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Handling Effects in Moderate to Late Preterm Infants in Neonatal Intensive Care

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Handling Effects in Moderate to Late Preterm Infants in Neonatal Intensive Care

By

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Each person whose signature appears below certifies that this dissertation in his/her opinion is adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

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ABBREVIATIONS

NICU	Neonatal intensive care unit
SCP	Stressful care procedure
TDP	Tissue damaging procedure
NIRS	Near infrared spectroscopy
CINAHL	Cumulative index of nursing and allied health
PaO_2	Partial pressure of arterial oxygen
ADL	Activities of daily living
HR	Heart rate
RR	Respiratory rate
SpO_2	Systemic peripheral oxygen saturation
TcO_2	Transcutaneous oxygen tension
BP	Blood pressure
NIPS	Neonatal inventory pain scale
PIPP	Premature infant pain profile
PSG	Polysomnography
MABP	mean arterial blood pressure
ICP	Intracranial pressure
$TcSaO_2$	Transcutaneous oxygen saturation
$TcPcO_2$	Transcutaneous carbon dioxide
ACTH	Adrenocorticotropic hormone
VLGA	Very low gestation age
UA	Uric acid

MDA	malondialdehyde
GAS	General adaptation syndrome
AR	Alarm reaction
SR	Stage of resistance
SE	Stage of exhaustion
RAM	Roy’s adaptation model
STD	Synactive theory of development
IVH	Intraventricular hemorrhage
CITI	Collaborative institution for training initiative
SNAPPE II	Score of neonatal acute physiology- perinatal extension II
SNAP	Score of neonatal acute physiology
FiO_2	Fraction of inspired oxygen
ROC	Receiver operating characteristics
AUC	Area under ROC curve
SCP_S	Single stressful care procedures
SCP_C	Clustered stressful care procedure
Both_C	Clustered stressful care procedure with TDP
StO_2	Regional oxygen saturation
ANOVA	Analysis of variance
BW	Birthweight
Hb	Hemoglobin

ABSTRACT OF THE DISSERTATION

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by

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Doctor of Philosophy, Graduate Program in Nursing
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Dr. Ellen D'Errico, Chairperson

Providing a thriving environment to preterm infants receiving care in the neonatal intensive care unit is an ongoing area of interest to stakeholders interested in infant health. With advances in monitoring technology, there are new methods to assess the effects of care on preterm infants. Effects of neonatal handling have been analyzed in terms of physiological, behavioral, and pain responses. Further assessment of the effects of handling is needed to determine the impact, if any, on renal and cerebral regional oxygenation in moderate to late preterm infants (34-$36^{6/7}$ gestation). A conceptual model was developed based on pertinent theoretical frameworks that include General Adaption Syndrome, Roy's Adaptation Model, and the Synactive Theory of Development. This conceptual model identifies the preterm neonate, the influence of the environment, and the adaptation processes exhibited by the neonate. In this study a descriptive design using prospective observation was utilized and was conducted in the neonatal intensive care unit at a Magnet® designated acute care hospital. Moderate-late preterm infants were observed for a continuous maximum six-hour period. Moderate to late preterm infants were monitored by near-infrared spectroscopy and pulse oximetry. The handling events were logged in real time into a time-stamped procedure log in Microsoft® Excel and demographic information was collected. The goal of the study is to examine the effects of single versus ‘clustered’ or multiple handling procedures on regional (cerebral and renal) oxygenation, heart rate, and systemic oxygenation. The data was analyzed using analysis of variance (ANOVA), Kruskal Wallis, and multiple linear regression models were used in the statistical analysis. The results of this study were that reductions in cerebral and renal oxygen saturation were significantly greater in neonates exposed to clustered care procedures. Similar results were also found with systemic oxygen saturation and heart rate. The results suggest that care delivery to preterm neonates may need to be modified. However, despite the statistical significance of these results, the clinical significance is not yet known. A larger sample size as well as an examination of specific outcome measures (biochemical markers of hypoxia, weight gain, number of days in the hospital etc.) are required.

CHAPTER ONE

INTRODUCTION

As recently as the late 19th century, the chances of survival for a baby born prematurely was 5-15%. There were no institutions dedicated to the care of such infants, except for foundling homes, where abandoned infants were sent (Guha, 2007). In Europe, interest in the care of infants was brought about by the fear of depopulation and military vulnerability. This gave rise to movements, between the 1870s-1920s, propelling neonatal medicine with the primary focus of decreasing infant mortality (Guha, 2007).

During this time several pioneers emerged, including obstetrician Stephan Tarnier, who advanced the first incubator by adding a warming chamber similar to ones used for rearing poultry and thereby demonstrated the importance of thermoregulation (Guha, 2007; Lusky et al., 2005). In 1878, thermoregulation decreased infant deaths from 66% to 38% for those weighing under 2000 grams. Another obstetrician, Pierre-Constant Budin, expanded on Tarnier's work by putting into place principles and methods of neonatal medicine. A student of Budin's, Martin A. Couney, became the "incubator doctor", moving to the United States in 1896, becoming the first to offer specialty care to preterm infants (Lusky et al., 2005).

Although neonatal medicine was in the early stages of development, there was a lack of recognition of vital neonatal equipment. To raise awareness, Couney began to display the incubators with live preterm infants at exhibitions, commonly known as the "child hatchery" (Gartner & Gartner, 1992). Couney traveled with this exhibit to various fairs and other events until about the 1940s. Although he desired recognition in the scientific arena, his exhibition was perceived as merely a sideshow and was compared to five-legged mules, peep shows, wild animals, and clowns (Gartner & Gartner, 1992). The exhibits were staffed with rotating nurses and physicians who provided on-site care for the infants. It was unknown how premature these infants were. It was not until the 1950s that the use of birthweight to define prematurity was found to be inadequate in determining the risk of perinatal mortality and morbidity. In response, researchers began utilizing gestational age along with birth weight to assess mortality. These researchers determined that a longer gestation was associated with a decrease in mortality (Hughes et al., 2017).

In the United States, modern neonatology began in the 1960s. The opening of the first neonatal intensive care unit dedicated to the care and survival of premature infants opened in October 1963 at Yale-New Haven Hospital (Gluck, 1992). Prior to this, the care of infants was divided; sick newborns born at term age were sent to the pediatric units, well premature infants were cared for by the premature infant nurseries and sick premature infants were transferred to either the pediatric ward or placed in isolation and usually cared for by obstetric nurses (Gluck, 1992). The care of newborn infants was disjointed and medical personnel in charge of the care of these infants had limited knowledge about the premature population.

In 1960, Alexander Schaffer, a physician, was credited with coining the term *neonatology* (Philip, 2005). During the early 1960s a significant differentiation was made between infants born prematurely (<38 weeks' gestation) and those born at term gestation who were small due to intrauterine growth restriction. Prior to this any infant born less than 2500 grams was considered premature (Philip, 2005). Theoretical knowledge was quickly moving forward in this century, but clinical changes did not happen until the late 1960s to early 1970s (Philip, 2005).

The criteria used to determine prematurity have evolved. Distinctions in the severity of prematurity have historically been based on weight, length, and other general characteristics such as skin texture, undeveloped nails, cry, temperature stability, and history of expected birth (Hughes et al., 2017).

Currently, preterm birth is any infant born before 37 weeks' gestation. Preterm infants are categorized based on gestational age at birth: a) extremely preterm are born at or before 25 weeks' gestation, b) very preterm are born at less than 32 weeks' gestation, c) moderately preterm are born between 32-33 weeks' gestation, and d) late preterm are born between 34-36 $^{6/7}$ weeks' gestation (*Premature Birth*, 2017). In the United States, preterm births accounted for 10.1% of all births in 2021(Osteman et al., 2022). Of all preterm births, approximately 82% are moderate to late preterm (32-36 $^{6/7}$ weeks gestation) which is the target population for this study (Dolezel, 2019).

Problem

Moderate to late preterm infants are at high risk for morbidity due to their systemic immaturity and are at risk for respiratory distress, apnea, temperature instability, hypoglycemia, hyperbilirubinemia, and poor feeding (Engle et al., 2007; Huff et al., 2019). These morbid conditions require evaluation and monitoring, thus necessitating neonatal intensive care unit (NICU) hospitalization. The intensity of care is in part dependent on the gestational age at birth. Infants born at a younger gestation typically require high levels of intense surveillance and care. Many care components, including basic routine care during a NICU hospitalization can cause physiological distress in a premature infant, which can result in untoward effects.

