JPPT | Retrospective Review

Comparison of Two Morphine Dosing Strategies in the Management of Neonatal Abstinence Syndrome

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OBJECTIVE The incidence of neonatal abstinence syndrome (NAS) has increased in recent years. Treatment approaches usually involve opioid replacement; however, the optimal treatment strategy is unknown. This study sought to determine the impact of weight- and symptom-based morphine dosing strategies on LOS and medication exposure in patients with NAS.

METHODS A retrospective review was conducted from May 2015 to June 2017 at 2 NICUs within a health-system using different dosing approaches for NAS. Data were compared using Fisher exact tests for categorical data and *t* tests and Wilcoxon ranked sums for continuous data.

RESULTS Baseline demographics were well-matched except for postmenstrual age at morphine initiation ($p = 0.04$). The weight-based group had a larger initial morphine dose ($p < 0.001$) and fewer number of steps to maximum morphine dose ($p = 0.009$). There were no differences between groups in LOS, number of dose adjustments, doses administered, weaning steps, maximum dose, or need to re-escalate dosing. There was also no difference between the first 3 modified Finnegan scores (MFS) after transferring patients to a neonatology service. Neonates with symptom-based dosing had a higher maximum MFS ($p = 0.024$). Neonates in the symptom-based group required adjunct therapy more often ($p < 0.0001$).

CONCLUSIONS Data indicate the dosing strategy impacts number of steps to reach maximum dose and need for adjunctive therapy. Weight-based dosing may decrease the number of steps required to reach the morphine maximum dose and the need for adjunctive therapy by controlling NAS symptoms earlier.

ABBREVIATIONS LOS, length of stay; MFS, modified Finnegan score; NAS, neonatal abstinence syndrome; NICU, neonatal intensive care unit

KEYWORDS morphine; NAS; neonatal abstinence syndrome; withdrawal

J Pediatr Pharmacol Ther 2022;27(2):151–156

DOI: 10.5863/1551-6776-27.2.151

Introduction

The incidence of neonatal abstinence syndrome (NAS) has increased in recent years resulting in an increased use of health care resources.[1,2] A plethora of treatment options have been explored, but no 1 treatment has been deemed superior in managing NAS. Non-pharmacologic approaches such as swaddling, positioning, and low stimulus environments are the backbone of management of NAS and should be used in each infant exhibiting signs and symptoms of withdrawal.[3] When non-pharmacologic approaches fail, pharmacologic treatments usually involve opioid replacement with morphine or methadone; however, the optimal treatment strategy has yet to be determined.[4] The goals of pharmacologic management include improving infant comfort and promoting proper nutrition and growth, studies typically target LOS and cumulative medication exposure as endpoints.[3] Despite not having a clear first choice for treatment, it is recommended that institutional guidelines be implemented to standardize evaluation, dosing, treatment, and discharge criteria for infants with NAS.[5]

Approximately 80% of centers in the United States use morphine as the primary option for pharmacologic treatment.[3] Within each medication choice there are a variety of approaches for dosing, escalating, and weaning. Little evidence is available comparing dosing strategies of the same medications. One center compared LOS and total morphine exposure between weight-based and symptom-based dosing strategies and found no difference in LOS or cumulative morphine exposure in a subgroup of patients receiving morphine. The comparison evaluated a weight-based strategy for 6 years followed by a symptom-based strategy for the next 8 years ending in 2014.[6] Health care providers continue to seek optimal care for these infants to relieve the financial burden and to improve outcomes.

Within a large health-system, each neonatology group at individual hospitals uses different morphine dosing strategies when managing NAS. A standardized weight-based strategy is used at 1 hospital that is the primary delivery center for a region. The other hospital, 1 of 6 delivery hospitals within a different metropolitan area, uses a symptom-based dosing approach. Both hospitals

Table 1. Symptom-Based Dosing Strategy

Modified Finnegan Score	Starting Oral Morphine Dose, mg*
0–8	Monitor every 3 hr
9–12	0.04
13–16	0.08
17–20	0.12
21–24	0.16
≥25	0.2

* Given every 3 hr.

deliver approximately 6000 neonates per year. The symptom-based doses are smaller initially compared with the weight-based doses. The institution adopting the symptom-based dosing anticipated the potential to use less morphine overall. The purpose of this study was to compare a weight-based dosing strategy and a symptom-based dosing strategy both using morphine in the management of NAS to determine if the treatment approach impacted LOS and overall medication exposure.

