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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 $\pm$ 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.

Keywords

Neonatal abstinence syndrome; Objective assessment; Skin conductance; Sympathetic arousal; Assessment at discharge

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

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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 (Forsberg et al., 2014).

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 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.

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.

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 treatment 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 the time of discharge, skin conductance responses to auditory stimuli (ringing a bell for 3 s) were collected and recorded from the thirteen infants reported here. Pre-stimulation skin conductance responses were obtained from all infants at for ten minutes without any stimulation or handling. The data was subsequently analyzed offline using a software package provided by the manufacturers. The SC variables of interest include the electrodermal responses (EDR)/second (peaks per second) and the mean of peaks in MicroSiemens, which is the average value of all peaks in a given time frame.

Above measurements were carried out in the NICU family room (quiet room, located away from the patient care areas) under three separate conditions: 1) at rest, baseline (pre-stimulus) levels were measured with the infant calm with very minimal handling and soothed with a pacifier for non-nutritive sucking, 2) response levels were measured after giving an auditory stimulus using a bell for 3 s and finally 3) SC was measured during a recovery or post stimulus phase. These measurements occurred sequentially near the time of discharge as an objective assessment for discharge.

2.3.2. Statistical tests—The infants were divided into two groups based on the need for later pharmacotherapy: morphine treated (MT) and non-morphine treated (non-MT) groups. To test our hypotheses, the Mann-Whitney U-test was used to compare between group differences of the SC measures and the Wilcoxon test was used to test between phase SC differences in response to a sound stimulus. The outcomes of interest were the need for pharmacologic therapy for NAS, the duration of hospitalization, and recommendations for care post-discharge. Comparison of the peak morphine doses, duration of medical therapy and LOS for the MT versus the non-MT groups were conducted using independent sample t-

test descriptive statistics. All tests were two tailed at a 5% significance level. The IBM SPSS statistical software version 24 (IBM Corporation, Armonk, NY, USA) was used for all data analysis.

3. Results

3.1. Demographic information

Twelve opiate exposed infants that met the eligibility criteria with complete data including SC measures at the time of discharge were included in this study. Seven (54%) of the twelve infants studied did not have NAS symptoms severe enough to require pharmacologic therapy. The mean $\pm$ SE gestation for the 12 infants was 38.8 ± 0.34 weeks and mean $\pm$ SE birth weight was 2831.3 ± 421 g. All infants had normal Apgar Scores at birth without concerns for perinatal depression; their median (inter-quartile range) 5-min Apgar score was 9(7-9). Seventy percent of the 12 infants' mothers were identified by the maternal and fetal medicine (MFM) team and maintained on the methadone program. Other opiate use (i.e. morphine, buprenorphine, and oxycodone) in mothers accounted for 30% of substance use. All the 12 mothers reported cigarette use during the index pregnancy. Infant and maternal characteristics are presented in Table 1.

3.2. Descriptive results

3.2.1. Pre-Auditory stimulus—Mean $\pm$ SE skin conductance measures obtained at baseline (pre-AS) for the non-MT infants were: 13.74 ± 4 μ Siemens, mean $\pm$ SE EDR/sec was 0.232 ± 0.03 , and mean $\pm$ SE mean of peaks was 0.109 ± 0.04 . The SC measures, including the mean of peaks and basal levels (mean $\pm$ SE 18.54 ± 12.99 and 0.298 ± 0.17 , respectively), were higher in the MT group, but did not achieve statistical significance (Table 2).

3.2.2. Auditory stimulus—There were no SC differences between groups during the actual 3-s bell ring ($p > 0.05$).

3.2.3. Post-Auditory stimulus—Following the bell ring in the post-auditory stimulus phase, a two-group analysis indicated that the MT group had higher SC responses on all three measures (basal, EDR/Seconds and mean of peaks) compared with the non-MT group (Table 2). Of the aforementioned SC measures, the mean of peak response was noted to be statistically significant (Fig. 1). The within group analysis of all infants showed there were significantly higher phase differences in EDRs/second (peaks/sec) from the auditory stimulus phase to the post auditory stimulus phase (response/recovery phase); with $p < 0.05$ using the Wilcoxon Signed Rank tests.