During the hospitalization, infants are exposed to various necessary procedures and events due to the high care intensity needed for survival. These may be therapeutic measures such as intubation/extubation and intravenous line placement, routine caregiving activities such as bathing and feeding, or comfort measures such as containment and parental fondling. Many of the measures or procedures performed to care for preterm infants have the potential to disrupt an infant's physiologic stability. Although not all forms of handling or touch may be detrimental, studies have been conducted to assess infants' physiologic responses to or consequences of care. Research studies have measured heart and respiratory rates, oxygen saturation, transcutaneous oxygen tension, blood pressure, and cerebral tissue oxygenation (Levy et al., 2017; Limperopoulos et al., 2008; Norris et al., 1982). Studies found that commonly performed NICU caregiving procedures increased episodes of bradycardia, apnea, and/or oxygen desaturation leading to hypoxemia and/or hypoxia possibly contributing to detrimental premature infant outcomes such as intraventricular hemorrhage (Gross et al., 2021).

Preterm infants experience many necessary handling events needed to provide care. It is now known that these events may contribute to negative outcomes such as disruptions in growth, development, and long-term outcomes (Vinall et al., 2014). Given that NICU caregiving procedures are required and necessary, it is important to quantify the individual and cumulative effects of these procedures to develop evidence-based, gestational age-appropriate caregiving procedures that will decrease the adverse effects of prematurity and hospitalization. This is especially important to examine in moderate to late preterm infants. Because this group is often similar in size and weight as some full-term infants, they are often treated as developmentally mature and at low risk of morbidity, a notion which may lead to increased risk of harm (Engle et al., 2007).

A substantial body of literature exists regarding the effects of various types of handling on extremely and very preterm infants (Allinson et al., 2017; Cabral & Velloso, 2014; Hyttel-Sorensen et al., 2015). Less is known about the effects of handling in the moderate to late preterm population. Tissue or organ oxygen supply and demand, otherwise known as regional oxygenation, has not been studied widely in the moderate to late preterm population. Regional oxygenation has been used to assess various disease processes, like necrotizing enterocolitis, cardiac defects, and hypoxic-ischemic encephalopathy, to name a few; however, the literature is limited on its measurement associated with basic handling events (Evans & Rubarth, 2017; Howarth et al., 2020; van der Laan et al., 2016). Therefore, the purpose of this research study was to further assess the effects of handling events on regional oxygenation, specifically renal and cerebral oxygenation, in moderate to late preterm infants.

The measurement of renal regional oxygenation is important because the kidney reflects an early reduction in blood flow during hypoperfusion (Hanson et al., 2009). During states of shock and dehydration, the sympathetic nervous system is activated and redistributes blood flow away from renal, mesenteric, and splenic regions to preserve cerebral blood flow (Hanson et al., 2009; Tweddell et al., 2010). Additionally, ongoing research revealed preliminary data showing that renal regional oxygenation has the potential to decrease with delivery of care in extremely preterm infants (Mousselli et al., 2019) . Moreover, the study demonstrated that cerebral regional oxygenation tended to remain steady during most caregiving procedures in extremely preterm infants showing a brain injury sparing effect. This preliminary data is based on the extremely premature population. Therefore, in this study the moderate to late preterm population were assessed by the researcher.

Purpose

The purpose of this study is to describe the relationship between routine caregiving procedures and renal and cerebral regional oxygenation in hospitalized preterm infants at 32-36 $^{6/7}$ weeks gestational age (moderate to late preterm infants). For this study routine care giving procedures are further categorized as stressful care procedures and tissue-damaging procedures. Stressful care procedures (SCP) are those defined as direct or indirect procedures causing physical uneasiness or annoyance or that disrupt the balance between the neonate and its environment (e.g. taking of vital signs, diaper and position change) (Carbajal et al., 2008). Tissue damaging procedures (TDP) are those invading the neonate's bodily integrity, causing skin or mucosal injury (e.g. venipuncture, intravenous line placement, and tape removal) (Carbajal et al., 2008).

Research Questions

How is cerebral and renal oxygenation affected by routine procedures, monitored by near infrared spectroscopy (NIRS), in hospitalized moderate to late preterm infants (32-36 $^{6/7}$ weeks gestation)? How do participant characteristics affect cerebral and renal oxygenation in response to commonly performed routine procedures measured via NIRS in hospitalized moderate to late preterm infants?

Hypotheses

Hypothesis 1: Commonly performed NICU procedures have no impact on cerebral and renal oxygenation in preterm infants.

Hypothesis 2: Cerebral and/or renal oxygenation is not affected by gestational age, birth weight, hemoglobin, or risk of mortality during commonly performed routine procedures.

Aims

The aims of this research study are two-fold.

Aim 1: Describe the impact of single care procedures, clustered care procedures, and clustered care procedures with tissue damaging procedures on cerebral and renal oxygenation in moderate to late preterm infants as measured by NIRS.

Aim 2: Describe the relationship between cerebral and renal regional oxygenation and gestational age, birth weight, hemoglobin value, and risk of mortality value during commonly performed routine procedures in moderate to late preterm infants as measured by NIRS.

Theoretical Framework

The primary theoretical framework guiding this study is Heidelise Als synactive theory of development. This theory describes the infant's interaction with the environment through five interacting subsystems; the autonomic, motoric, state, attentional/interactive, and self-regulatory subsystems (Liaw et al., 2006). The synactive theory of development acknowledges that preterm infants are quicker to become stressed and show signs of distress due to physiologic instability. The focus of a premature infant in maintaining physiologic stability during times of distress is the foundational autonomic system (Peters, 2001). Additional frameworks guiding this study include Hans Selye's general adaption syndrome and Calista Roy’s adaptation model.

The premature infant's primary developmental task is to control, stabilize, and integrate autonomic functions such as heart rate, respiration, temperature control, digestion, and elimination, however, a premature infant struggles to accomplish this (Peters, 2001). Responses to stimuli can be assessed by measuring variables such as heart rate, respiratory rate, sleep/wake states, crying, and color changes (Als, 1982). Some displays of instability in this system can be seen as an apneic episode, tachycardic episodes, and color changes such as mottled or pale color. The synactive theory of development focuses on the threats to optimal growth and development presented by an infant’s immature system and the NICU care and environment (Peng et al., 2009).

Significance

Improvements in technology have increased the survivability of preterm infants, necessitating a closer look at the effects of care. Previous research has shown that the handling of these fragile, preterm infants is not without risk to their physiological well-being that may have long-term negative effects such as decreased verbal comprehension and working memory due to repeated stimulation of physiologically immature neurons, in addition to attention-deficit disorder, difficulties in social-emotional functioning and self-regulation (Kaye, 2016; Vinall et al., 2014). There are still many factors that are unknown about the physiological consequences of handling events in preterm infants. This study adds to the body of knowledge in neonatology and provides a guideline for the threshold of an infant's ability to maintain normal physiologic stability at the organ level, which may not be visually observable without special monitoring.

The outcomes of this study can influence the methods used to deliver necessary care to this vulnerable population. Policy and/or procedure change should be initiated from the results of this study, by reassessing how active handling episodes interspersed by rest periods could be optimized. Reassessing nurse-to-patient ratios during the first few days of life of a premature infant can ensure appropriate handling procedures are maintained. Additionally, the implementation of soothing interventions during prolonged handling events can potentially minimize undue stress and pain. The results of this study should prompt changes in the NICU by reevaluating staffing models and the utilization of non-licensed personnel such as patient care assistants to help in providing developmentally appropriate patient care. Finally, the significance of this study can have clinical implications and questions the adequacy of current standard monitoring procedures.

Chapters Overview

Chapter 2 is a review of the current literature on stress and infant handling in premature infants. Moreover, an assessment of theoretical frameworks is delineated. Theoretical frameworks reviewed include Calista Roy's Adaptation Model, Heidelise Als Theory of Synactive development, and Selye's Stress theory. In chapter three, the research plan is outlined, including sample, procedure, and descriptive and inferential statistical analysis. To conclude, analysis and results of data collected and a discussion inclusive of strengths and limitations, implications for practice, and recommendations for future research are provided.

CHAPTER TWO

LITERATURE REVIEW

The literature review and theoretical framework are fundamental to a research study, as they help identify knowledge gaps, and provide a rationale and guidance for the study endeavor. In the following section, a description of the literature review and the theoretical framework will be provided. The purpose of this literature review is to explore the current state of knowledge related to the care of preterm neonates and explore the relationship between neonatal handling and infant response.

Search Strategy

To identify literature for this study, the Cumulative Index of Nursing and Allied Health (CINAHL), Embase, Web of Science, and PubMed databases were searched. Initially, the search date range for available articles was 2013-2019, which was expanded due to a lack of supporting articles informing the study. The search strategy used by the researcher included the following keywords and mesh term combinations to identify relevant articles: *infant, newborn, preterm, premature, baby, prematurity, neonatal handling, routine caregiving, routine procedures, routine care procedures, routine-based interventions, neonatal care, caregiving procedures, caregiving events, nursery care events, nursery care, repositioning, diaper change, diapering, diaper changing, assessment, oral care, temperature measurement, temperature reading, feeding, effects, consequences, responses, impact, influence, outcomes, stressors, stressing, regional oxygenation, near infrared spectroscopy, NIRS, and cell respiration*. For this literature search, regional oxygenation and its related terms were used as it is the primary outcome variable of interest.