Methods

An institutional review board-approved retrospective chart review was conducted from May 2015 to June 2017 at 2 NICUs within a health-system using different approaches for management of NAS. Patients were identified via electronic health record reports for oral morphine in the respective NICUs. Patients with a diagnosis of NAS were included. Patients were excluded if no oral morphine was administered, the indication for morphine was not NAS, intravenous opioid was administered, or the patient was under 35 weeks' gestation. The weight-based dosing strategy initiates morphine at a dose of 0.05 mg/kg orally every 3 hours. The symptom-based strategy initiates standard doses based on the modified Finnegan score (MFS) (Table 1). Pharmacologic treatment was started after 3 MFS of ≥8 or 2 scores ≥12 consecutively in both strategies.

Data points collected include the following: weight (birth and medication initiation); postnatal and postmenstrual ages at medication initiation; first 3 and maximum MFS after transferring to the neonatology service; medication dosages (milligrams per kilogram); total amount of medication administered (milligrams); number of dosage increases and weans; need for dose re-escalation; LOS (days); and scheduled and as needed adjunct treatment use for NAS. As needed adjunct treatments were only included if indicated for NAS and at least 1 dose was administered. Symptom-based doses were standardized into a milligram-per-kilogram dose for analysis. Categorical data were assessed using Fisher exact tests and continuous data were analyzed using *t* tests or Wilcoxon ranked sums depending on data distribution in SAS version 9.4 TS Level 1M3 (Cary, NC) using a priori significance of 0.05. Shapiro-Wilk tests of normality were used to assess data distribution.

Results

A total of 151 charts were reviewed including 74 using a weight-based dosing strategy and 15 using a symptom-based dosing strategy. Sixty-two patients were excluded due to the following: indication for morphine was pain management (n = 35), no diagnosis of NAS (n = 8), patients <35 weeks' gestation (n = 8), indication for morphine was iatrogenic withdrawal (n = 5), patient received intravenous opioid (n = 4), and no morphine was administered (n = 2). Baseline characteristics including birth weight, weight at medication start, postnatal age at medication initiation, and *in utero* substance exposures were the same between groups except for postmenstrual age at morphine initiation ($p = 0.04$) and buprenorphine exposures ($p = 0.018$) (Table 2). Although not significant, the weight-based dosing group had a decreased LOS ($p = 0.36$), required fewer total morphine dose adjustments ($p = 0.09$), and fewer weaning steps ($p = 0.07$). The weight-based group had a larger initial morphine dose ($p < 0.001$) and the symptom-based group required more steps to reach the maximum morphine dose ($p = 0.009$) (Table 3).

There was no difference between groups in maximum dose of morphine ($p = 0.08$) or in the need to re-escalate dosing ($p = 0.08$). There was no difference between first, second, and third MFS after transferring the patient to the neonatology service ($p = 0.55$, $p = 0.98$, $p = 1$, respectively). However, neonates with symptom-based dosing had a significantly higher maximum MFS ($p = 0.024$) indicating the symptom-based dosing group might have been less well controlled. Neonates in the symptom-based dosing group also required the addition of adjunct therapy more often ($p < 0.0001$). Adjunct therapies indicated for NAS included the following: as needed acetaminophen (n = 5), scheduled clonidine (n = 7), as needed midazolam (n = 1), and scheduled phenobarbital (n = 1) (Table 3). The symptom-based group had 2 patients requiring multiple adjunct medications; one was given acetaminophen and clonidine, the other phenobarbital, acetaminophen, and clonidine. As needed, medications were added to prevent halting a morphine wean. Scheduled adjunctive therapies were added after morphine reached 0.2 mg/kg/dose or initiated when otherwise indicated. For instance, scheduled phenobarbital was initiated for seizures determined to be unrelated to withdrawal.

