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ORIGINAL ARTICLE

Neonatal abstinence syndrome: transitioning methadone-treated infants from an inpatient to an outpatient setting

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Objective: Each year in the US ~50 000 neonates receive inpatient pharmacotherapy for the treatment of neonatal abstinence syndrome (NAS). The objective of this study is to compare the safety and efficacy of a traditional inpatient only approach with a combined inpatient and outpatient methadone treatment program.

Study Design: Retrospective review (2007 to 2009). Infants were born to mothers maintained on methadone in an antenatal substance abuse program. All infants received methadone for NAS treatment as inpatient. Methadone weaning for the traditional group (75 patients) was inpatient, whereas the combined group (46 patients) was outpatient.

Result: Infants in the traditional and combined groups were similar in demographics, obstetrical risk factors, birth weight, gestational age (GA) and the incidence of prematurity (34 and 31%). Hospital stay was shorter in the combined than in the traditional group (13 vs 25 days; $P<0.01$). Although the duration of treatment was longer for infants in the combined group (37 vs 21days, $P<0.01$), the cumulative methadone dose was similar (3.6 vs 3.1 mg kg^{-1}, $P=0.42$). Follow-up information (at least 3 months) was available for 80% of infants in the traditional and 100% of infants in the combined group. All infants in the combined group were seen ⩽72 h from hospital discharge. Breastfeeding was more common among infants in the combined group (24 vs 8% $P<0.05$). Following discharge there were no differences between the two groups in hospital readmissions for NAS. Prematurity (34 to 36 weeks GA) was the only predictor for hospital readmission for NAS in both groups ($P=0.02$, OR 5). Average hospital cost for each infant in the combined group was $13 817 less than in the traditional group.

Conclusion: A combined inpatient and outpatient methadone treatment in the management of NAS decreases hospital stay and substantially reduces cost. Additional studies are needed to evaluate the potential long-term benefits of the combined approach on infants and their families.

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Introduction

Opioid dependence during pregnancy has significant implications for the infant, most notably neonatal abstinence syndrome (NAS).[1,2] NAS is a constellation of physiological signs and behaviors observed following *in utero* exposure to opiates.[1,3] Although the recreational and addictive use of opiates during pregnancy continues to receive more attention in the medical community, prescription narcotic use among women of childbearing age has increased significantly.[4] Among exposed infants, the incidence of NAS ranges from 21 to 94%, with about half of the infants requiring some form of pharmacotherapy.[5–7]

In the United States, the number of drug affected newborns (including opiates) has increased 300% since the 1980s and the health care expenditure in their treatment has been estimated to be as much as 112.6 million dollars per year.[2,5] Much of this cost is because of prolonged hospital stays in neonatal intensive care units.[7,8]

The benefits of participating in an antenatal drug treatment program include a reduction in drug-seeking behavior, illicit substance abuse, preterm birth and infant mortality.[9–12] Methadone use for narcotic-abusing women in an antenatal program improves health care utilization and preparation for parenting responsibilities, although some continue to misuse illicit substances.[13,14]

In clinical practice, NAS is commonly observed among infants born to mothers on methadone maintenance for opiate addiction.[2,15] Traditional strategies for the care of infants with NAS have focused mainly on inpatient management that has led to prolonged hospital stays (that is, median of 25 days, range of 8 to 105 days).[7,15–18] However, following initial stabilization, many infants with NAS are otherwise healthy and may not require intensive inpatient care.[11,13,18,19] Considering that prolonged

hospital stays limit opportunities for maternal–infant bonding and consume hospital resources, alternative strategies that reduce unnecessary hospitalization are highly desirable.[7,13,20–22] A recent national survey of the management of NAS in the United Kingdom and Ireland revealed that 29% of neonatal units discharge infants' home on medication.[19] Other investigators reported no adverse events among infants with NAS administered medication by their caregivers in the community setting.[23] However, the paucity of available data on the safety, feasibility and resources required to care for infants with NAS on an outpatient basis has limited widespread adoption of this approach.