3.2.4. Length of stay—The groups were similar in gestational age at birth, birth weight, and maternal drug exposures. Their lengths of stay in hospital, however, were statistically different with the MT group having a longer hospitalization compared with the non-MT group: 32 days vs. 7 days, respectively. Correlation analysis of skin conductance (mean of peaks) as a function of length of stay (LOS) indicate a direct positive relationship with Spearman's correlation coefficient of 0.77 ($p = 0.003$) Fig. 2.

4. Discussion

Skin conductance measures were noted to be higher in the MT group at discharge in support of our hypothesis. The results of the present study showed that infants with higher NAS symptoms, evidenced by the need for pharmacotherapy with morphine (MT group), continue to have increased sympathetic arousal (higher mean of peaks SC) following exposure to an auditory stimulus 24–48 h after discontinuation of medical therapy. In our prior study, the babies requiring morphine treatment for NAS had higher pre-heel lance SC than those that did not require treatment and we also noted distinctive phase differences in response to heel lance between groups (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). Consistent with our findings, other studies that have examined infant's SC responses to stimuli such as heel lance and noise report increased EDRs/sec and mean of peaks (Macko et al., 2013; Salavitarab et al., 2010; Harrison et al., 2006). These studies, however, were not done in opiate dependent infants. Salavitarab et al. examined healthy preterm infants with mean post menstrual age of 32 weeks and found that the mean heart rate during resting or pre-care time was directly associated with higher SC increases to sound stimuli, and this effect was even higher at increased sound levels (Salavitarab et al., 2010). In addition to group differences, we also noted unique phase differences in response to the auditory stimulus in all infants. To our knowledge this is the first study to report heightened sympathetic arousal to sound in NAS infants near the time of hospital discharge. We speculate that the level of withdrawal from opiates alters sympathetically driven mechanisms of response. These responses persisted in infants even when the apparent need for morphine therapy had ceased as determined by the clinical scoring tool (MFSS).

Studies examining the care for infants with NAS are largely conducted in the hospital setting; for example, “rooming-in” with the mother was shown to reduce the length of stay, decrease hospital costs, and the need for pharmacologic therapy (Holmes et al., 2016; Hünseler et al., 2013). The advantage of this intervention is that it strengthens the mother-infant bond, promotes breast feeding when not contra-indicated, and encourages maternal participation in the infant's care. Mothers' rooms in the post-partum ward are single rooms such that noise and environmental stimuli can be easily controlled. Future research on sympathetic activity using skin conductance should be conducted to examine the impact of maternally driven interventions to reduce sympathetic arousal.

In NAS, delayed withdrawal symptoms can occur. The timing of abstinence symptoms is determined by the half-life of the opiate or drug in question. Symptoms in methadone exposed neonates are largely noted at 48–72 h following birth, but delayed manifestation of NAS symptoms following methadone exposure could be up to 4 weeks and could persist up to 6 months (Desmond and Wilson, 1975; Steg, 1957). 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, socioeconomic 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).

Follow up by pediatricians and other primary care clinicians for ongoing symptoms or rebound of NAS symptoms is essential. Early intervention services, home skilled nursing visits, parental education, improving access to health resources, and home based therapy/ intervention could further reduce emotional, neurologic, and medical problems in these high risk children.

The strengths of this study are that it creates a new area for exploration, with emphasis on objectively evaluating NAS infants before discharge. This was a prospective pilot study; we excluded poly-substance exposed infants based on toxicology testing and not maternal reports alone. We carefully controlled for confounding factors by obtaining SC measurements at the same time of day when there was reduced staff activity and to control for circadian influences (12-3PM). Also, infants were moved to a separate quiet testing area, and we ensured low ambient light and normal room temperature to control for confounding stimuli. All infants in this study were similar at birth, and we ensured that they all had documentation of a normal newborn hearing screen before assessing their SC responses to an auditory stimulus. We also controlled for infant's state, as SC data were obtained with the infants calm, several minutes after handling associated with feeding and diaper changes. We recognize that the most important limitation of this feasibility study is the small sample size; this could explain why we did not find statistical significance in all the SC measures (EDR/ second and Basal) between the MT versus non-MT groups. We, however, noted a difference in the mean of peaks in the post-AS phase between the groups, and between phase differences in EDR/seconds in all infants following the stimulus.

