborn toxicology positive for opioids. Where infant toxicology was lost or inconclusive, at-risk infants were identified as NAS by positive toxicology for the mother and symptoms consistent with NAS according to Finnegan scoring.[5] Institutional review board approval was obtained, and a waiver for informed consent was granted for this retrospective chart review.

Infants with an ICD-9 code for NAS, but having one or more of the following criteria were excluded from this study: (1) infants born less than 37 weeks gestation as determined in acute care, (2) infants identified with major congenital and genetic syndromes, (3) concurrent acute or complex medical issues, and (4) infants with a do not resuscitate order.

Inpatient Rehabilitation Program

Infants were admitted from acute care hospitals where treatment for withdrawal was initiated with either morphine or methadone. Each infant in our study was continued on their admission replacement opioid and tapered in accordance with American Academy of Pediatrics guidelines for treatment of infant withdrawal.[6]

Medication taper was guided by use of Finnegan scores of infant withdrawal, assessed by a core team of nurses who maintain yearly competencies. Infants were examined daily by a select team of physicians and advanced practice nurses and medication tapers ordered in accordance with our pharmacy protocol.[6] Each taper was specific to the dosing guidelines for either morphine or methadone. Infant doses were weaned by 10% every 24 to 48 hours for scores less than 8. Morphine was discontinued when total dose was less than 0.04 mg/kg/dose, and methadone was discontinued when total dose was less than 0.05 mg/kg/dose.

Comorbidities such as gastroesophageal reflux, constipation, poor weight gain, and feeding intolerance were managed by a multidisciplinary team that included physicians, nurses, nutritionists, pharmacists, and therapists. Families were included in daily rounds and supported by a team of psychologists, social workers, and parents who themselves previously had children within our institution.

Infant and family caregiver progress was shared with child welfare organizations, to prepare for transition to the community with appropriate support services. An inpatient team of psychologists and social workers encouraged mothers to continue compliance with their own medication-assisted and counseling treatments.

An intensive developmental evaluation was performed by a team of therapists for each infant. Developmental weaknesses were identified and a therapy program was customized to each infant's needs. Infants received therapy in the domains of language,

Table 1. Bayley-III Scores: Group Comparisons Between Treatment Groups[a].

Variable	Methadone (n = 15)	Morphine (n = 18)	*P*
Cognitive Scaled	6.6 (2.38)	8.28 (1.96)	.0341
Cognitive Composite	83 (11.92)	91.39 (9.82)	.0341
Cognitive %Rank[b]	18.93 (18.01)	26.5 (21.22)	.2080
Language ExpScaled[b]	6.87 (1.92)	7.22 (1.63)	.6448
Language RecScaled	6.4 (2.26)	7.22 (2.53)	.3375
Total Language Scaled	13.27 (3.47)	14.39 (3.53)	.3671
Total Language Composite	80.67 (10.27)	83.72 (10.26)	.4011
Total Language %Rank[b]	14.4 (9.51)	18.5 (15.46)	.5489
Motor FineScaled	8.6 (1.55)	9.33 (1.37)	.1593
Motor GrossScaled[b]	7.93 (1.62)	9.44 (1.2)	.0073
Total Motor Scaled	16.53 (2.97)	18.78 (1.9)	.0132
Total Motor Composite	89.67 (9.05)	96.33 (5.69)	.0149
Total Motor Rank[b]	24.53 (18.36)	40.44 (14.13)	.0084

[a]Data presented are mean (standard deviation).
[b]Nonparametric Kruskal-Wallis method is applied for group comparison.

feeding, fine motor, gross motor, and cognition during medication treatment. Attention was paid to creating a nurturing environment that catered to each infant's sensory needs.

Goals were established with family input for a meaningful and realistic outcome. Each parent completed an educational program prior to discharge, designed to ensure a safe transition home. Areas of training included cardiopulmonary resuscitation, medication administration, feeding protocols and therapy carryover, and guidance for continued optimal development.

Developmental Testing

On each infant's completion of opioid replacement therapy, they were administered the Bayley-III, a standardized tool used to identify developmental delays in children age 1 to 42 months. Scales and subscales were administered in the domains of Cognition, Receptive and Expressive Language, Gross and Fine Motor.

Assessments were performed 3 to 7 days prior to discharge with a mean age at testing for the morphine treated group 50 days and 46 days for the methadone treated group.