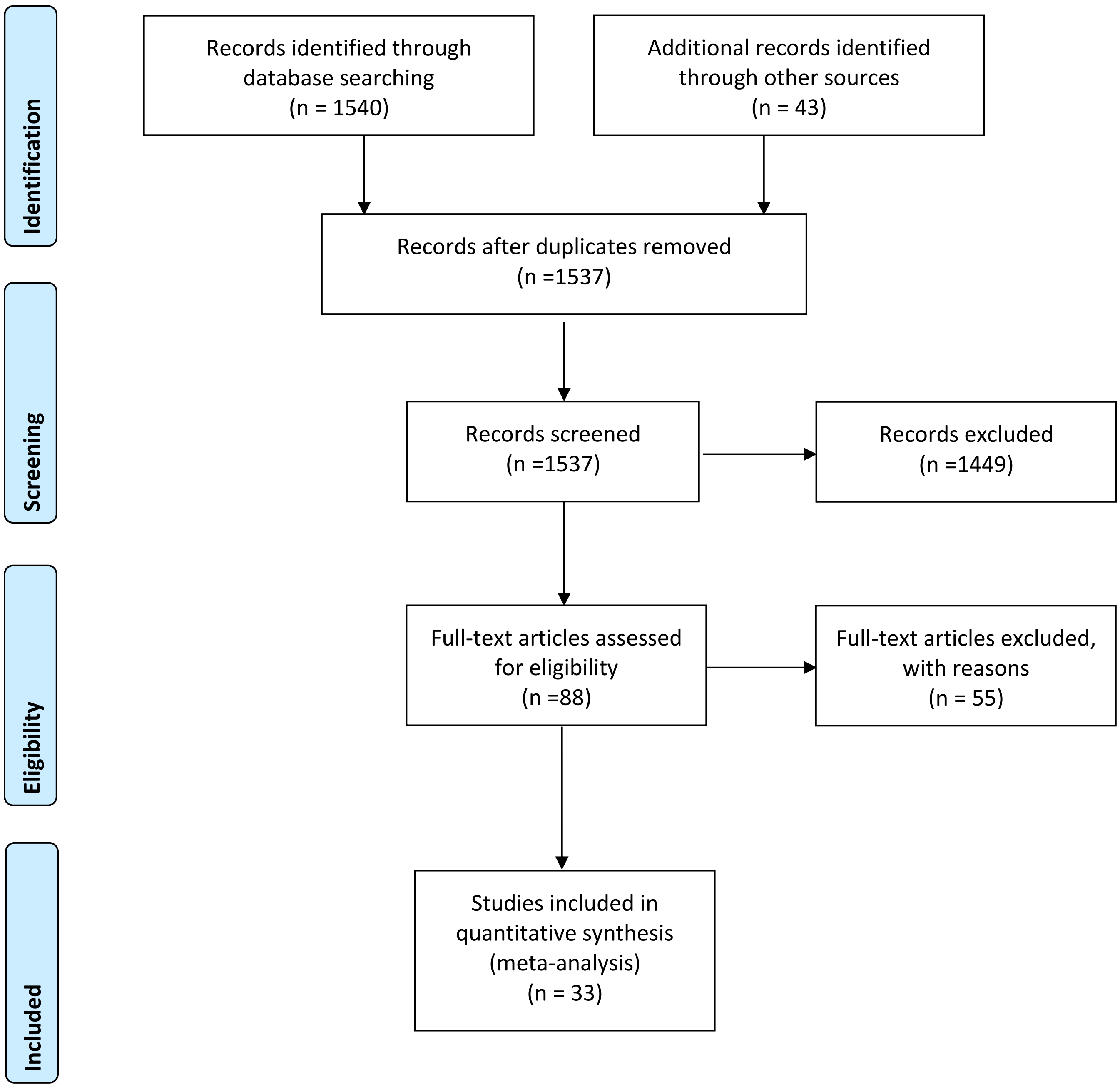
This initial search yielded 1456 articles. After reviewing the titles and skimming the available abstracts to determine relevance, 153 articles were identified. After applying delimiters (i.e., articles found in journals, full-text, and English language), eliminating duplicates, and further reviewing for relevance, 79 articles were selected for further review. These 79 articles were then further screened to determine if they met inclusion criteria for this review (i.e., original empirical research that measured the effects of neonatal handling on physiological and behavioral parameters of preterm neonates). Articles were eliminated if they were not reports of research (i.e., literature reviews, care guidelines), were disease-specific, or did not inform the study of interest. Additionally, several articles found were best utilized for background information. This process resulted in the identification of 29 articles reporting research, all of which used quantitative designs. It is important to note that some articles were identified through other sources, specifically from references of articles reviewed (Figure 1).

In addition to the initial literature review, an additional search was conducted to search for recently published resources. The date parameters for this additional search included the time frame of 2015-2020. In this review, the Embase and PubMed databases were searched utilizing the keywords and mesh terms of *neuroscience, premature, premature infant*, *infant*, *NICU, cerebral oxygenation, touch, tactile, stimulation, handling, tissue-damaging procedures, stressful care procedure, effects, consequences.* During this search, 84 articles were identified, of these, eight articles were removed, three as duplicates, and five were animal studies. The remaining 76 articles were reviewed for inclusion. After reviewing available abstracts to determine relevance and applying delimiters, nine articles were selected for full article review. After an analysis of the remaining articles, three were excluded, two because they were not reports of research (i.e. literature review, case report) and one did not inform the study of interest.

Two limitations of this literature review are noteworthy. First, there is a lack of abundant research specific to the moderate to late preterm population, which is the population of interest for this study. Second, much of the literature found focusing specifically on routine caregiving procedures, was older than five years, however, was still pertinent to the literature review.

Figure 1.

PRISMA flowchart of the strategy employed



Note. Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Literature Results

Stress is something experienced by all humans though it may be for different reasons and may be felt with varying intensities. Stress can be a catalyst for resilience, or it may lead to a detrimental propelling of a disease process. Hans Selye first identified stress and defined it as non-specific changes in the system or the non-specific response of the body to any demand for change (Tan & Yip, 2018; Viner, 1999). Premature infants thrust to extrauterine life suddenly experience a change in demand for survival causing various responses. Moreover, to further distinguish the inducing agent from the response, Selye coined the term ‘stressor’ to describe the agent causing the physiologic stress (Selye, 1965). In the premature infant, the stressors can be contained within the NICU environment in which premature infants’ attempt to survive and thrive. Stress in itself is not always something bad for the organism and the same agents do not always cause the same degree of stress in all organisms (Selye, 1950, 1965).

In his work Selye (1950) learned that though not all agents cause stress in organisms, when distress was encountered it manifests similarly. The manifestation of stress, according to Selye, is a triad of gastrointestinal ulceration, thymico-lymphatic atrophy, and adrenocortical ulceration. Preterm infants can have similar responses to stress which can manifest in physiological and/or behavioral ways. “Adaptability and resistance to stress are fundamental prerequisites for life, and every vital organ and function participates in them” (Selye, 1950, p. 1383).

Selye’s work proposes that organisms experience stress induced by stressors. The responses to stress may be manifested in similar ways however the stressor may be different and experienced with varying intensities. The care of preterm infants can be viewed the same way. Infants are exposed to a variety of stressful events in the NICU, however, not all infants become distressed by the same event. Infants are limited in the scope of their expression to stress. One way distress manifests is physiological. Despite the stressor, the manifestation of stress can be viewed similarly in all infants in the NICU.

The NICU environment has advanced in its practices and technology to improve mortality and to promote optimal patient outcomes among preterm infants. Historically, the emphasis on the advancements of neonatal care has been focused on disease processes and technological improvement, with minimal concern for the environment of care. In the 1970s changes started to emerge, as there was increased awareness that parents, families, and healthcare professionals are important components of neonatal care (Jorgensen, 2010). In the early 1980s Berry Brazelton and Heidelise Als, focused on the observation of infants and their interactions with their environment (Kaye, 2016). Brazelton focused on the development of an observation scale to assess infant cues and signs of distress and social interactions. This approach recognized the infant as a highly developed individual with identified strengths, adaptive responses, and vulnerabilities (Kaye, 2016).

Heidelise Als developed the synactive theory of infant development to provide a framework for understanding the behavior of premature infants (Als, 1986). She developed several programs intended to observe and assess preterm and at-risk newborn infants to individualize behaviorally based developmental care. These programs were also developed to educate and train staff to support parents in recognizing infant cues that indicate a sensitivity to care, such as hypertonicity, flaccidity, irritability, respiratory pauses, color changes, and hiccupping (Als, 1982; Kaye, 2016).

