**Postnatal Age at which Neonatal Abstinence Syndrome (NAS) Require Pharmacological Treatment in Infants with** **Intrauterine Exposure to Opiates**

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**Abstract**

**Objective**:

To determine the hour of life at which NAS require pharmacological treatment and short-term outcomes in infants with intrauterine exposure to opiates.

**Study design:**

Medical records of all mothers and infants from the Mother and Child Dependency Program from July 2015 to June 2016 were reviewed. Clinical characteristics of mothers and their newborn infants with opiate exposure were abstracted to determine the hour of life at which NAS develops and short and long term morbidities.

**Results:**

Between July 1, 2015 and June 30, 2016, 124 infants were identified with intrauterine exposure to opiates. 82 out of the 124 infants (66%) received pharmacological treatment, which was started on average at two days of life. Two infants required treatment beyond 7 days of life. The average length of stay was higher in the pharmacological treatment group (26.4 ±14.6), compared to those who required non- pharmacological treatment (14.4 ±25.1) (p=0.001).

There was no significant difference among the two groups in regards to receiving prenatal care; however 70.4% of the mothers with infants requiring pharmacological treatment initiated prenatal care in their first trimester. These mothers also had higher adverse social circumstances; 41.4% had previous children in DCFS custody and 33.8% of them were victims of assault. There was a higher incidence of maternal GC or chlamydia infections as well. Rate of smoking in mothers of NAS infants requiring medications was also significantly higher (p=0.002).

The average total cumulative dose of morphine (mg) was significantly different among infants with mothers on a methadone maintenance program (56.9 ±53.4), in comparison to infants with mothers on a subutex maintenance program (24.4 ±26.9) and those not on an opiate dependency program (25.6 ±17.2) (p=0.04). There was no significant difference in duration of NAS treatment among the three maintenance program subgroups. Mothers on a maintenance program showed more compliance with first PCP visit (78.9%).

**Conclusion:** Current practice of observing at risk for developing NAS infants for 7 days is appropriate.

**Introduction**

Illicit drug use in pregnancy and its associated adverse effects in infants are continually growing in most developed countries. Although many opiate dependent mothers are transitioned to an opiate maintenance program, typically methadone or subutex, it is very likely that the infants experience withdrawal symptoms. Neonatal abstinence syndrome (NAS) is a result of the sudden discontinuation of fetal exposure to substances (such as opiates) that were used or abused by the mother throughout pregnancy. In a recent national study, the incidence of NAS has risen from 1.2 to 3.4 per 1000 live births. NAS has become more complex, imposing additional social, economic, and health care costs on society.

Drug abuse, including opiate (heroin, prescription opiates) abuse, can be associated with fetal growth restriction, feeding difficulties, irritability and increased risk of seizure from opiate withdrawal. The Finnegan scoring system is generally used to evaluate the severity of NAS, as scoring can be helpful for initiating, monitoring, and weaning treatment in neonates. Finnegan scores that remain less than eight do not warrant a NAS pharmacological treatment and the infant may be safely discharged. If the scores surpass eight, pharmacological treatment is initiated in order to ameliorate the withdrawal symptoms, establish consistent weight gain and adequate sleep patterns, and allow for successful integration into his or her social environment.

There is much variability regarding the appropriate duration of observation before discharge, as it is dependent on maternal drug history and the infant's NAS scores. At MetroHealth, all such infants at risk of developing NAS are observed for seven days before being discharged. The purpose of this study was to review and determine whether all infants who develop NAS do so by five days and are safe to be discharged six days onward.

**Methods**

This is a retrospective cohort study of newborn infants born at MetroHealthMedical Center (Cleveland, OH), between July 2015 and June 2016, who were prenatally exposed to opiates. For the purpose of this study clinical characteristics of mothers and their newborn infants with opiate exposure were abstracted from their medical records and entered in the "Mother and Child Dependency Database."

An infant was considered to have intrauterine exposure to opiates or other illicit drugs if the mother voluntarily admitted to abusing illicit drugs during the current pregnancy, was enrolled in a methadone/subutex program, if she or the neonate had a positive urine toxicology screen, or if the neonate had noteworthy abstinence syndrome following birth that required treatment. The hour of life in which severe NAS developed was determined by the initiation of pharmacological treatment, specifically morphine.

The charts of 124 infants and their mothers were reviewed. Among the infants and their mothers, two groups were identified:

-Infants with NAS that received pharmacological treatment and their mothers.

-Infants who did not require pharmacological treatment and their mothers.

The infants with NAS that received pharmacological treatment were then subdivided into three groups by mother maintenance program: no opiate dependency program, methadone, and subutex.

Interval data was reported as mean ±SD, whereas the ordinal and nonparametric data was reported as percentage. The Chi square test was used for categorical variables. ANOVA was used for continuous variables. Statistical significance is defined as p<0.05 (two-tail). Data was analyzed using Social Science Statistics (<http://www.socscistatistics.com/>).

