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Research report

Heightened sympathetic arousal is demonstrated by skin conductance responsivity to auditory stimuli in a small cohort of neonates with opiate withdrawal

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ABSTRACT

To determine the effects of auditory stimulus on skin conductance (SC) in infants with severe neonatal abstinence syndrome (NAS) that required morphine treatment (MT) compared with NAS infants that did not require morphine treatment (non-MT). We prospectively enrolled opiate-exposed term infants without poly-substance exposure. Skin conductance responses to an auditory stimulus (ringing a bell for 3 s) near the time of discharge were obtained. Skin conductance was measured before, during, and after the stimulus. Non-parametric tests were used to determine between group and within phase differences. Infants were off MT at the time of SC measurement in response to an auditory stimulus. In a 2-group comparison of MT vs. non-MT infants, there was significantly higher SC responsivity to an auditory stimulus ($p < 0.05$) in the MT group as compared with the non-MT group near discharge. The mean +SE peak morphine dose was 0.85 + 0.20 mg/kg/day in the MT group. The mean Length of Stay (LOS) was 32 vs. 7 ($p < 0.05$) days respectively, for the MT vs. the non-MT group. Our preliminary data suggest that in infants with severe NAS symptoms, higher sympathetic arousal in response to an auditory stimulus persists at discharge, underscoring the need for ongoing evaluation and specialized care at home.

1. Introduction

Substance abuse and misuse remain an ongoing and growing global problem, particularly among young people, with increasing incidence in substance dependence among all people, adolescents and young adults (Degenhardt et al., 2016). Pregnant women can be affected by substance use and dependence, including licit and illicit substances (Kandel et al., 1998; McFarlane et al., 1996). Opiate use among pregnant women is a significant public health concern. The use of prescription and non-prescription opiates amongst pregnant women continues to grow from year to year as shown by studies published by Patrick et al. (2015a, 2015b). When pregnant women use opiates or other substances for prolonged periods of time during pregnancy, the fetus is affected, and the clinical phenotype that results from this was first recognized in the 1970s as neonatal abstinence syndrome (NAS) (Finnegan et al., 1975; Jansson et al., 2008). Neonatal abstinence syndrome is well described following maternal opiate dependence; however, symptoms similar to NAS can be associated with other drugs or medications that a pregnant woman consumes. Common drugs that equally lead to, or worsen, NAS symptoms include, but are not limited to, nicotine, selective serotonin receptor inhibitors (SSRIs), anxiolytics, barbiturates and benzodiazepines.

NAS is a form of drug withdrawal symptoms that are present in the newborn infant following birth due to the cessation of transplacental transfer of the offending maternal drug. The incidence of NAS continues to be on the rise; recent data suggest an increase to 5.8 from 1.2 per 1000 live births in the United States of America (USA) alone from the year 2000–2010 (Patrick et al., 2015b). Methadone is the most commonly used opiate for the treatment of heroin addiction in pregnant women; buprenorphine is also widely used as a safe alternative to methadone (Jones et al., 2010).

The clinical characteristics of NAS include central nervous system (CNS) irritability, gastrointestinal (GI) disturbances and autonomic nervous system (ANS) instability (Chasnoff, 1988; Desmond and

Abbreviations: NAS, Neonatal Abstinence Syndrome; MFNSS, Modified Finnegan Neonatal Scoring System; SC, Skin Conductance; GA, Gestational Age; BW, Birth Weight; NBN, New Born Nursery; NICU, Neonatal Intensive Care Unit; MFM, Maternal Fetal Medicine; SE, Standard Error; IQR, Inter Quartile Range; EDR, Electrodermal Response (Peaks/s); MP, Mean of Peaks (peak amplitude)

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Wilson, 1975). The action via opiate receptors present in the CNS and GI system is the underlying mechanism by which these drugs lead to the clinical syndrome of withdrawal. The CNS symptoms include increased muscle tone, poor sleep, tremors, excessive crying (high pitch cry), hyperreflexia, and seizures. The GI issues most commonly described include poor feeding, regurgitation, and diarrhea, all of which can lead to failure to thrive when unrecognized or untreated. The ANS can also be significantly impacted by this syndrome, such that affected neonates are noted to have excessive sweating, temperature instability, hypertension, and tachycardia (Kocherlakota, 2014). Animal data suggest that in opiate withdrawal, CNS and ANS disturbances can occur through different mechanisms (Hamburg and Tallman, 1981; Mulder and Schoffelmeer, 1985). In a study carried out in prenatally methadone-exposed rats, abnormal catecholamine effects were noted in the CNS and peripheral nervous systems (Lau et al., 1977). Human studies also postulate increased levels of adrenalin and noradrenergic hyperactivity leading to ANS disturbances in infants of substance dependent mothers (Ward et al., 1991; Little et al., 1996). Ward and his colleagues speculated that in infants of substance abusing mothers, increased and altered catecholamine levels (noradrenaline) in the blood of these infants versus non-opiate exposed control infants contributed to the ANS dysregulation noted in infants with NAS (Ward et al., 1991). Infants affected by NAS are at increased risk of adverse neurodevelopmental outcomes, i.e., attention deficit hyperactivity disorder and behavioral problems at school age (Hunt et al., 2008; Thompson et al., 2009). Given the risk for adverse outcomes, early recognition and treatment are highly recommended. The pathophysiologic effects of illicit substances on the developing fetal brain are yet to be clearly delineated. Several factors such as type of substance (opiate versus non-opiate), poly-substance exposure (including alcohol, cocaine, nicotine, etc.), duration of exposure, socio-economic status (SES) of the family and ongoing intervention during infancy and early childhood all are possible factors that influence adverse neuro-developmental outcomes (Hunt et al., 2008; Singer et al., 2012; Nygaard et al., 2016).