The potentially detrimental effects of the NICU environment, such as handling, noise, and light, propelled the emergence of developmental care practices in the 1980s. Developmental care practices are defined as actions that support normal development by reducing environmental stressors and actively supporting the behavior-organization (i.e. sleep and wake activity) while emphasizing an infant's response (Becker et al., 1997). The effects of the environment were observed through infant behaviors and autonomic responses.

The NICU has established care guidelines, many that emphasize developmental care procedures to soften or lessen the negative responses or consequences of care. Neonatal care guidelines vary among institutions, but most incorporate attention to noise, light, and touch methods. The responses that preterm infants display as a result of care have been researched focusing on physiological indicators, behavioral cues, and pain responses.

Some landmark studies have brought the effects of the handling to the forefront. A study by Speidel (1978) assessed the adverse effects of routine procedures on three preterm infants with the gestational ages of 30, 33, and 36 weeks. The researchers found even the most minor procedures can cause a sharp fall in arterial oxygen tension (PaO_2) in all three gestational ages. As one of their objectives, a study by Long et al. (1980) sought to define the relationship between oxygen abnormalities and handling. Their study demonstrated that 75% of the time spent in hypoxemia was associated with handling.

A study by Pohlman and Beardslee (1987) continued to study the handling of preterm infants. They found that the majority of direct contact experienced by infants was performed by the nurses. The most common direct contact that infants experienced was moderately intrusive procedures, for example, peripheral intravenous placement, measurement of vital signs, and physical assessment to name a few. Another study by Zahr and Balian (1995) studied the effects of routine caregiving and noise on preterm infant physiologic and behavioral responses. The main effect of nursing care alone was a decrease in oxygen saturation, indicating hypoxemia. A study by Limperopoulos et al. (2008) indicated that systemic and cerebral changes occurred during diaper change. These landmark studies indicate that nurses are challenged to provide necessary high-quality care that is therapeutic and supportive in the least stressful way possible.

Handling Events

Handling events are defined as physical manipulation of the infant for monitoring, therapeutic, or caregiving procedures (Peters, 1992). Becker et al. (1999) defined caregiving as an intervention repeated frequently throughout hospitalization. Recent literature categorizes routine caregiving procedures as stressful or noxious procedures and tissue-damaging or painful procedures (Ganguly et al., 2020). During hospitalization, infants undergo many handling events to be provided necessary care. These handling events may be invasive, non-invasive, direct, indirect, essential, non-essential, disruptive, or comforting. In this study, neonatal handling or neonatal handling events are equated with caregiving events, be they episodic or sequenced.

Table 1

Preterm Infant Handling Events in the NICU

Event	*Invasive*	*Non-invasive*	*Direct*	*Indirect*	*Essential*	*Non-essential*	*Disruptive*	*Comforting*
Heel lance	√		√		√		√	
Feeding tube insertion	√		√		√		√	
Bathing		√	√		√		√	
Position Change		√			√			√
Pick-up, Put down		√	√			√		√
Noise		√		√	√		√	
Diaper change		√	√		√			√
Suctioning	√		√		√		√	
Vital Signs-BP, Temp	√		√		√		√	
Electrode Changes		√	√		√			
Venipuncture	√		√		√		√	
Auscultation		√	√		√			
Intravenous Blood Collection	√		√		√		√	

Several studies have examined data to determine the types of neonatal caregivers. Pohlman and Beardslee (1987) revealed five caretakers: registered nurses, physicians, respiratory therapists, family members, and other personnel such as x-ray technicians, physical and occupational therapists, and laboratory technicians. They discovered that registered nurses are the primary providers producing 60% of direct contact. Most of these direct contacts were noted as being intrusive, all the while still providing most activities of daily living caregiving and a small amount of comfort care. In a study by Murdoch and Darlow (1984) nurses provided 48% of handling procedures, nurse care events were mainly associated with activities of daily living. In this study, 17% of handling procedures were designated as monitoring (i.e., placement, adjustment, or removing of monitoring devices) and were also likely to be performed by nurses. A study conducted by Cameron et al. (2007) found that nurses performed, on average, more handling events compared to medical staff, parents and technicians during their 24-hour observation period, though the study did not report a specified amount of handling. Lastly, a study by Werner and Conway (1990) identified that nurses provide the largest amount of direct and indirect contact, 87.8% and 79.8% respectively. It is evident by the literature that nurses are the primary caregivers of preterm neonates in the NICU and therefore, can impact patient responses.

Types of Handling Events

The synopsis of the literature classifies handling events in various ways depending on its severity of disruption or its purpose. Some handling events are medically necessary, while others are activities of daily living (ADL) or for comfort. Godarzi et al. (2018) identified handling episodes as those that are for care, therapeutic, and supportive measures. Likewise, Pohlman and Beardslee (1987) classified handling procedures as treatment-oriented, activities of daily living, and comforting touch. They further delineate the treatment-oriented procedures as highly, moderately, or minimally intrusive. Werner and Conway (1990) used the categories established by Pohlman and Beardslee and added incidental contacts, such as sound.

Murdoch and Darlow (1984), also categorized the handling that infants are subject to such as monitoring, investigational/therapeutic, nursing, and parental. Liaw et al. (2012) distinguished patterns of caregiving as; social interaction, routine caregiving, and intrusive caregiving. Brandon et al. (1999) defined the nurse caregiving context with three categories; contact care, routine care, and procedural care. Maki et al. (2017)

grouped handling into three categories; therapeutic/diagnostic, hygiene/comfort, and feeding, based on their findings. They also identified direct handling as contact with the infant's skin or any device attached and indirect/ambient handling as manipulation of anything in the infant's microenvironment.

A study by Wang et al. (2020) identified 27 procedures that they deemed painful and divided them into five categories; basic nursing care, respiratory care, administration, blood sampling, and auxiliary examination. Other literature categorized the intensity of painful procedures as; extremely severe, severe, moderate, mild to moderate, and mild (Laudiano-Dray et al., 2020). Cignacco et al. (2009) categorized routine procedures as very painful, painful, and non-painful. Lastly, a study by Orovec et al. (2019) simplified painful procedures and categorized them as tissue-breaking procedures and non-tissue-breaking procedures. It is important to note that despite categorizing procedures experiences by infants, they can exhibit similar physiologic stress responses to invasive versus non-invasive procedures (Zeiner et al., 2016).

The literature shows a variety of ways to define the care that infants experience. For this study, the most appropriate definition of neonatal handling events are defined as those events providing direct contact with the infant for therapeutic purposes, activities of daily living, and comfort care. Neonatal handling provided for therapeutic purposes can be further analyzed for its intrusiveness.

Activities of Daily Living

When assessing the generality of neonatal handling, activities of daily living (ADLs) are at the forefront of the care performed most often. The literature utilizes many care activities when describing activities of daily living. For example, Pohlman and

Beardslee (1987) include feeding, diaper changing, dressing/wrapping or undressing/unwrapping, supporting of body, and adjusting position as activities of daily living. According to Medoff-Cooper (1988), routine care includes turning, changing the diaper and linens, bathing, vital signs measurement, endotracheal suctioning, and feeding. Godarzi et al. (2018) combine care and monitoring as one category which includes changing sheets, diaper change, hygiene, and comfort.

Brandon et al. (1999) refer to activities of daily living as routine care and include feeding (bottle or gavage), diaper changing, or bathing. Murdoch and Darlow (1984) used the category title of ‘nursing’ to refer to infant ADLs and gives an example of cares such as position change, diaper change, and eye care. Maki et al. (2017) has the category of hygiene/comfort but does not elaborate or give examples of activities under this category. Liaw et al. (2012) describe routine caregiving with tasks such as measuring vital signs, diaper or clothes change, bathing, weighing, mouth care, position change, auscultation, and x-ray, to name a few. A study by Wang et al. (2020) identified basic nursing care, which includes diaper change, weight check, adhesive removal, and gastric tube removal and insertion. Hill et al. (2005) explained routine care as assessment, vital signs, temperature check, feedings, abdominal girth measurement, and diaper change. Lastly, a study by Levy et al. (2017) categorized diaper change, feeding, or comforting as routine infant care.

The literature identifies many ways in which basic nursing care can be categorized. For this study, the term activities of daily living are adopted to refer to neonatal handling events such as, but not limited to, dressing/undressing, diaper change, repositioning, oral care, eye care, linen change, and feeding. This category of handling events is expanded to incorporate any observed event related to hygiene or personal care.

Therapeutic Interventions

Therapeutic interventions are defined as activities needed to support life and are categorized as highly, moderately, or minimally intrusive (Pohlman & Beardslee, 1987). Another way of describing therapeutic interventions may be as treatment-orientated procedures as expressed by Pohlman and Beardslee (1987). The highly intrusive procedures are suctioning, intubation/extubation, line placement, suture removal, and skin puncture for example, while moderately intrusive procedures are activities such as measurements, physical examination, tape application and removal, chest physiotherapy, and performance of range of motion of extremities. They further illustrate minimally intrusive procedures as cleansing or prepping the skin, administration of extravascular medication, irrigation/aspiration of nasogastric tubes, intravenous lines, and arterial lines. These descriptions are also supported and utilized in subsequent research by Werner and Conway (1990).