In conclusion, the physiologic measure of heightened sympathetic arousal in NAS reported here has great potential for use in clinical practice. The SC hardware is very portable and has potential to be configured into the bedside cardio-respiratory monitoring system. We speculate that substance exposed infants with symptoms severe enough to require pharmacologic treatment should be tended to very carefully during hospitalization. After discharge, these infants will continue to require additional surveillance for short term signs of withdrawal and long term neurologic complications. Studies suggest that infants remain at increased risk for adverse neurologic outcomes as children (Hunt et al., 2008) and teens (Oei et al., 2017). These infants are at increased risk of neurodevelopmental impairment when compared to healthy controls when standardized tests were carried out at 18 and 36 months (Hunt et al., 2008). School performance was significantly lower in high school students with a diagnosis of NAS at birth as suggested by a large population study in Australia (Oei et al., 2017). Further studies are needed to evaluate autonomic system arousal and other systemic disturbances at the time of discharge to determine readiness for discharge given the risks for long-term developmental sequelae.

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Abbreviations:

NAS	Neonatal Abstinence Syndrome
MFNSS	Modified Finnegan Neonatal Scoring System
SC	Skin Conductance
GA	Gestational Age
BW	Birth Weight
NBN	Newborn Nursery
NICU	Neonatal Intensive Care Unit
MFМ	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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Fig. 1.

Skin conductance in response μS (Mean $\pm$ SE) in response to auditory stimulus near hospital discharge. $N = 12$. MT = morphine treatment; EDR = electrodermal response; AS = auditory stimulus; $\mu S = \mu Siemens$. * $p < 0.05$ (Mann Whitney-U test).

Fig. 2. Correlation between skin conductance mean of peaks (μS) from the post-auditory stimulus phase and length of stay (treated group vs non-treated group, representing those that required morphine treatment vs those that did not require treatment). The Spearman's (r^s) correlation coefficient 0.77 ($p = 0.003$).

Table 1

Infant and Maternal Characteristics.

Infant Characteristics (N = 12)	Mean	SD	Min	Max
Postmenstrual age at birth (weeks)	38.8	1.18	37.3	41.1
Birth weight (grams)	2831	421	2350	3615
Male gender (%)	67	–	–	–
5-min Apgar score (median, IQR)	9(7-9)	–	–	–
Mode of delivery (%)				
Vaginal delivery	75	–	–	–
C-section	25	–	–	–
Morphine Treated for NAS (%)	42	–	–	–
Maternal Characteristics (N = 12)	Mean	SD	Min	Max
Age (year)	25	4.58	20	33
Level of education (%)				
High School	58	–	–	–
College	42	–	–	–
Received prenatal care (%)	100	–	–	–
Substance use in pregnancy (%)				
Methadone	70	–	–	–
Other opiates	30	–	–	–
Cigarette smoking during pregnancy (%)	100	–	–	–

Table 2

Between group comparisons of skin conductance responses to auditory stimulus.

SC Measure	Non-treated infants (n = 7)	Treated infants (n = 5)	<i>p</i>
Pre-Auditory Stimulus			
<i>Mean (SE)</i>			
Basal Level SC	13.74 (4.78)	18.54 (12.99)	<i>ns</i>
EDR/Sec	0.232 (0.03)	0.129 (0.05)	<i>ns</i>
Mean of Peaks SC	0.109 (0.04)	0.298 (0.17)	<i>ns</i>
Auditory Stimulus			
<i>Mean (SE)</i>			
Basal Level SC	14.28 (4.98)	14.50 (6.80)	<i>ns</i>
EDR/Sec	0.27 (0.27)	0.37 (0.07)	<i>ns</i>
Mean of Peaks SC	0.21 (0.08)	0.24 (0.08)	<i>ns</i>
Post-Auditory Stimulus			
<i>Mean (SE)</i>			
Basal Level SC	14.59 (5.10)	16.06 (5.05)	<i>ns</i>
EDR/Sec	0.17 (0.03)	0.29 (0.09)	<i>ns</i>
Mean of Peaks SC	0.11 (0.05)	0.51 (0.23)	<i>< .05</i>
Peak Morphine Dose(mg/kg/day)	–	0.85 (0.20)	–
<i>Mean (SE)</i>			
Length of Stay(days)	7 (1.49)	32 (4.9)	<i>< 0.01</i>
<i>Mean (SE)</i>			

Note: SC = skin conductance; EDR = electrodermal response; μS = μ Siemens.