These issues affecting the general medical community led to the development of a multidisciplinary combined inpatient and outpatient treatment program for infants with NAS. An attending physician (CRB) willing to care for these infants as outpatients following initial inpatient stabilization offered this option to mothers in an antepartum substance abuse program. The purpose of this paper is to compare the safety and efficacy of a traditional inpatient only approach vs a combined inpatient and outpatient weaning strategy for infants with NAS.

Methods

This was a retrospective review conducted at The Ohio State University Medical Center between January 2007 and January 2009. This investigation was approved by the Institutional Review Board. Outpatient records (private physician, primary care clinics and emergency room) were also used.

The Ohio State University Medical Center is a tertiary referral center for obstetrics and gynecology, serving a population of $\sim$9 00 000, with over 5000 births per year. We identified 244 infants born to women receiving methadone as part of an antenatal outpatient treatment program. Of these infants 121 (50%) required treatment for NAS. Infants exposed *in utero* to illicit drugs (that is, cocaine, heroin and so on) only were excluded. To ensure the validity of the maternal history provided, infants had a meconium or urine toxicology performed immediately after birth.

Initial inpatient management of NAS

On the basis of attending physician preference, we have two treatment strategies for infants with NAS at our hospital. We identified 75 infants who received methadone for NAS entirely in the inpatient setting (traditional group) and 46 infants who initially received methadone treatment as inpatients then completed the weaning process in the outpatient setting (combined group). The initial hospital management of infants with NAS was similar between the two groups. Infants born to mothers receiving methadone were observed for signs and symptoms of withdrawal immediately after feeding using the Finnegan scoring system.[3] Methadone was initiated (0.05 mg kg^{-1} every 12 h) if the infant achieved 3 scores $\geqslant$8 or 2 scores $\geqslant$12. The dose was increased (0.025 to 0.05 mg kg^{-1} per dose, maximum dose 0.15 mg kg^{-1} per day) and the interval was changed to every 8 h if the withdrawal score remained >8. If NAS scores continued to be >12, phenobarbital was added (10 mg kg^{-1} per load, 5 mg kg^{-1} per day maintenance). Non-pharmacological management, including swaddling, pacifier use and provision of a quiet environment, was also used for both groups.[21]

Traditional group: inpatient methadone weaning strategy

For infants in the traditional group methadone was decreased by 0.025 to 0. 05 mg kg^{-1} per dose every 3 days if the average withdrawal score (in a 24-h period) remained <8. When the maintenance dose was 0.05 mg kg^{-1} twice daily, the dosage interval was lengthened to once daily. NAS scores continued to be monitored and methadone was discontinued after 3 to 7 days of 0.05 mg kg^{-1} per day if the average score remained <8. Once the infant was successfully weaned off methadone, an additional 5- to 7-day period of monitoring for withdrawal was completed before discharge home. Following discharge infants in the traditional group were seen in primary care clinics and/or at a dedicated NAS clinic (Nationwide Children's Hospital) where a team of physicians, nurses, social workers, lactation specialists and physical/occupational therapists were available.

Combined group: outpatient methadone weaning strategy

To be included in the combined group infants and caregivers had to fulfill specific medical and social work criteria (Figure 1). As a safeguard, only the amount of methadone needed for 3 days before the infant's initial outpatient appointment was prescribed. All caregivers underwent intensive instruction on administration of methadone for their infants and were made aware of the symptoms of drug overdose or withdrawal. Methadone was prescribed weekly and dispensed from the hospital pharmacy in sealed, unit dose oral syringes.