Liaw et al. (2012) categorize therapeutic interventions under the name of intrusive caregiving. They designated procedures like suctioning, skin puncture, line removal, injections, heel-stick, eye examination, intubation, tape removal, lumbar puncture, chest tube placement, and insertion of a gastric tube, to name a few, under this category. The study by Godarzi et al. (2018), identified therapeutic caregiving, however, only gave an example of two procedures, drug and fluid administration and medical examination. Murdoch and Darlow (1984) use two terms synonymously, investigational/therapeutic care, and provided examples such as umbilical artery catheter placement, endotracheal tube suctioning, and injections. Maki et al. (2017) also used two terms to describe this category, therapeutic/diagnostic. For this category, they only give one example, which is the administration of drugs via a gastric tube, as it was the predominant procedure noted in their study.

Wang et al. (2020), who separated painful procedures into categories, divided them into the categories of therapeutic care, respiratory care (suctioning and chest physiotherapy), administration (intravenous infusion, dressing change, and injections), blood sampling (heel stick and blood draw), and auxiliary examination (ultrasound, lumbar puncture, and eye exams). Lastly, Levy et al. (2017) identified procedures, such as vital sign measurements, medication administration, and physical examination, as medical interventions.

The literature is varied in its description and categorization of invasive neonatal handling events. This study will utilize the term therapeutic care procedures to identify neonatal handling events with the focus of providing medically necessary care. The observed events will then be categorized by their level of invasiveness; minimally, moderately, or highly invasive. Some events included, but not limited to, are potentially tissue-damaging procedures or those that puncture the skin, x-ray, tape removing, etc.

Comfort Care

Many terms have been used to describe the act of comforting an infant. Pohlman and Beardslee (1987) describe comforting touch as contact experienced by the infant while being held or smoothed. Werner and Conway (1990) refer to comforting as comforting measures and describe it as contact for an infant's physical and emotional gratification, for example, gentle touch and containment. Although Godarzi et al. (2018)

refer to this type of touch as supportive measures, they define it as parental fondling, Kangaroo care (held on bare chest), or breastfeeding. Liaw et al. (2012) refer to this type of care as social interaction and describe it as pacifier use, gentle touch, Kangaroo care, containment, feeding, and position change. Murdoch and Darlow (1984), use the term parental to describe comforting touch. Maki et al. (2017) combine hygiene and comfort, noting position change as the most prominent handling procedure in this category. Lastly, Brandon et al. (1999) call this type of care contact care and describe it as touching, holding, or carrying.

Although the literature is varied in what is considered comfort care, the notion is important to the care of neonates. For this study, the definition of comfort care by Werner and Conway (1990), where it is defined as contact for an infant’s physical and emotional gratification is utilized. Handling events included in this category will be containment, gentle touch, Kangaroo care, holding, or postural care. Events may be added if observed during the study period.

Other Forms of Handling

Several studies did not classify handling episodes into separate categories but instead identified individual types of handling events. For example, a study by Peters (1992) examined individual responses to obtaining vital signs, change in position, perineal hygiene, removal of monitoring probes, radiographic examinations, weighing, adhesive removal, and suctioning. Likewise, a study by Limperopoulos et al. (2008) analyzed responses to minor manipulations (e.g. auscultation, involving tactile stimulation), diaper changes, endotracheal suctioning, endotracheal repositioning, and complex events (e.g. 2 or more events in 10 minutes) independently. Cameron et al.

(2007) also assessed individual procedures. The most frequently observed procedures were repositioning, suction, diaper change, eye care, repositioning of blood pressure cuff, and stroking. Thomas et al. (2008) identified individual caregiving acts as measuring vital signs, diaper change, feeding, positioning, stroking, sensory stimulation, pacifier, and medication procedures.

A concept familiar to the NICU environment is cluster care. Cluster care is described as a string of caregiving events that are grouped (Thomas et al., 2008). Cluster care is used to describe the completion of tasks or caregiving in one time period to then allow the infant to have prolonged uninterrupted rest time. Despite the good intentions of cluster care, not all infants may be capable of handling this intense amount of touch all at once. This study has examined the neonatal handling events and observed how clustered care affected moderate to late preterm infants in cerebral and renal oxygenation.

Outcomes of Handling

Studies have measured physiological, behavioral, pain parameters, or a combination of these when assessing for infant responses to handling events (Danford et al., 1983; Hill et al., 2005; Wang et al., 2020; Zahr & Balian, 1995). Although the variables of interest here are the physiologic responses, the literature also revealed a vast amount of research conducted to assess behavioral indicators of stress associated with neonatal handling. Physiologic indicators include the measure of heart rate (HR), respiratory rate (RR), oxygen saturation (SpO_2), transcutaneous oxygen tension (TcO_2), blood pressure (BP), and cerebral tissue oxygenation. Prominent behavioral indicators of stress that have been studied are sleep-wake cycles and state of arousal. Motor activity has also been noted in various behavior states. An additional indicator that has been studied is pain responses. Pain scoring tools for neonates typically use a combination of physiologic, motoric, and behavioral cues to determine pain scores (Cameron et al., 2007; Donia & Tolba, 2016; Hill et al., 2005). In the following studies, on average, the infants were ‘very preterm’ which signifies a gestational age of less than 32 weeks. The exception was a study by Donia and Tolba (2016), whose participants had a mean gestational age of 34.4 weeks (late preterm).

Pain Responses

Several studies have focused on pain responses concerning handling in preterm infants. Different pain scales are used to evaluate if an infant is experiencing pain as a result of care and/or disease processes. A study by Cameron et al. (2007) utilized the Neonatal Inventory Pain Scale (NIPS) which assesses six factors; facial expression, cry, breathing patterns, arm movement, leg movement, and state of arousal. They utilized this pain scale to assess acute pain before, during, or after caregiving procedures, a lower score indicating less pain or stress. This study found that NIPS was significantly higher after handling than before, and handling episodes caused an increase in the pain score. This study, however, found that infants’ pain responses were not affected by a specific type of handling but rather handling in general (Cameron et al., 2007).

A research study utilizing the NIPS pain scale by Donia and Tolba (2016) sought to evaluate the short term effects of early procedural pain on subsequent responses. This study had two groups: group 1 was composed of infants exposed to painful procedures, and group 2 was composed of infants who had not been exposed to any painful procedures. As a whole, using the NIPS pain scale, they found behavioral and physiologic changes in response to a painful heel stick which produced a significant decrease in pain score after the procedure than during. Additionally, when comparing these groups, the researchers found behavioral pain responses were blunted in group 1, where they had lower scores during and after the heel stick procedure (Donia & Tolba, 2016).

A study by Hill et al. (2005) utilized the Premature Infant Pain Profile (PIPP) pain scale under two conditions of providing care to premature infants. These two conditions include, 1) the utilization of a second caregiver supporting the infant in a tucked position, and 2) no tucking. PIPP used measures of physiological activity (heart rate and oxygen saturation), behavioral state (wake, asleep), and motor indicators specifically facial expressions (brow bulge, eye squeeze, and nasolabial furrow). These researchers found that by incorporating facilitated tucking into routine care, infant stress levels were reduced (Hill et al., 2005). Likewise, Ganguly et al. (2020) utilized the PIPP pain scale to assess pain associated with specific routine procedures. These researchers found that blood sampling, heel prick, suction, and weight measurement produced the highest pain scores. They also noted that some routine non-stressful procedures like abdominal girth, temperature measurement, and weight measurement also produced high pain scores. Most literature evaluating pain does so to examine the infant responses to painful stimuli, not infant handling specifically.

Behavioral Responses

Behavioral responses are, in part, those that refer to an infant's state of arousal and/or an infant's sleep cycle. Sleep and awake arousal states may also be accompanied by different levels of motor activity. Sleep cycles play an important role in growth and development, particularly in the brain cortex and sensory nerves (Godarzi et al., 2018).

Godarzi et al. (2018) studied a sample size of 15 preterm infants and found that supportive handling (e.g. parent fondling, Kangaroo care, feeding) increased the amount of active and quiet sleep. Their findings also suggest that a high frequency of handling, particularly medical and nursing care, decreased the amount of sleep. Zahr and Balian (1995) found that 78% of infants changed their behavior state in response to nursing interventions and noise, changing from regular sleep to fussy/crying state. Brandon et al. (1999) also studied the effects of handling on behavioral state organization. They found that nurse caregiving appeared to decrease sleep and increase awake time.