Neonatal Abstinence Syndrome also contributes significantly to additional length of hospitalization stay and increased medical costs. The current method for assessment and diagnosis of NAS involves the use of a clinical scoring system-the Modified Finnegan Scoring System (MFSS). Neonatal Abstinence Syndrome is scored and treated based on a numerical value determined by the clinician, but the critical threshold number for MFSS is yet to be validated. The MFSS or similar tools are used in centers across the globe for instituting pharmacologic therapy, and algorithms for guiding treatment, and weaning from pharmacotherapy. The MFSS scores play a significant role not only in commencing treatment, but more importantly in monitoring treatment response and readiness for discharge. Criteria for hospital discharge include cessation of pharmacotherapy for withdrawal by 48–72 h before discharge with average MFSS score below eight. Anecdotal experience of pediatricians and other practitioners is that these infants' neurological examination is not completely normal at the time of release from the hospital. These infants will continue to have mild symptoms of NAS that require ongoing evaluation by the outpatient practitioners. Symptoms such as tremors and CNS irritability could persist for weeks or present later; hence the need for careful evaluation, follow-up and supportive care after hospital discharge (Kandall and Gartner, 1974).

Skin conductance (SC) is an important tool that has been used in assessing sympathetic nervous system arousal in adults and children. Skin conductance measures sympathetic activity by surface electrodes placed on the palmar and plantar surfaces with increased sweat release enhancing electrical properties of the skin. Sweat release by eccrine sweat glands occurs with increased emotional arousal. Such arousal can be induced by various stimuli such as pain, noise, tactile stimulation, etc., under both naturalistic and experimental situations. Skin conductance has been utilized in clinical studies as a method for assessing pain and arousal in neonates and infants (Hellerud and Storm, 2002; Macko et al., 2013). The lack of objective methods of assessment in NAS is an ongoing problem that must be solved because the subjective nature of available screening tools, to date, has contributed to improper diagnosis, increased length of hospital stay, infant and maternal distress, and additional challenges to families and health care systems. To this end, skin conductance is a promising tool for physiologic measurement of pain and sympathetic arousal in NAS. In a recent study by our group, we showed that baseline SC measures obtained at 24–48 h of life were higher in infants with severe NAS symptoms (defined as the need for later pharmacologic therapy). This group had a higher response to painful stimuli and the SC measures of interest correlated with the clinical scoring tool (Oji Mmuo et al., 2016). Another recent study corroborates with our findings; showing that the SC of newborns treated for NAS were significantly higher compared with unexposed controls (Schubach et al., 2016).

The main aim of the present study was to examine the utility of skin conductance, an objective measure of sympathetic nervous system (SNS) activation in NAS. It was hypothesized that SC responses would remain high near discharge in infants treated for NAS compared to opiate exposed infants that did not require treatmement for NAS. Further, this objective assessment will provide insight into the infant's condition after pharmacologic therapy for NAS and the need for ongoing care post-discharge.

2. Methods

2.1. Human subjects

This study was a prospective single center study performed on fourteen term neonates. The infants were all greater than 37 weeks completed postmenstrual age (PMA) at birth. All the infants in this study were admitted to the newborn nursery (NBN) and neonatal intensive care unit (NICU) of Penn State Health Children's Hospital. Infants were born to opiate dependent mothers that were followed prenatally by the maternal fetal medicine or obstetric team. We obtained written informed consent from the mother before enrolling maternal-infant pairs. The study was reviewed and approved by the Pennsylvania State University College of Medicine review board for human subject research.

2.2. Procedures

Following birth, infants were admitted to the NBN and monitored for signs and symptoms of NAS using the MFSS to rate symptoms of withdrawal every four hours as per the standard care protocol. Meconium toxicology screen was performed on the infants to confirm drug exposure. For infants without meconium toxicology, the mothers' medical records were reviewed for medication use during pregnancy and urine drug screen when available. Relevant maternal and infant characteristics were collected from the patients' medical charts.

2.3. Apparatus, data acquisition, data processing and analysis

2.3.1. Skin conductance device and software

Skin conductance activity was measured using the Med-Storm™ device. The device is approved for medical use in Europe and complies with safety regulations (IEC 60601). Low-frequency electrical conductance indicated by the ionic conduction in the stratum corneum of the skin is determined by sweat duct filling. Three surface electrode systems (Conmed ® Corporation) were applied to the infants' foot: a measuring electrode, a counter current electrode and a reference voltage electrode to ensure that a constant voltage was applied across the stratum corneum beneath the measuring electrode.

Infant's skin conductance responses to heel stick recorded at 24–48 h of life and before the need for pharmacologic treatment have been previously published by our group (Oji Mmuo et al., 2016). Near