Following discharge infants in the combined group were seen in another dedicated outpatient clinic by the same physician (CRB) that provided inpatient care. This clinic is staffed by trained nurses and had ancillary staff (social workers, lactation specialists and physical/occupational therapists) available for consultation. In the outpatient clinic, a comprehensive evaluation of the infants' general health (anthropomorphic data, physical examination) and state of abstinence using the Finnegan method was performed. When possible, scores were obtained immediately after feeding. Caregivers were asked to keep records of their infants' behaviors in the home setting and had 24 h access to their physician (CRB) to immediately address any concerns. For withdrawal scores >12, the methadone dose was increased by 0.025 to 0.03 mg kg^{-1} per dose to a maximum dose of 0.12 mg kg^{-1} day. Infants requiring an increase in their methadone dosage were seen within 72 h for re-evaluation. If NAS scores continued to be >12, phenobarbital

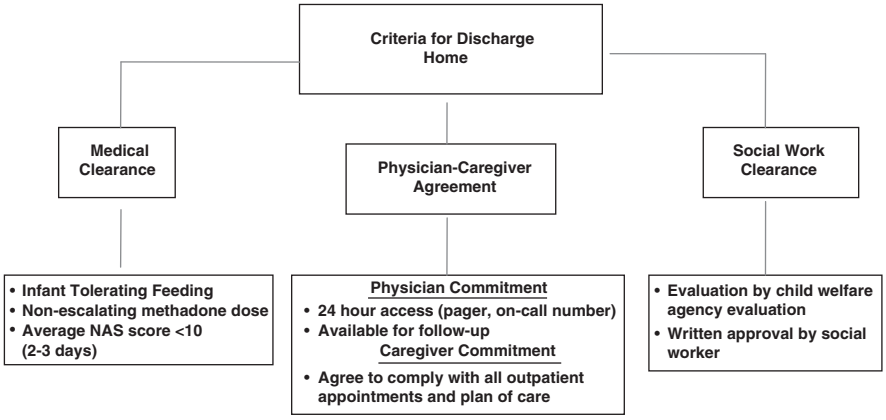

Figure 1 Criteria for discharge home for infants in the inpatient–outpatient (combined) methadone treatment group.

was added (10 mg kg^{-1} load, 5 mg kg^{-1} day maintenance). If scores remained >12 despite maximum methadone dosing and concurrent phenobarbital, infants were readmitted to the hospital for inpatient monitoring.

Conversely, methadone was weaned at a rate of 0.025 to 0.05 mg week^{-1} for withdrawal scores <8. When the maintenance dose was 0.03 to 0.05 mg kg^{-1} twice daily, the dosage interval was lengthened to once daily for 1 week. At that time, if withdrawal scores remained <8 and there were no concerns regarding the infant's behavior in the home setting, methadone was discontinued. Infants were monitored for possible withdrawal symptoms for 1 to 2 weeks following the discontinuation of medication. If the infant was on both phenobarbital and methadone, phenobarbital was weaned first.

Considering patterns of referral and proximity (zip code), the assumption was made that if acute care for these infants were needed it would be provided at the only children's hospital in the county (Nationwide Children's Hospital). Outpatient and inpatient hospital and clinic records were reviewed to determine whether infants in either group were seen in the emergency room, readmitted to the hospital and/or restarted on inpatient treatment for NAS.

Data analysis

Comparisons between groups and subgroups of infants with NAS were made with χ^2, Fisher's and *t*-test. To evaluate the independent relationship between variables that may be associated with readmission to hospital for NAS, a logistic regression model was constructed using the following variables: gestational age (34 to 36 weeks gestation, >37 weeks gestation), highest NAS score (day), patient also on phenobarbital and patient in the combined group (Table 3). When available, data were presented as mean ± s.d.

Results

Of the 121 infants that required treatment for NAS, 82 (68%) were cared for in the neonatal intensive care units and 39 (32%) in the intermediate care nursery. Of 69 mother–infant dyads evaluated for possible inclusion in the combined group, 46 (67%) met all medical and social work criteria for outpatient methadone weaning. The 23 infants who did not meet criteria were included in the traditional group that then comprised 75 mother–infant dyads. Mothers in these two groups were similar in demographic and clinical characteristics (Table 1). Of these, 96% of the mothers were Caucasian, 2% African-American and 2% Hispanic. Smoking, hepatitis B and hepatitis C infections occurred with similar frequency in both groups. Employment status and level of education were similar between the two groups.