Liaw et al. (2012) studied the effects of different stress-inducing caregiving activities on infants' state of arousal. They found that the occurrence of infants' wake and fussy or crying states increased with greater amounts of intrusive caregiving. Lastly, Levy et al. (2017) used polysomnography (PSG) to determine sleep/wake cycles. PSG monitoring includes brain wave activity, several respiratory components (including but not limited to oxygen saturation, oronasal airflow), and electrocardiogram (i.e., heart rate) (Levy et al., 2017). These researchers found that hands-on care resulted in arousal and awakening in 57% of all contact episodes while the infant was initially sleeping. Additionally, handling followed by hypopnea (decrease in nasal pressure followed by desaturation) was more likely to occur during the active sleep state (Levy et al., 2017). This suggests that avoiding handling during active sleep may contribute to a clinically significant reduction in hypopneas and apneas.

Physiologic Responses

Premature infants can display distress by changes in heart rate, respiratory rate, and oxygenation. These physiologic responses are those that are produced by the autonomic system. These responses can display as increases or decreases in parameter levels or a significant change from baseline as measured through monitoring devices attached to the baby.

Zahr and Balian (1995) studied 55 infants on the effects of a combination of noise and nursing interventions. They found that nursing interventions alone caused a drop in SaO_2 in 18% of infants, an acute increase in heart rate in 16% of infants and an increase is respiratory rate in 12% of infants. Omar et al. (1985) assessed blood pressure among 22 neonates in response to care procedures. Researchers found blood pressure to be complex and determined; that decreases in blood pressure due to care procedures was seen in infants who were the most ill. Conversely, rises in BP were seen in infants who were less ill.

A study by Long et al. (1980) measured transcutaneous oxygen ($TcPo_2$) in 45 infants to define a possible relationship between handling and oxygenation. They discovered that when personnel handling the infant are aware of $TcPo_2$ readings, infants experience fewer undesirable events (less time out of normal range) and fewer falls in $TcPo_2$. They also found that 75% of the hypoxemia experienced by the infant is associated with handling. A study by (Norris et al., 1982), examined the effects of three specific care procedures on 25 infants. They found that during three procedures; suctioning (nasal or endotracheal), repositioning, and heel-stick, that infants experience a significant decrease in $TcPo_2$ from baseline in suctioning and repositioning.

Murdoch and Darlow (1984) studied five infants and the effects of handling on undesirable events which are described as hypoxemia and hyperoxemia (measured by $TcPo_2$), bradycardic episodes, or apneic episode. They found that the endotracheal suctioning was the procedure most associated with an undesirable event, mainly hypoxemia and occasional bradycardia and apnea. Additionally, they noted that undesirable events also occurred with peripheral blood sampling, capillary blood sampling, intubation, chest x-ray, position change, blood pressure cuff placement, axillary temperature measurement, and diaper changes.

Peters (1992) studied ten premature infants and their responses to handling. The author measured changes from baseline in heart rate, mean arterial blood pressure (MABP), intracranial pressure (ICP), transcutaneous oxygen tension ($TcPo_2$), transcutaneous oxygen saturation ($TcSao_2$), and transcutaneous carbon dioxide ($TcPCo_2$). The researchers conducting the study found that neonatal care continues to be associated with periods of hypoxia, hyperoxia, and increased ICP when responding to handling events. These similar results were seen in Danford et al. (1983) where, 123 $TcPo_2$ recordings were captured on 36 infants, their data indicated that care-oriented procedures can result in a fall in $TcPo_2$. The most frequent immediate effect was in seen in chest x-ray procedures, where a decrease was noted in all infants. Most procedures tested noted an immediate fall in $TcPo_2$ in approximately 40-70% of infants, while 29% of infants experienced a decrease with a diaper change.

Evans (1991) studied the association of caregiving and hypoxemia among 13 preterm infants. The author found that the most frequent caregiving activities were suctioning, repositioning, and blood sampling for blood gas analysis. Additionally, suctioning and repositioning had the biggest decrease in $TcPo_2$.

A study that is inconsistent with the majority of research reviewed concluded that touch or tactile stimuli (medical and social) did not significantly, by itself, precipitate a bradycardic event or lower transcutaneous oxygenation (Gorski et al., 1990). In this study, medical and social touch was not described, however, the results associated tracheal suctioning with some bradycardic episodes. This study which had 37 days of observations in 18 infants, suggests the activation of a compensatory mechanism which increases its heart rate at the time of impending autonomic instability. A subsequent bradycardic effect could then result from an infant's inability to sustain this mechanism. In this study, the bradycardic events that were captured were deemed not statistically significant. Additionally, this study argues that touch itself does not lower oxygenation, which subsequently lowers heart rate, but rather may increase its effects in an already physiologically compromised infant (Gorski et al., 1990).

Levy et al. (2017) study of 25 infants assessed sleep/wake cycles and handling utilizing polysomnography (which includes a respiratory component). They found that handling was frequently followed by a respiratory event (i.e., hypopnea, apnea, desaturation) within 60 seconds. Additionally, the researchers found that clinical care (i.e., vital sign measurement, medication administration, diaper change, feeding, etc.), as opposed to technical care (adjustments for PSG equipment), was more likely to result in a decrease in oxygen saturation.

Lastly, two studies looking at the effects of a neurobehavioral assessment on the physiologic variable in preterm infants were reviewed. Sweeney and Blackburn (2013) studied the impact of neurobehavioral assessment on heart rate in 72 infants. These researchers compared heart rate during portions of the neurobehavioral assessment that required handling (including but not limited to lifting, pulling up to sit, and stepping reflex) and portions of the assessment that require little to no handling (i.e., movement observation). They found that infants had a higher heart rate, blood pressure, and a decreased peripheral oxygenation when a neurobehavioral assessment was done with required handling. Likewise, a study by Allinson et al. (2017) with 34 participants also found that neurobehavioral assessment that requires handling was associated with an increased incidence of tachycardia.

Biomarker Responses

During the literature review, a shift in the literature became evident over the last 15 years. Literature has moved from assessing primary physiologic responses, like heart rate, blood pressure, and oxygen saturation, in the ’80s and ’90s to examining stress biomarkers like cortisol, xanthine, hypoxanthine, and uric acid concerning routine handling and painful procedures. Studies are examining the effects of stress, including routine caregiving.

A study of 37 infants by Peng et al. (2014) examined energy expenditure based on heart rate as a base for the energy expenditure calculation and found a positive relationship between nursing interventions and increased energy expenditure. Another study assessed adrenocorticotropic hormone (ACTH) and cortisol in response to cluster care (Holsti et al., 2007). This study of 90 infants found that very low gestation age (VLGA) infants showed a strong positive correlation between clustered care and ACTH and cortisol production. An article by Slater et al. (2012), assessed procedural pain and oxidative stress. In this study, of 80 infants, oxidative stress was quantified by assessing uric acid (UA), malondialdehyde (MDA) concentrations. This research found an increase in MDA in preterm neonates exposed to a painful procedure when compared to infants who were not exposed to one.

Physiologic responses are prominent assessment criterion among studies analyzing the effects of care. This literature review has revealed that despite the type of handling event, a preterm infant can experience fluctuations in physiologic stability.

Other Relevant Literature

As the primary outcome variable for this study, literature for regional oxygenation and neonatal handling was gathered. Regional oxygenation or end-organ oxygen supply and demand is measured by non-invasive near infrared spectroscopy (NIRS) (Korcek et al., 2017). NIRS has been used extensively since it was developed in 1977 by F.F. Jobsis to measure deep tissue oxygenation in relation to disease processes (Jobsis, 1977). NIRS can estimate the oxygenation levels in various regions like the brain, muscles, kidney, and liver (Zienhenberger et al., 2016). To further explain the use of NIRS, according to Sood et al. (2015) pulse oximetry measures oxygen supply to tissue via arterial oxygen saturation, whereas NIRS regional oxygenation reflects a balance of tissue oxygen supply and demand. The use of NIRS in neonates has been researched and used to detect hypoxia in certain disease processes like cardiac defects, hypoxic-ischemic encephalopathy, patent ductus arteriosus, and necrotizing enterocolitis (Sood et al., 2015).

Regional Oxygenation

The literature revealed that cerebral regional oxygenation is most prominent when studied in response to neonatal handling. A study by Gagnon et al. (1999) revealed that a variety of handling events having physiologic effects measured by NIRS, like cerebral blood flow may not be seen clinically. This study found that NIRS can detect cerebral regional oxygenation changes associated with common stimuli that caregivers may have perceived as irrelevant. Demirel et al. (2012) studied the effects of position changes on cerebral and mesenteric tissue oxygenation. In this study, the mesenteric measurement was obtained by placing a probe on the abdomen just below the umbilicus. No significant changes in cerebral or mesenteric oxygenation with position change were found. Limperopoulos et al. (2008) utilized NIRS to detect cerebral hemodynamic changes during minor manipulations, diaper change, endotracheal tube suctioning and repositioning, and complex events (2 or more occurring in a 10-minute period). They found that circulatory changes in responses to handling were significantly greater than those that occurred during rest.