Analyses

Our analyses examined Bayley-III scores and other demographics for 36 infants treated with methadone (N = 17) or morphine (N = 19). A normality test was applied to check distributions of each variable. For normally distributed variables, *t* tests were applied to examine differences between groups treated with morphine or methadone. Welch's adjustment was used when there were unequal variances between groups. For variables not normally distributed, nonparametric Kruskal-Wallis rank sum tests were applied for group comparison.

Multiple variable models were applied to examine the effect of drugs on differences of Bayley-III scores, Finnegan scores, and infant weight gain. Potential confounding factors were baseline measurements at admission, gender, age, and gestation age. Residual analysis was used to evaluate influential observations. Final models were selected based on adjusted R^2.

Results

Table 1 provides comparisons of Bayley-III scores between treatment groups. The differences in Cognitive Scaled and Composite and Total Motor Scaled and Composite scores between treatments were statistically significant. Using morphine in treatment, rather than methadone, resulted in increased cognitive and motor measurements. Model building process suggests that covariates had no influence on the relationship between drugs and cognitive or motor measures (Table 2).

Comparisons between groups found no significant difference among babies treated with methadone and those treated with morphine in demographics (Table 3), baseline measurements (Table 4), and time treated (Table 5). Univariate analyses show no differences in measurements at discharge (Table 6). However, a borderline significance is found for drugs on differences of Finnegan scores after adjusting covariates. On average, babies treated with morphine had Finnegan scores of 1.59 less in admission-discharge difference of Finnegan scores (Table 7). Drugs difference had no effect on weight gains.

Table 2. Effects of Morphine (Versus Methadone) on Bayley-III Scores.

Response	Estimate	95% Confidence Interval	*P*	Variables in the Best Models
Cognitive Scaled	1.68	0.13, 3.22	.0341	—
Cognitive Composite	8.39	0.67, 16.10	.0341	—
Total Language Scaled	1.86	−0.42, 4.14	.107	Age
Total Language Composite	5.21	−1.48, 11.89	.1222	Age
Motor FineScaled	0.61	−0.57, 1.79	.295	Gestation age
Motor GrossScaled	1.51	0.51, 2.51	.004	—
Total Motor Scaled	2.24	0.50, 3.99	.0132	—
Total Motor Composite	6.67	1.39, 11.94	.0149	—
Total Motor Rank	15.91	4.38, 27.44	.0084	—

Table 3. Demographics by Treatment Groups[a].

Variable	Methadone (n = 17)	Morphine (n = 19)	*P*
Male	9 (52.9%)	12 (63.2%)	.7778
Age	24.65 (13.16)	20.58 (9.09)	.4652
Birth gestation age (weeks)	37.5 (2.1)	38.76 (1.56)	.0894
High calorie formula	11 (64.7%)	13 (68.4%)	1

[a]Data presented are n (%) or mean (standard deviation).

Table 4. Measurements at Admission by Treatment Groups[a].

Variable	Methadone (n = 17)	Morphine (n = 19)	*P*
Finnegan on admission	4.03 (1.77)	4.97 (1.18)	.0683
Weight on admission	3.61 (0.97)	3.43 (0.6)	.5037

[a]Data presented are mean (standard deviation).

We found that change from admission Finnegan score was highly correlated with admission Finnegan score. High admission Finnegan score was related to the small change from admission Finnegan score. The morphine-treated group had higher baseline Finnegan scores (mean 4.97) than the methadone group (mean 4.03). After adjusting this baseline difference, the morphine group had a much bigger change from baseline (adjusted mean decrease 1.94) than the methadone group (adjusted mean decrease 0.35), although the observed changes from admission on Finnegan scores were 0.55 and 0.81 for morphine- and methadone-treated groups, respectively.

Discussion

As previously stated, the rate of opioid use during pregnancy is rising at an alarming rate. The Academy of Obstetrics and Gynecology Policy Statement regarding maternal opioid use during pregnancy stresses the importance of methadone treatment for mothers to ensure a safe pregnancy, prevent fetal demise, and deter illicit drug seeking behaviors.[2] While NAS is problematic for the newborn and concerning for health care providers, it is a treatable condition.

The treatment for infant withdrawal is delineated by Hudack in the American Academy of Pediatrics consensus recommendations. The effects of opioid withdrawal in the newborn period are a direct consequence of maternal opioid use resulting in dysregulation in the CNS, autonomic, and gastrointestinal systems. Expert opinion is currently split; however, with proponents of both longer acting methadone and shorter acting morphine for NAS treatment, an intervention is necessary in 50% to 70% infants prenatally exposed to opioids.