The dose of maternal methadone at delivery (median 80 mg day^{-1}, range 20 to 180 mg day^{-1}) was similar between the two groups. By history or urine toxicology, illicit drugs were noted in 20% and 13% of mothers in the traditional and combined groups, respectively (Table 1).

Table 1 Maternal characteristics

	Traditional	*Combined*	P-*value*
Patients no.[a]	75	46	
Maternal age (years)	26 ± 4[b]	26 ± 4	NS
Primigravida no. (%)	11 (15)	10 (22)	NS
Cesarean delivery no. (%)	24 (32)	8 (17)	<0.05
Smoking no. (%)	55 (73)	36 (78)	NS
Hepatitis B no. (%)	0 (0)	1 (2)	NS
Hepatitis C no. (%)	17 (23)	10 (22)	NS
Methadone alone no. (%)	48 (64)	29 (63)	NS
Methadone and THC no. (%)	12 (16)	11 (24)	NS
Methadone and illicit drugs[c] no. (%)	15 (20)	6 (13)	NS
⩾High school diploma no. (%)	42 (56)	19 (41)	NS
Unemployed no. (%)	65 (87)	38 (83)	NS

Abbreviation: THC, tetrahydrocannabinol.
[a]Number.
[b]Mean ± s.d.
[c]Illicit drugs (cocaine, barbiturates, benzodiazepines and heroin).

Table 2 Neonatal outcomes

	Traditional	*Combined*	P-*value*
Infants no.[a]	75	46	
Gestational age (weeks)	37 ± 3[b]	38 ± 2	NS
34–36 weeks gestation no. (%)	26 (34)	14 (31)	NS
⩾37 weeks gestation no. (%)	49 (66)	30 (69)	NS
Males no. (%)	33 (44)	20 (43)	NS
Birth weight (g)	2677 ± 580	2858 ± 426	NS
Discharge weight (g)	3156 ± 634	3012 ± 470	NS
Breastfeeding no. (%)	6 (8)	11 (24)	<0.01
Highest NAS score	13 ± 3	13 ± 4	NS
Peak NAS score (day)	3 ± 2	3 ± 3	NS
Hospital stay (days)	25 ± 15	13 ± 5	<0.01
Methadone treatment (days)	21 ± 14	37 ± 20	<0.01
Cumulative methadone dose (mg/kg)	3.1 ± 5	3.6 ± 3	NS
Patients also on phenobarbital no. (%)	18 (24)	13 (28)	NS
Phenobarbital treatment (day)	14 ± 11	19 ± 14	NS

Abbreviation: NAS, neonatal abstinence syndrome.
[a]Number.
[b]Mean ± s.d.

Neonatal outcomes

Neonatal outcomes for the 75 infants in the traditional and the 46 infants in the combined group are presented in Table 2. The two groups were similar in birth weight, gestational age, rate of prematurity and the caregiver at the time of discharge (72% with mothers or family relatives, 28% with child welfare agencies). The number of infants exclusively breastfed or breast fed with supplementation (>50% breast milk) was higher in the combined group (24% vs 8%, $P<0.05$).

Duration of hospitalization and treatment

The overall length of hospital stay was 25 ± 15 days for the traditional and 13 ± 5 days for the combined ($P<0.001$). Although the duration of methadone treatment was longer for infants in the combined group (37 ± 20 days vs 21 ± 14 days, $P<0.001$), the cumulative methadone dosage was similar (3.6 ± 3 vs 3.1 ± 5 mg kg^{-1}, $P=0.42$). A similar number of infants in both groups required inpatient phenobarbital to control NAS symptoms (28% in combined and 24% in traditional group). Although 7 of 46 (15%) infants in the combined group compared with 5 of 75 (7%) in the traditional group required outpatient phenobarbital, there were no differences in the total duration of phenobarbital therapy between the two groups (combined 19 ± 14 days vs traditional 14 ± 11 days vs $P=0.28$).