Additional uses of NIRS in premature infant studies have been seen in various descriptive studies. An example of these studies includes the use of NIRS in assessing regional oxygenation in infants receiving treatment for patent ductus arteriosus (Arman et al., 2020; Bhatt et al., 2012; van der Laan et al., 2016), infants who are diagnosed with intrauterine growth restriction (Terstappen et al., 2018), those who developed acute kidney injury (Bonsante et al., 2019), infants exposed to intrauterine maternal antihypertensive medication (Richter et al., 2016) and those undergoing gastrostomy tube placement (Muñoz et al., 2020).

Summary of Literature Review

Although the handling of neonates, specifically extremely to very preterm in the NICU has been researched extensively concerning physiologic and behavior responses, there remain some unanswered questions. We know that handling events affect physiologic parameters such as heart rate, oxygen saturation, oxygen tension, respiratory rate, in addition to behavior states, like sleep-wake cycles and states of arousal. The literature has established that heart rate may increase or decrease in responses to handling. Oxygen saturation and oxygen tension are affected by significant changes from baseline. The respiratory rate can also increase or decrease due to handling. Physiologic trends associated with caregiving vary and are not often observable, as with the measurement of regional oxygenation.

Despite what is known, more needs to be learned about how handling affects deep tissue perfusion or rather tissue supply and demand. Studies looking at the effects of neonatal handling on regional oxygenation are minimal and are focused on very premature infants. This review of the literature reveals a gap. First, the study of moderate to late preterm infants was not exclusive, but rather this population is often included in neonatal studies. Most exclusive studies are focused on very premature infants. Second, research assessing the effects of handling on regional oxygenation, specifically renal regional oxygenation is minimal.

Overall, the quality of the majority of the literature was sound. Procedures and methodology were clearly defined. A substantial amount of literature identified physiologic and behavioral effects of infant handling; however, a lot of the literature identified was older and changed over time. A shift occurred in the literature from assessing essential physiologic variables (heart rate, respiratory rate, oxygen saturation, etc.) to biomarkers of stress like ACTH, cortisol, and oxidative stress variables (uric acid, xanthine, and hypoxanthine, etc.). Likewise, as technologies advance and their use in neonates become mainstream, there are additional methods in which we can learn what the effects of handling may be.

The majority of the literature identified measured the effects of neonatal handling on infants 25-32 weeks' gestation. There is minimal research solely focused on the moderate to late preterm population (32-36 weeks' gestation). Additional research is needed in this area to have a more complete picture of the effects of handling and its long-term clinical significance. Assessing renal and cerebral oxygenation in the moderate to late preterm population can provide a new perspective in the care of premature infants.

Theoretical Framework

Theories are developed to assist in clarifying the relationships existing within nursing phenomena and are the foundation of scholarly inquiry. A theoretical framework provides a way to look at phenomena by organizing concepts, making inferences about how the concepts are related, and ultimately providing plausible explanations that help us better understand a topic of interest (Meleis, 2018). A theoretical framework is an imperative component that sets a foundation for guiding research and developing nursing knowledge.

The topic of interest for this study is the assessment of moderate to late preterm infants' response to nurse handling. How infants respond to varying types of caregiving activities, from activities of daily living, like diaper and position change, to medically necessary activities, like assessment and vital sign measurement was observed. The infants observed were in the moderate to late preterm population, 32-$36^{6/7}$ weeks' gestation. The primary variable of interest in response to handling was the physiologic response of regional oxygenation of the brain and the kidney. The theories reviewed for this study have the basis to support this research study.

Review of Relevant Theories

In reviewing relevant theories for the topic of interest, related theories fall into the following categories - stress and stressors, neonatal handling practices, and behavioral organization. For example, the stress and stressor-based theories focus on an infant's response and adaptation to external factors, the neonatal handling practice-based theories focus on procedures or methods of handling infants, and the behavioral organization-based theories focus on behavioral responses elicited by infants. The theories chosen to support this study are the following: General Adaptation Syndrome (Selye, 1950), Roy's Adaptation Model (Roy, 1976), and the Synactive Theory of Development (Als, 1986).

As the utilization of these theories is applied to this particular research study it is important to acknowledge that not all events produce an immediate negative stress response. An individual can limit the detrimental effects of a stressor to build resilience (Anisman, 2015). Although neonates may be vulnerable due to their pathologic condition of prematurity, they can build resilience through many predisposing factors such as genetics and their defense system (Anisman, 2015). These predisposing factors in conjunction with the neonate's experience in the NICU environment can guide their response to stimuli.

Stress Theory and General Adaptation Syndrome

A middle-range theory developed by Hans Selye is the Stress Theory and the General Adaptation Syndrome (GAS). In the 1930s, Selye used the term stress to describe the stimuli causing non-specific reactions. During this time there was confusion and the term stress was used interchangeably to describe both the noxious stimuli and the non-specific response ("Diseases of adaptation," 2010). Later Selye, coined the term “stressor” to describe the stimuli and named the non-specific signs of damage about the stimuli with the ‘general adaptation syndrome’ (Viner, 1999). In the 1940s, Selye established the definition of stress as the sum of all non-specifically induced changes in a biological system or the non-specific response of the body to any demand for change. ("Remembering Hans Selye," 2010; Viner, 1999).

The general adaptation syndrome is composed of 3 stages that are closely interrelated adaptive reactions to a non-specific stimulus (Selye, 1950). The ‘alarm reaction’ (AR), the ‘stage of resistance’ (SR), and the ‘stage of exhaustion’ (SE) are the stages encompassing the general adaptation syndrome and describe the way an organism adapts and responds to the environment (Viner, 1999). Selye proposes that most stress responses manifest in similar common ways (tissue catabolism, hypoglycemia, gastro-intestinal erosion, and activation of the adrenal cortex to name a few) (Selye, 1950). Most things that cause stress have the potential to endanger life unless they are met with adequate adaptive responses (Selye, 1950).

The first stage in the general adaptation syndrome sequence is the ‘alarm reaction’ stage. In this stage, the body’s defenses are initiated in a rapid response to ‘biologic stress’, which result in the initiation of the sympathetic branch of the autonomic nervous system resulting in an increased heart rate, blood pressure, and respirations, as well as other adrenal and sympathetic nervous system activities ("Diseases of adaptation," 2010). This response is also known as the flight or fight response (Burgess, 2017).

If the stressor continues the organism proceeds to the second stage, the stage of resistance. In this phase, the manifestations initiated in the ‘alarm reaction’ disappear or become reversed with the initiation of the parasympathetic nervous system which attempts to return the body to hemostasis (Burgess, 2017). By reducing the amount of cortisol produced the heart rate and blood pressure will begin to normalize. If the stress-producing event terminates during this stage the body will return to normal (Burgess, 2017).

If the stressful event continues, the stress hormones continue production and the organism enters the 'stage of exhaustion' phase (Selye, 1951). In this phase, the organism may deplete its energy resources by continually attempting to recover from the alarm reaction (Burgess, 2017). At this point, the body is not able to continue the flight or fight response. According to Selye (1951), this occurs because of the finite amount of adaptive energy that is largely dependent on genetic factors.

In the neonate, the AR stage can be seen as an increase in autonomic functions that respond to stimuli, such as increased heart rate, blood pressure, and respiration. In the stage of resistance, it would appear as though the neonate has recovered from the initial alarm response; therefore, it is possible that the stimuli would continue to occur as it would give the impression that the neonate is tolerating the stimuli. Lastly, in the stage of exhaustion, the infant could exhibit signs of decompensation such as a decrease in heart rate, blood pressure, and respirations. In considering this theory's applicability to this study, some components could be adapted to provide a foundation to the study of interest.

Two additional prominent theoretical frameworks resonating with an infant's response to handling are Roy's Adaptation Model (RAM), and the Synactive Theory of Development (STD). These frameworks have components that can be adapted to where a focus emerges on the physiologic responses exhibited by the preterm infant to the environment and the handling infants' experience in the NICU. The adaptation of these theories forms a foundation for an analysis of the ability or inability of an infant to be able to maintain physiologic stability when in the NICU environment.

Roy's Adaptation Model

Roy's Adaptation Model (RAM) is a middle-range theory developed by Sister Callista Roy, and defines the recipient of nursing care, the goal of nursing, and nursing activities (Roy, 1976). Utilizing the four metaparadigms of nursing, Roy's Adaptation Model views the person, who is the recipient of nursing care as one with modes of adapting to the changing environment. RAM is explained through the metaparadigms of nursing.