Our retrospective review of 36 infants failed to show significant differences for infants treated with morphine versus methadone in weight gain, length of treatment days, or length of overall hospital stay. Statistically significant differences were detected, however, in Bayley-III performance for cognitive and motor function. Infants treated with morphine had higher scores in these areas

Table 5. Time Treated by Treatment Groups[a].

Variable	Methadone (n = 17)	Morphine (n = 19)	*P*
Length of stay	42.65 (10.95)	45.42 (12.22)	.4774
Days treated	22.67 (14.54)	21 (10.33)	.7565
Length of treatment at CSH	26.53 (12.07)	30.17 (9.0)	.3175
Total days of treatment	52.1 (13.19)	49.0 (14.23)	.7882

[a]Data presented are mean (standard deviation).

Table 6. Measurements at Discharge by Treatment Groups[a].

Variable	Methadone (n = 17)	Morphine (n = 19)	*P*
Finnegan 3-day average (1 day prior and postdischarge)	3.34 (1.79)	4.41 (2.18)	.1450
Finnegan difference	0.81 (2.33)	0.56 (2.75)	.7784
Weight on discharge	4.97 (1.11)	4.89 (0.44)	.8011
Weight difference per day	32.32 (8.39)	32.62 (8.19)	.9142

[a]Data presented are mean (standard deviation).

Table 7. Effects of Morphine (Versus Methadone) on Finnegan Scores and Weight Gains.

	LS Means			
Response	Methadone	Morphine	*P*	Covariates in the Best Model[a]
Difference in Finnegan scores	0.35	1.94	.0365	Gender, Finnegan scores at admission, gestation age
Weights gains	33.89	33.85	.9884	Gender, age, gestation age, high calorie formula

[a]The best model is the one which give the largest adjusted R^2.

compared to methadone-treated newborns, though these scores for both groups were still significantly lower than a historical control nonexposed population.[10]

A review of the literature does not provide a clear physiologic explanation for this difference in humans. Yet a study of fetal rat pups given methadone revealed increased production of oligodendrites and myelin proteins.[11] It is hypothesized that this accelerated rate of myelination may disrupt the normal sequence and maturation of the myelin network and subsequent electrical connectivity. This finding may have implications for myelin disruption during fetal exposure through maternal methadone use.

It is difficult to extrapolate fetal rat findings to human development, where one of the most vulnerable periods of myelin creation occurs in the early fetal period. Certainly, human clinical conditions exist where accelerated and disrupted myelination in the developing brain results in dysfunction, as seen in children with epilepsy and Sturge Weber disorder.[12]

Another animal study in 2008 reviewed outcomes of female pregnant rats treated with oral morphine. A period of reduced placental blood flow with coincidental reduced cortical thickness and decreased numbers of neurons in the frontal cerebral cortex was established.[13] In a different study of fetal rats with morphine exposure enhanced neuronal cell apoptosis was observed.[14] However, under specific conditions of pain and stress, modulation of morphine dosage may have a neuroprotective effect.[15] Human studies of preemptive morphine analgesia in preterm infants showed no difference in cognition or academic performance, but did reveal increased social problems.[16]

These findings may have implications for in utero management of maternal opioid addiction and postnatal treatment of infant withdrawal. In utero exposure to opioids may have a greater impact over several months throughout pregnancy than the 14 to 21 days of postnatal treatment in the newborn period. The fact that methadone is well established as the treatment protocol in antenatal methadone centers, rather than morphine, may explain why the longer fetal exposure to methadone versus morphine has a greater negative impact on developing oligodendrocytes, resulting in abnormal maturation of myelin in animal studies.[11]

The resulting abnormal pattern of electrical connectivity in a developing brain may impact postnatal patterns of development as well. Further controlled studies

need to explore prenatal exposure of both morphine and methadone with respect to potential for neurotoxicity, with attention to dosage, critical time of exposure during fetal development, as well as postnatal treatment. It appears from animal studies that both opioids affect the developing brain in different regions, which may have implications on development and/or behavior.

Our small, retrospective study revealed higher scores in the domains of cognition and motor function in infants with NAS, post-morphine treatment. This finding may be related to a number of factors including but not limited to (1) prenatal methadone exposures during maternal treatment in pregnancy, (2) pharmacokinetics of methadone metabolism and clearance, and/or (3) a possible drug effect on fetal development itself.

More studies are needed to assess antenatal doses and classes of opioids used by the mother, with developmental follow-up assessments of the child. Controlled prospective trials would better define differences between opioids with respect to impact on fetal development, with potential long-term consequences. Furthermore, larger studies are needed to conclude if this finding is persistent throughout childhood.

Author Contributions

SB: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
AMB: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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