Outpatient follow-up

Follow-up information for at least 3 months was available in 80% of infants in the traditional and 100% of infants in the combined group. All infants in the combined group were seen within 72 h of hospital discharge. No families were lost to follow-up while the infant was receiving outpatient medication for NAS. In the combined group, 13 (17%) required an increase in the methadone dosage for NAS symptoms. Not surprisingly, the continued need to refill prescriptions led to a higher number of primary care patient visits (first 3 months) in the combined group (9 vs 4, $P<0.05$).

Overall, 12 month follow-up data were available in 52% of the traditional and 80% of the combined group. A comparison of clinical and demographic variables (neonatal and maternal) between infants seen at 12 months and those lost to follow-up showed no distinctions except for the fact that those lost to follow-up were four times more likely to reside farther than 25 miles from the reference hospital/clinic (16/36, 44% vs 4/37, 11% $P<0.05$). No infant deaths were noted during the duration of the study. Two infants in the combined group were referred to child protective service for concerns regarding infant neglect or abuse.

Among patients with follow-up data available, the number of emergency room visits per patient for NAS-related symptoms (protracted diarrhea, weight loss and possible seizures) was similar between the two groups (11% traditional, 11% combined). Readmission to the reference hospital for NAS symptoms was also similar between the two groups (5% traditional and 7% combined). There were no differences in the proportion of infants in either group that required restarting inpatient medication for treatment of severe NAS symptoms (4% traditional, 5% combined). On the basis of the logistic regression model (Table 3), the only variable to predict hospital readmission for NAS in the first 3 months of life was prematurity (34 to 36 weeks). We found that maternal methadone dose, infant group, highest NAS score or need for phenobarbital therapy did not increase the risk for hospital readmission.

The average hospital cost per infant was $27 546 for those in the traditional group and $13 729 for those in the combined group. Treatment in the combined approach resulted in a reduction of in-hospital costs of $635 582 over the 2 years in review.

Table 3 Results of a univariate logistic regression on hospital readmission for NAS

Variable	*Number*	*OR*	*95% CI*	P *value*
34–36 weeks gestational age	40	5.0	1.2–20.6	0.02
Highest NAS score (day)	121	1.1	0.9–1.4	0.39
Patients also on phenobarbital	31	0.4	0.08–2.0	0.26
Patients in the *combined* group	46	0.4	0.08–1.8	0.23

Abbreviations: CI, confidence interval; NAS, neonatal abstinence syndrome; OR, odds ratio.

Discussion

Traditional management of infants with NAS has focused primarily on inpatient care strategies leading to prolonged hospitalization

and extended separation of infants from their primary caregivers.[15,18] However, following initial inpatient stabilization, infants with NAS are typically healthy and may not require hospital-based care.[13,18,19] This has led to interest in developing community-based strategies in the care of infants with NAS.[7,13,20–22] Concern regarding the stability of the home environment and ability of drug-abusing caregivers to adequately comply with outpatient requirements has limited widespread adoption of this approach.[24]

We have shown that a combined inpatient and outpatient treatment program resulted in a 48% reduction in length of hospitalization compared with infants managed with a traditional inpatient approach. Importantly, we found no increased risk of short-term adverse outcomes, emergency room visits, hospital readmission or need for restarting inpatient treatment for NAS. Infants in the combined group were exposed to a longer course of methadone treatment. However, the cumulative dose of methadone was similar between the two groups. Given that opiates or other medications for NAS may adversely affect development, the fact that infants in both groups were exposed to similar cumulative doses is noteworthy.[25–27]