Discussion

Snowden et al[7] surveyed 54 medical centers with NICUs and found 92% used a standardized protocol for treatment initiation and 94% of wean treatments were

Table 2. Baseline Characteristics

	Dosing Strategy		p value
	Weight-Based (n = 74)	Symptom-Based (n = 15)	
Birth weight, mean ± SD, kg	2.88 ± 0.47	2.91 ± 0.38	0.4
Weight at initiation, mean ± SD, kg	2.79 ± 0.43	2.77 ± 0.35	0.91
Postmenstrual age at initiation, mean ± SD, wk	38 5/7 ± 1 4/7	39 4/7 ± 1 2/7	0.04
Modified Finnegan Score, median (IQR)*			
First	10 (9–12)	11 (9–13)	0.55
Second	11 (10–13)	10 (9–14)	0.98
Third	11 (8–14)	11 (10–11)	1
Maximum	13 (11–15)	15 (13–19)	0.024
Postnatal age at initiation, median (IQR), days	3 (2–4)	3 (3–4)	0.47
Initial morphine dose, median (IQR), mg/kg	0.05 (0.05–0.051)	0.017 (0.015–0.029)	<0.001
Polysubstance exposure, %	36.5	40	0.78
Amphetamines	4	13.3	0.2
Barbiturates	4	0	1
Benzodiazepines	10.8	13.3	0.67
Buprenorphine	29.7	0	0.018
Cannabinoids	17.6	13.3	1
Cocaine	17.6	20	0.73
Methadone	27	53.3	0.07
Other opioids	50	46.7	1

* Modified Finnegan scores obtained after patient transfer to a neonatology service.

based on a standardized approach. Patients receiving NAS treatments who were weaned following a standardized protocol experienced shorter LOS, duration of opioid treatment, and weaning times.[8–10] After adoption of standardized protocols, institutions that previously did not use protocols experienced shorter LOS and duration of opioid treatment compared with patients treated without a protocol previously.[11] Institutions in the current review used standardized but different morphine dosing protocols for NAS treatment and weaning. The LOS was not statistically significant in the current study; however, a potential clinical difference might be experienced due to the significantly increased number of titration steps to reach the maximum morphine dose in the symptom-based group (Table 3). The number of dose escalations might indicate infants in the symptom-based group took longer to be adequately treated. Although not statistically significant, the symptom-based group doubled the percentage of morphine re-escalations required compared with the weight-based group. Although not significantly different when compared with the symptom-based approach, the weight-based dosing approach LOS approximates the national LOS average of just over 16 days from 2009–2016 for all neonates treated pharmacologically or non-pharmacologically, whereas the symptom-based dosing approach exceeded the national average by 5 days.[12] Millren et al[13] determined the average LOS as 18.7 days for both pharmacologic and non-pharmacologic treatments, a subset of pharmacologically treated neonates averaged a 22-day LOS, which is more in line with the symptom-based group in the current review.

Prenatal exposures may impact outcomes for neonates with NAS. Two per-protocol analyses by Jones et al[14,15] of neonates exposed to methadone or buprenorphine *in utero* experienced a significantly longer LOS; 17.5 days compared with 10 days ($p < 0.01$)[14] and 8.1 days compared with 6.8 days ($p = 0.021$).[15] A meta-analysis conducted by Brogly et al[16] concluded neonates treated for NAS after exposures to methadone compared with buprenorphine *in utero* had an approximate 7-day longer LOS. Jones et al[14] determined the buprenorphine exposed group required less morphine overall. However, a previous study by Jones et al[15] did not find a significantly increased need of opioid agonist between buprenorphine and methadone exposed neonates treated for NAS; however, exposure was more than 3 times more in the methadone group. Brogly et al[16] also concluded less, but not significantly less, morphine was needed in the buprenorphine group. The weight-based group in the current study had a significantly higher percentage of exposures to buprenorphine compared with the symptom-based group with a higher percentage of methadone exposures, which has the potential to affect LOS. The current study did not conclude the weight-based group needed less morphine overall. The difference in metha-

done and buprenorphine exposures across groups might have impacted LOS and is a limitation.