**Results**

**Table1**: Comparison of infants with severe NAS requiring medications versus others.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Infants exposed to inuteroopiates** | **Severe NAS requiring medications** | | **Without Severe NAS** | **P value** |
| N=124 | | N= 82 (66%) | N = 42 (34%) | |
| Male gender | 48 (58.5%) | | 17 (40.5%) | 0.057 |
| Gestational age (wk) | 38.0 (±2.5) | | 36.9 (±3.8) | 1.000 |
| Vaginal delivery | 51 (62.2%) | | 25 (59.5%) | 0.773 |
| APGAR at 5 minute | 8.7 (±1.0) | | 8.9 (±0.4) | 0.237 |
| Birth weight (grams) | 2869.0 (±601.0) | | 2640.9 (±758.1) | 0.073 |
| Urine toxicology (N= 59) | | N=44 | N=15 | |
| **Positive** | **37 (84.1%)** | | **5 (33.3%)** | **0.00018** |
| Type of infant feeding (N=120) | | N=79 | N=41 | |
| Breast milk only | 1 (1.3%) | | 3 (7.3%) | 0.080 |
| Formula only | 51 (64.6%) | | 26 (63.4%) | 0.901 |
| BM-formula | 27 (34.2%) | | 12 (26.3%) | 0.586 |
| Type of formula (N=113) | | N=77 | N=35 | |
| Regular (Similac/Neosure) | 63 (81.8%) | | 30 (85.7%) | 0.524 |
| Soy/Hydrolysate | 14 (17.9%) | | 5 (14.3%) | 0.787 |
| DOL when reach full feed | 6.2 (±6.9) | | 8.6 (±23.3) | 0.426 |
| DOL when gain birth weight (N=85) | | N=71 | N=14 | |
| 11.6 (±5.3) | | 12.2 (±6.3) | 0.534 | |
| **NICU admission** | **56 (68.3%)** | | **15 (35.7%)** | **0.001** |
| **Length of hospital stay** | **26.4 (±14.6)** | | **14.4 (±25.1)** | **0.001** |
| Discharge to (N=120) | | N=79 | N=41 | |
| Parents | 56 (70.9%) | | 32 (78.0%) | 0.400 |
| DCFS/Relative | 19 (24.1%) | | 6 (14.6%) | 0.228 |
| Adoption | 4 (5.1%) | | 3 (7.3%) | 0.617 |
| Death | 2 (2.5%) | | 2 (4.9%) | 0.605 |
| Prematurity/Infection | 0 | | 0 | 1.000 |
| Other | 2 (100%) | | 2 (100%) | 0.605 |

Between July 1, 2015 and June 30, 2016, we identified 124 babies exposed to in utero opiates and their mothers. Of these 124 babies, 82 developed severe NAS that required pharmacological treatment. Characteristics of those who requiring pharmacological treatment were compared to those who did not. There were a total of four deaths, two among the NAS (respiratory failure; severe RDS) babies two among those that did not develop NAS (SIDS; intrauterine fetal demise).

**Figure1:** The hour of life at which severe NAS was diagnosed due to intrauterine exposure to opiates and pharmacological treatment with morphine was initiated.

**Table2:** Comparison of maternal characteristics of infants with severe NAS requiring medications versus without.

|  |  |  |  |
| --- | --- | --- | --- |
| **Maternal characteristics** | **NAS requiring medications** | **Without Severe NAS** | **P value** |
| N= 82 (66%) | | N = 42 (34%) | |
| Age (year) | 29.7 (±7.6) | 27.9 (±4.0) | 0.147 |
| Race (N=122) | N=81 | N=41 | |
| White | 73 (90.1%) | 34 (85.4%) | 0.253 |
| Black/Hispanic | 8 (9.9%) | 6 (14.6%) | 0.549 |
| Gravida | 3.75 (±2.2) | 3.78 (±2.8) | 0.954 |
| Received prenatal care | 71 (86.6%) | 36 (85.7%) | 0.894 |
| **Initial visit in 1st trimester (N=66)** | **50/71 (70.4%)** | **16/36 (44.4%)** | **0.009** |
| Number of visits | 6.7 (±3.9) | 6.4 (±3.1) | 0.757 |
| Serology positive for HCV | 35/76 (46.1%) | 15/32 (46.9%) | 0.938 |
| GC or Chlamydia positive | 5/62 (8.1%) | 0/32 (0%) | 0.162 |
| Social | | | |
| **Previous children in DCFS custody** | **24/58 (41.4%)** | **19/29 (65.5%)** | **0.034** |
| Street worker | 0/63 (0%) | 2/35 (5.7%) | 0.055 |
| Incarceration | 13/69 (18.9%) | 5/34 (14.7%) | 0.603 |
| **Assault** | **22/65 (33.8%)** | **3/37 (8.1%)** | **0.004** |
| Rape | 1/65 (1.5%) | 1/35 (2.9%) | 0.653 |
| Maternal report of substance abuse | | | |
| **Heroin** | **73 (90.1%)** | **29 (69.0%)** | **0.006** |
| Other Opiates | 61 (74.4%) | 30 (71.4%) | 0.724 |
| **Prescription Opiates Pre-Heroin** | **45 (54.9%)** | **14 (33.3%)** | **0.023** |
| Cocaine | 40 (48.8%) | 13 (31.0%) | 0.058 |
| **Marijuana** | **46 (56.1%)** | **14 (33.3%)** | **0.016** |
| **Other** | **27 (32.9%)** | **6 (14.3%)** | **0.026** |
| **Smoking** | **77 (93.9%)** | **31 (73.8%)** | **0.002** |
| Alcohol use | 30 (36.6%) | 14 (33.3%) | 0.720 |
| History of psychiatric disorder | 57/77 (74.0%) | 27/40 (67.5%) | 0.457 |
| Abnormal 1st Urine Tox (N=88) | 41/53 (77.3%) | 26/35 (74.3%) | 0.801 |
| Abn. Urine Tox at delivery (N=113) | 51/73 (69.9%) | 25/40 (62.5%) | 0.530 |
| Maintenance Program (N=84) | N=66 | N=18 | |
| **Methadone** | **36 (53.8%)** | **5 (27.8%)** | **0.044** |
| **Subutex** | **30 (46.2%)** | **13 (72.2%)** | **0.044** |

