

STUDY PROTOCOL

TITLE: AROMATHERAPY AS AN ADJUNCTIVE THERAPY FOR NEONATAL ABSTINENCE SYNDROME

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ABBREVIATIONS: NAS, NEONATAL ABSTINENCE SYNDROME

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STUDY BACKGROUND

The United States, Appalachia, Eastern Kentucky in particular, is in the midst of a major opioid abuse epidemic. This current epidemic is driven by misuse of prescription painkillers, i.e. Subutex and Saboxone. As prescription pills become more expensive and harder to acquire, addicts are seeking similar, cheaper drugs; such as heroin. From 1998 to 2011, the prevalence of opioid abuse and dependence amongst pregnant women has increased by 127%, from 1.7 per 1000 to 3.9 per 1000. Neonatal Abstinence Syndrome (NAS) or neonatal opioid withdrawal syndrome is a condition produces gastrointestinal and autonomic neurologic dysfunction. Infants with severe withdrawal experience dysregulation of autonomic functions, resulting in feeding difficulty, diarrhea, excessive sleepiness, and tremors. Nearly two thirds of all babies exposed to opioids during gestation will require admission to a neonatal intensive care unit for management of withdrawal symptoms. During a typical year the Neonatal Intensive Care Unit (NICU) at Kentucky Children's Hospital admits approximately 100-120 infants exhibiting NAS symptoms; these infants have a typical length of stay of 24 days if they require pharmacologic treatment.

The mainstay of treatment for NAS involves opioid replacement therapy with morphine to minimize withdrawal symptoms. Once symptoms are well controlled, the infant is said to have been "captured." At this point a slow weaning of his morphine dose occurs. The infants' clinical status is assessed with the Finnegan Scoring system, which examines symptoms such as crying, excessive sleepiness or difficulty sleeping, insomnia, or tremors along with objective findings such as temperature and respiratory rate.

In addition to pharmacotherapy, alternative and complementary medicine techniques are slowly entering the NAS treatment algorithm. Treatments such as music therapy infant massage, kangaroo care, aromatherapy, and acupressure are now employed in NICUs in addition to traditional opioids replacement. However, few studies exist in the literature to evaluate their effectiveness.

Aromatherapy is the practice of using natural essential oils to achieve a desired effect in an individual. Scents such as lavender and chamomile have been documented to have a soothing calming effect. Studies involving infants shown that lavender not only reduce crying and enhance sleep, but also reduce levels of salivary cortisol, a stress hormone. Additionally, aromatherapy is currently used as an adjunctive therapy at the University of Kentucky's Markey Cancer Center.

Salivary cortisol is a non-invasive biomarker that has proven useful for monitoring stress in neonates. It is a simple and painless method for monitoring the stress hormone cortisol. Salivary cortisol has been used successfully in infants as a method to assess infant stress associated with prone position versus supine positioning. These studies have shown that salivary cortisol levels vary with stressful or soothing stimuli.

To date, no dangerous or deleterious effects have been described from traditional inhalational use of aromatherapy or with salivary cortisol sampling. Studies have shown aromatherapy to be an effective adjunctive therapy by proving a calming effect. In our patient population it may prove to be a useful complimentary therapy ultimately reducing infant stress, hospital length of stay, and burden of opioid use. Additionally, salivary cortisol's ease of collection and non-invasive nature make it an ideal biomarker to study.

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria:

- Infants greater than or equal to 36 weeks EGA
- Intrauterine opioid exposure
- Primary diagnosis of NAS
- Parental permission to participate

Exclusion Criteria:

- Infants less than 36 weeks EGA
- Major congenital anomalies
- Latrogenic drug withdrawal
- Diagnosis of infection or respiratory distress
- Prior initiation of opioid replacement therapy
- Non-English speaking
- Infants with respiratory conditions

ENROLLMENT

Patients will be evaluated at admission or transfer to the University of Kentucky NICU and consent obtained from the mother. Patients will be randomized to one of two groups using block randomization in groups of four. The study will not be blinded (open-label).

STANDARD OF CARE AND INTERVENTION

Standard of care will include quiet environment, occupational therapy, music therapy and infant massage. Kangaroo care and breast feeding will be encouraged based on clinical recommendations.

Interventional treatment will include all aspects of the standard of care in addition to aromatherapy. Patches will be obtained from BioEsse Technologies™ and will have an 80:20 mixture of Lavender and Chamomile in a 55-microliter standard dose. When activated, each patch releases, the mixture over a 2-8 hour period by design and a

constant diffusion rate. These will be attached to a positioning device placed in the infant's bassinet 6-8 inches from the infant's nose for a period of 4 hours twice a day.

ASSESSMENT

Comfort levels will be assessed using the MOTHER-NAS scoring system. After three consecutive scores of greater than or equal to 9 or two consecutive scores of greater than or equal to 13, replacement morphine (0.05mg/kg/dose every three hours) will be initiated. After 48 hours of symptom control, morphine will be weaned by 0.02mg/day. Any significant increase in scores that accompanied the wean will induce a return to the previous dose.

DATA COLLECTION AND STATISTICAL ANALYSIS PLAN

Data will be collected from hospital electronic medical records and stored in a secure manner. Data will include: 1) date of birth, 2) date of admission, 3) birth weight, 4) gender, 5) APGAR scores, 6) mode of delivery, 7) place of birth, 8) type of prenatal drug exposure, 9) prenatal care, 10) Finnegan scores, 11) average daily heart rate, 12) daily morphine dose, 13) total morphine dose per day, 14) length of treatment, and 15) length of hospitalization.

Data will be analyzed using standard statistical techniques. The two treatment groups will be compared with a two-tailed t-test, while dichotomous variables will be examined with a Chi-Square test. Statistical significance will be set at $p=0.05$.

Anticipated CONSORT Diagram showing the flow of participants through each stage of the trial.