In the current study, the symptom-based group experienced higher maximum MFS. This group also had more methadone exposure compared with the weight-based group. Neither study by Jones et al[14,15] showed a difference in peak Finnegan scores between neonates exposed to the individual agents. In the current study, buprenorphine exposure was documented. However, its use in combination with the naloxone was not noted. Wiegand et al[17] compared neonates exposed to buprenorphine and naloxone in combination to neonates exposed to methadone *in utero* and determined the peak NAS score and LOS were significantly lower in the buprenorphine and naloxone exposed group. Neonatal morphine use was not significantly different between groups. The impact of buprenorphine use in combination on the difference between the weight-based and symptom-based peak MFS in the current study cannot be fully evaluated.

A retrospective review by Chisamore et al[6] evaluated weight-based and symptom-based morphine protocols in the same unit during consecutive windows over 14 years for all patients with *in utero* exposure to an opioid. One difference between the Chisamore et al[6] review and the current review was the study windows used. Chisamore et al[6] compared consecutive cohorts whereas the current review compared concurrent cohorts. Standard approaches to patient care and NAS non-pharmacologic treatments might have changed over 14 years, confounding the results of Chisamore et al.[6] An additional difference between the findings of Chisamore et al[6] and the current study was the MFS required to initiate morphine was not the same between groups. The symptom-based group started morphine after 1 score ≥9, whereas the weight-based group initiated morphine similarly to the current study, which used 3 scores ≥8 or 2 scores ≥12 for both groups. A subgroup analysis of those who only received morphine found, similarly to the current study, that the maximum MFS was higher in the symptom-based group ($p < 0.01$). In the Chisamore et al[6] evaluation similar to the current study, the gestational age of the weight-based and symptom-based groups were similar at 38 and 39 weeks, respectively. Like the current study, the review did not identify a difference in LOS between the 2 approaches. However, the LOS in the symptom-based approach in the current review was similar to the Chisamore et al[6] subgroup analysis. The LOS for the weight-based and symptom-based approaches were 24 and 20 days, respectively.[6]

The weight-based approach in the current review initiated morphine at a significantly larger milligram per kilogram per dose and required fewer dose escalations compared with the symptom-based approach although not significant. The symptom-based approach's maximum dose approximated the starting dose in the weight-based group. Therefore, initiating the symptom-based approach at a higher dose may decrease number of dose titrations required. DeAtley et al[18] evaluated the effectiveness of 2 morphine treatment protocols with varying starting doses, 0.04 mg/kg every 4 hours and 0.06 mg/kg every 3 hours, respectively, the larger dose approach decreased LOS by 7 days, although not a statistically significant decrease. The study also noted oversedation in the larger dosing group. At the time, DeAtley et al[18] were investigating an initial morphine regimen of 0.05 mg/kg every 3 hours, which coincided with the starting dose in the current weight-based protocol. Monotherapy was used more often with the weight-based approach. Also, starting the symptom-based group at a higher morphine dose might decrease adjunctive therapy requirements.

The symptom-based approach required significantly more adjunctive treatment compared with the weight-based morphine dosing approach. Gullickson et al[19] compared morphine monotherapy to morphine with adjunctive clonidine. Similar to the current study, LOS was not different between the groups. The LOS in both groups was 3 weeks, similar to the current review's symptom-based dosing group. The combination group required nearly 8 days longer of total pharmacologic treatment ($p < 0.01$) and nearly 7 days more of morphine treatment ($p = 0.02$). Nearly a week of additional morphine in the combination group increased total infant morphine exposure. Of note, total morphine exposure in the Chisamore et al[6] study approximated 9 mg in the weight-based group and 7 mg in the symptom-based group. The current study found the median total morphine exposures approximates 8 mg in the weight-based group and 5 mg in the symptom-based group ($p > 0.05$). Combination therapy may increase exposures for infants requiring morphine treatment for NAS. There is limited evidence on long-term neurodevelopmental outcomes related to cumulative morphine exposure in the NICU. However, morphine has been shown in preclinical and clinical data to increase neuronal apoptosis in a concentration dependent fashion.[20,21] More data are required to determine a possible correlation.

Since the current study was conducted, new approaches for management of NAS have been introduced, including the use of sublingual buprenorphine and the eat-sleep-console method that focuses on maximizing non-pharmacologic management and family participation in care.[22,23] Both of these treatment approaches demonstrated reduction in LOS in their respective cohorts and may offer advantages over traditional morphine dosing as described in the current study. However, for institutions using traditional, scheduled morphine approaches with MFS, weight-based dosing may be beneficial.