It is known that drug-abusing caregivers have poor compliance with outpatient appointments.[28] In that regard, the retention rate seen among mother–infant dyads in the combined program is significant and warrants explanation. A single, dedicated physician (CRB) who provided both inpatient and outpatient care was able to establish a long-term relationship with these families. As noted before, extended monitoring of infant growth and neurodevelopment, together with routine assessment of caregiver–infant interactions, are paramount.[25,26] Also, the outpatient clinic was able to meet the primary care needs of the infant (vaccinations, referrals, routine well visits and sick visits). This effort to provide comprehensive care in a non-threatening, non-punitive and supportive environment likely contributed to better compliance.[29]

Success of the outpatient program is largely dependent upon patient selection. The combined approach was only offered to mothers enrolled in an antenatal drug treatment program on methadone. Furthermore, only those who met all social and medical work criteria were included (Figure 1). Considering that most NAS symptoms occur during the first 7 days following delivery, it is imperative that infants be monitored in the hospital throughout this time.[30] This approach offers the opportunity to individualize medication dosages, evaluate the stability of the home environment and assess the motivation of the caregiver.[24] It is possible that some infants in the combined group had subclinical withdrawal. However, this has also been known to occur among infants managed entirely as inpatient.[28] This underscores the need for close outpatient follow-up among infants with NAS regardless of the treatment approach used.[18]

We recognize that providing access to any opioid may place the caregiver at risk for relapse.[24] However, the average maternal methadone dose at delivery was 80 mg day^{-1} (range 20 to 180 mg day^{-1}) compared with an average infant dose of 0.15 mg day^{-1} (range 0.1 to 0.5 mg day^{-1}). Thus, the average infant dose is $<0.2\%$ of the maternal dose.

We found that preterm infants were five times more likely to be readmitted for NAS than term counterparts. Previous studies have shown that these patients are less likely than term infants to show classic signs of NAS exposure, and many exhibit withdrawal symptoms later than term counterparts.[31] Although NAS scoring systems provide clinicians with a systematic and objective evaluation of affected infants, they may lack the sensitivity to detect subtle manifestations of withdrawal in the preterm infant.[18] Additionally, there is evidence that some NAS scoring systems, including the Finnegan method, are too complex for regular use in a clinical setting.[5]

The American Academy of Pediatrics encourages breastfeeding for mothers on methadone noting that, irrespective of its dosage, the transfer of methadone into human milk is minimal.[32] Considering that breastfeeding has been shown to improve maternal–infant bonding, increase maternal self-esteem, minimize NAS symptoms and decrease the need for NAS treatment, the higher incidence of this practice in the combined group is encouraging.[18,33,34]

Not surprisingly, infants in the combined group had a significant reduction in inpatient cost ($13 817/infant), with an estimated savings of over $635 000 in a 2-year period. However, developing and maintaining an outpatient *(combined)* strategy requires an investment in health care resources difficult to quantify.[35]

The main limitations of our study are the retrospective design and small study population. Additionally, the applicability of our findings to a wider range of NAS populations is limited because we included only 'motivated' mothers enrolled in an antenatal substance program on methadone who were further screened for potential compliance with the outpatient strategy. Thus, we recognize that our comprehensive set of discharge criteria for the combined group unavoidably created a selection bias.

We agree with investigators that reducing hospital length of stay alone in this population is not the primary objective.[24] However, the potential benefits of the combined approach for treatment of NAS highlights the need for randomized, controlled, prospective studies. Additional efforts to delineate subpopulations of infants with NAS, and select treatment strategies based on those distinctions, are needed.[18]

Conclusion

A combined inpatient and outpatient methadone treatment for infants with NAS decreases hospital stay and substantially reduces cost without short-term adverse outcomes. Additional studies are needed to evaluate the applicability of this strategy and to evaluate its potential long-term benefits on infants and their families.

Conflict of interest

The authors declare no conflict of interest.

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