**Table3:**Characteristics of infants who required pharmacological treatment.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Pharmacological Treatment Group** | **Mom not on opiate dependency treatment** | | | **Methadone** | | **Subutex** | | | **P value** |
| **(N =15 )** | | | **(N =36 )** | | | | **(N = 30)** | | |
| Hour of life Treatment started | 31.4 (±23.0) | | | 58.4 (±43.2) | | 60.7 (±39.2) | | | 0.060 |
| Earliest (hours)  Treatment started | 8 | | | 8 | | 10 | | | **-** |
| Latest (hours)  Treatment started | 106 | | | 248 | | 167.5 | | | **-** |
| Treatment started at ≥ 7 days | 0 (0%) | | | 1 (2.8%) | | 1 (3.3%) | | | 0.784 |
| **Total cumulative morphine (mg)** | **25.6 (±17.2)** | | | **56.9 (±53.4)** | | **24.4 (±26.9)** | | | **0.004** |
| Needed ≥ 2 NAS meds | 1 (6.7%) | | | 4 (11.1%) | | 3 (10%) | | | 0.889 |
| Duration of NAS treatment (days) | 16.7 (±7.6) | | | 24.9 (±16.1) | | 24.3 (±12.9) | | | 0.060 |
| Received breast milk | | 23 (±0) | | | 28 (±17.6) | | | 19.9 (±12.5) | |
| Did not receive breast milk | 17.3 (±6.8) | | | 21.5 (±13.3) | | 16.6 (±13.1) | | | 0.432 |
| Maternal Drug Abuse | | | | | | | | | |
| Only opiates (N=21) | | N=6 | | | N=9 | | | N=6 | |
| Smoking | 4 (66.7%) | | | 8 (88.9%) | | 6 (100%) | | | 0.240 |
| Alcohol | 3 (50%) | | | 1 (11.1%) | | 2 (33.3%) | | | 0.251 |
| Poly-drug (N=60) | | N=9 | | | N=27 | | | N=24 | |
| Smoking | 9 (100%) | | | 26 (96.3%) | | 24 (100%) | | | 0.537 |
| Alcohol | 5 (5.6%) | | | 11 (40.7%) | | 9 (37.5%) | | | 0.639 |
| Location of treatment administration | | | | | | | | | |
| NICU | 13 (86.7%) | | | 25 (69.4%) | | 17 (56.7%) | | | 0.122 |
| Nursery/PICU | 2 (13.3%) | | | 11 (30.6%) | | 13 (43.3%) | | | 0.122 |
| Number of readmissions | 2 (13.3%) | | | 2 (5.6%) | | 3 (10%) | | | 0.630 |
| N=14 | | | N=32 | | | | N=25 | | |
| PCP first visit compliant | 8 (57.1%) | | | 26 (81.3%) | | 19 (76%) | | | 0.220 |
| **Discharged to parents** | **3 (37.5%)** | | | **20 (76.9%)** | | **18 (94.7%)** | | | **0.007** |
| **Discharged to other** | **5 (62.5%)** | | | **5 (19.2%)** | | **1 (5.2%)** | | | **0.032** |

**Conclusions**

Current practice of observing at risk for developing NAS infants for 7 days is appropriate.

•Infants that received pharmacological treatment had a longer hospital stay and higher incidence of NICU admission.

•Infants with mothers on a methadone maintenance program had significantly higher cumulative dose of morphine.

•Mothers on an opiate maintenance program were more likely to comply with their infant’s first PCP visit.