A limitation of the review is the small sample size at 1 institution. The small sample size may impact objective analyses. Another implication of small sample size in 1 arm of the review is the potential for variability in MFS. Timpson et al[24] evaluated variation between pre-

training, post-training, and after training scoring. Training increased accuracy of scoring between the pre- and post-assessments. However, after an extended period of time, accuracy returned to pre-training baselines for nurses. Institutions with limited admissions of patients with NAS may have inaccuracies in Finnegan scoring related to the duration between patients. Timpson et al[24] also noted the inaccuracies during the pre-training assessments were higher compared with the targeted standard. Therefore, the NICU with a small sample size might have had falsely elevated MFS resulting in morphine initiation, adjunctive therapy initiation, and slower weaning.

Due to the retrospective nature of the study, another limitation is the inability to control for various factors between patients, which are known to affect NAS courses. One such difference is diet. Although there is variability among patients due to independent factors, each unit takes the same approach in promoting the use of maternal milk when available as long as no contraindications exist. Likewise, if formula is used, the preferred formula for infants with NAS is low lactose-containing formula. Similarly, both institutions promote a non-pharmacologic approach as a standard for caring for infants with NAS. Other differences that might impact the NAS course were handled in a similar manner between the 2 institutions include maximizing non-pharmacologic management, individual rooms, and allowance for parental rooming-in and involvement in care when the social situation allowed. Nurse-to-patient ratios are similar between units but can range from 2:1 to 4:1 depending on census in individual units.

A third limitation is the collection of drug toxicology screens. Cord, urine, and meconium collections were attempted. Results were not available for all patients. With a confirmed exposure, pharmacologic options might have been tailored to each patient, which might have resulted in decreased LOS and quicker time to NAS capture and control. Potential differences between health care teams within each institution in weaning might exist. The health care team decides to start a 10% to 20% wean at 24 or 48 hours after controlled on morphine. This variation is not unit or morphine dosing approach specific. If 1 health care team was more conservative using the 48-hour time course to start a wean, then the LOS might be increased. The number of wean steps required also varies based on health care team weaning of 10% every 24 hours or 20% every 48 hours, which might result in an increased number of wean steps over the same time course. Dose escalations were made when a patient had 2 consecutive MFS ≥9 for both morphine treatment approaches, a strength of the study. However, the symptom-based approach increased the fixed dose by 10% to 50% depending on MFS and the weight-based approach increased by 20%. Although the symptom-based approach might increase up to 50%, the 20% increase in the weight-based approach is a larger milligram-per-kilogram dose escalation. The smaller percentage increase in the symptom-based approach might account for the delay in gaining control of the patient's NAS. Future steps include adjusting the initial symptom-based starting morphine dose and evaluating a change to buprenorphine as the primary agent throughout the health-system.

Although not a part of the study, considerable costs are associated with NAS with LOS and medications contributing to the cost. Average admission costs for neonates with NAS were 10 times higher compared with other neonates and those treated pharmacologically approximated $44,720 per case.[13] For each day reduction in LOS, cost may be reduced by approximately $2500.[25] Shortening LOS and decreasing medication use of both the primary and adjunctive agents may lessen hospital charges estimated at $2.5 billion in the United States in 2016.[12]

Conclusion

The strategy, weight-based or symptom-based, used when dosing morphine for NAS impacts the number of steps to maximum dose and the need for adjunctive therapy. Weight-based dosing may decrease the number of steps required to reach the morphine maximum dose and the need for adjunctive therapy by controlling NAS symptoms earlier. Dosing strategy selection may impact LOS, total morphine exposure and doses, and number of dose escalations and weans. Larger studies are needed to assess the exact impact.

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Disclosures. The authors declare no conflicts or financial interest in any product of service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, or honoraria. The authors had full access to all data and take responsibility for the integrity and accuracy of the report.

Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation. Given the nature of this study, institutional review board review and patient informed consent were not required.

Acknowledgments. The authors thank Gina Burchett, PharmD for assisting with data collection. An abstract has been presented in poster form at the Pediatric Pharmacy Association's Annual Meeting in Salt Lake City, UT, in April 2018.

Submitted. May 25, 2020

Accepted. June 9, 2021

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