The first concept of RAM is a human being or person who is seen as the adaptive system (Andrews & Roy, 1986). This adaptive system receives inputs and processes them to produce a response or an output. Roy identified coping mechanisms for dealing with these inputs into two subsystems: the regulator subsystem or the cognate subsystem. The regulator subsystem is focused on the autonomic bodily responses and the cognate subsystem responds through cognitive-emotional channels (Rogers & Keller, 2009). The behaviors observed within these subsystems are categorized into four adaptive modes; physiologic mode, self-concept mode, role function mode, or interdependence mode (Andrews & Roy, 1986). Applying this concept to the neonatal population, the regulator subsystem with the physiologic adaptive mode could best be observed, however, the cognate and other adaptive modes mentioned above can also be applied as the neonate can bond and respond positively and negatively to the environment (Modrcin-McCarthy et al., 1997).

The second concept of environment, Roy notes that the environment influences the modes of adaptation or adaptive response. RAM identifies degrees of change by three types of stimuli (Andrews & Roy, 1986). The environmental components or types of stimuli are focal stimuli, contextual stimuli, and residual stimuli. Focal stimuli are those immediately confronting the person, where contextual stimuli are all other stimuli that influence the current situation. Lastly, residual stimuli are those that could influence the adaptation level, yet the stressor or its effect is not clear or confirmed. An example of residual stimuli can be relationships with friends and family, beliefs, personal experiences (Rogers & Keller, 2009; Ursavaş et al., 2014) and the institution or the world at large, which can be argued that neonates remember past pain experiences and are affected by institutional processes. In the context of neonatal care, focal stimuli can be direct handling events and contextual stimuli can be noise and/or temperature.

The third concept of health/illness is defined “as a state and process of being and becoming an integrated and a whole person” (Andrews & Roy, 1986, p. 8). This concept is derived from an understanding of the concepts of person and environment. It can further be described as a continuum that can range from optimal wellness to poor health or death (Andrews & Roy, 1991). Concerning the preterm population, health can be noted as physiological stability or decline.

The last concept is nursing, which according to RAM incorporates six steps to problem-solving (Andrews & Roy, 1986). These six steps include assessment of behavior, assessment of stimuli, nursing diagnosis, goal setting, interventions, and evaluation. These steps utilized by nursing are essential to promoting optimal outcomes and for the evaluation of implemented actions. Roy defines the goal of nursing as “the promotion of adaptation in each of the four modes, contributing to the person's health, quality of life, and dying with dignity" (Andrews & Roy, 1991, p. 20). The goal of nursing in the NICU is to provide handling that is individualized and guided by infant cues thereby promoting health through physiologic stability.

RAM theoretical framework can be used as a foundational framework for nursing research. Roy's, Adaptation Model can be adapted as a theoretical framework for this study. The concepts that are most fitting with the study of interest are the adaptive modes and the types of stimuli encountered by preterm infants.

Synactive Theory of Development

To guide this research, a situation-specific theory developed by Heidelise Als was selected as the foundational theoretical framework. The Synactive Theory of Development (STD) describes the infant's outward expression of internal functioning to the environment and caregiving. Since preterm infants are unable to escape the constant contact in the NICU, they are required to form some type of response to adapt to the frequent inputs (Peters, 1992). This theory allows one to understand the individual infant cues and their stage of development (Als, 1982). Als's synactive theory of development focuses on five interconnected interacting systems that guide an infants' response. According to Als (1982), the application of this framework underlies our assessment of the infant's responses to the extrauterine environment.

The five systems of Als STD include the autonomic system, the motor system, the state-organization system, the attention and interaction system, and the self-regulatory or balancing system (Als, 1986). The autonomic system is the infant's baseline functioning and is seen in respiratory patterns, color changes, and visceral signals (Als, 1982; Als, 1986). The motor system is where posture, tone, and movements of the infant are assessed (Als, 1982). The state-organization system is reflective in the range of states of consciousness such as sleep (deep sleep, light sleep, drowsiness) to various stages of arousal (calm/active, cry) (Maltese et al., 2017). The attention and interaction system shapes the social and inanimate world and looks at the infant's ability to come to an alert attentive state in order to obtain inputs from the environment (Als, 1982). Finally, in the regulatory system, the infant's strategies for balance maintenance are observed in their state of balance and relaxation. Although these five systems exist side by side, they are interactive and influenced by one another (Als, 1982).

The synactive theory of development describes four concentric circles that start with the innermost system to the outermost system. These circles are continuously in sync with one another, influencing and supporting each other (Als, 1982). The functioning and stability of each system can promote the maturation of the next system. Conversely, the instability of a system can affect other systems negatively (Maltese et al., 2017).

Autonomic System

The autonomic system is the innermost system, consisting of the nervous system which is observable through vital functioning and is the baseline functioning of the infant (Als, 1982; Maltese et al., 2017) and is the primary focus of medical care. Autonomic disorganization is defined as a lack of control, stabilization, and integration of basic functioning and may be seen as respiratory pauses, tachypneic respiration, skin color changes such as mottling, cyanosis, dullness, or grey (Als, 1982; Peters, 2001). Other autonomic stress signals include spitting up, hiccoughing, gagging, seizures, and twitching among others (Als, 1982). Autonomic stability is seen, in part, by smooth respiration, normal skin color, and stable digestion. This desired stability promotes optimal oxygenation. Ensuring autonomic stability necessitates recognition of infant distress and adjusting caregiving.

Motor System

The next circle representing the motor system surrounds the autonomic system. The motor system is comprised of movement patterns of the preterm infant and is based on tone and posture (Peters, 2001). This system unfolds early in the embryonic stage observable by flexor posture, and limb and trunk movements (Als, 1982). Stress cues in the motor system manifest in the infant as flaccidity of the trunk, extremities, or face, hypertonicity seen as hyperextension of the legs, trunk, arms, or finger-splay, facial grimacing, and tongue extensions. Motor stability is seen as smooth balanced posture and tone, and synchronous smooth movements such as hand clasping, foot clasping, finger folding, hand to mouth maneuvers, and suck searching and sucking (Als, 1982). One focus of providing developmental care is to support an infant’s motor system by providing postural support and containment.

Developmental care has its roots in the teachings of Florence Nightingale, where nurses are responsible for creating and maintaining a healing environment (Coughlin et al., 2009). Although developmental care practices vary across institutions, the goals include paying attention to the physical, emotional, and psychological vulnerabilities of critically ill and premature infants and their families (Coughlin et al., 2009). Developmental care has several core measures to achieve its goals. One core measure includes a focus on providing activities of daily living in a manner that ensures physiologic stability. This is done by positioning and handling in flexion, containment, and maintaining a midline alignment during caregiving activities (Coughlin et al., 2009). In development care, it is important to pay attention to infant cues (physiologic and behavioral) and adjust activities when an infant displays signs of distress.

State-Organization System

State organization is defined as the status of consciousness, sleep, wakefulness, and agitation and the transition from one status to another (Als, 1982; Maltese et al., 2017). The third circle contains the state-organization system which unpacks the various states of consciousness and the patterns of state transition, meaning that it exhibits the infant’s ability to maintain and regulate levels of alertness and irritability (Als, 1982; Als, 1986; DiPietro, 2005). Some state-related stress signals consist of diffuse sleep or awake states with whimpering sounds, strained fussing or crying, staring, active aversion, worried alertness, high-guard arm position, glassy-eyed strained alertness, gaze aversion, and irritability (Als, 1982). Stability in this system is seen as well-defined sleep/wake states, consolable, and self-quieting (Als, 1982). The recognition of stress signals in this system, with a subsequent adjustment in care, can promote healing and growth in preterm infants.

Attention-Interaction System

The outermost, fourth circle is the attention-interaction system in which the infant demonstrates its ability to come to an alert, attentive state and to use this state to take in cognitive and social information (Als, 1986). Stress signs of an infant’s inability to come to an alert state are seen in a combination of autonomic, motor, and state organization cues. Als (1986) describes a scenario in which an infant who shows reluctance to come to an alert state may move into hypertonic, high-guard arm position with clinched fists, become pale, tachypneic with irregular respirations, and have a pained facial expression. Additionally, instability in the autonomic, motor or state-organization systems may cause an infant to be unable to come to an alert state. Signs that an infant can properly come to alert state include robust, focused, alertness with intent and/or animated facial expression producing the ability to relate to the environment and caregiver (Als, 1986; Maltese et al., 2017).

Regulatory system

The regulatory system is not represented by the concentric circles, rather it encompasses all the systems to balance and organize their interaction as it responds to inputs (Als, 1986). As the infant matures so does the regulatory system, the earlier the gestation the less self-regulatory behaviors are available, thus prompting assistance to regulate (Maltese et al., 2017). The regulatory system has strategies to maintain a balance, which is a stable and relaxed state. However, if the capacity to regulate is beyond the infant's threshold, the infant will be unable to achieve a balanced state, therefore the quality and type of environmental encouragement must be assessed (Maltese et al., 2017).

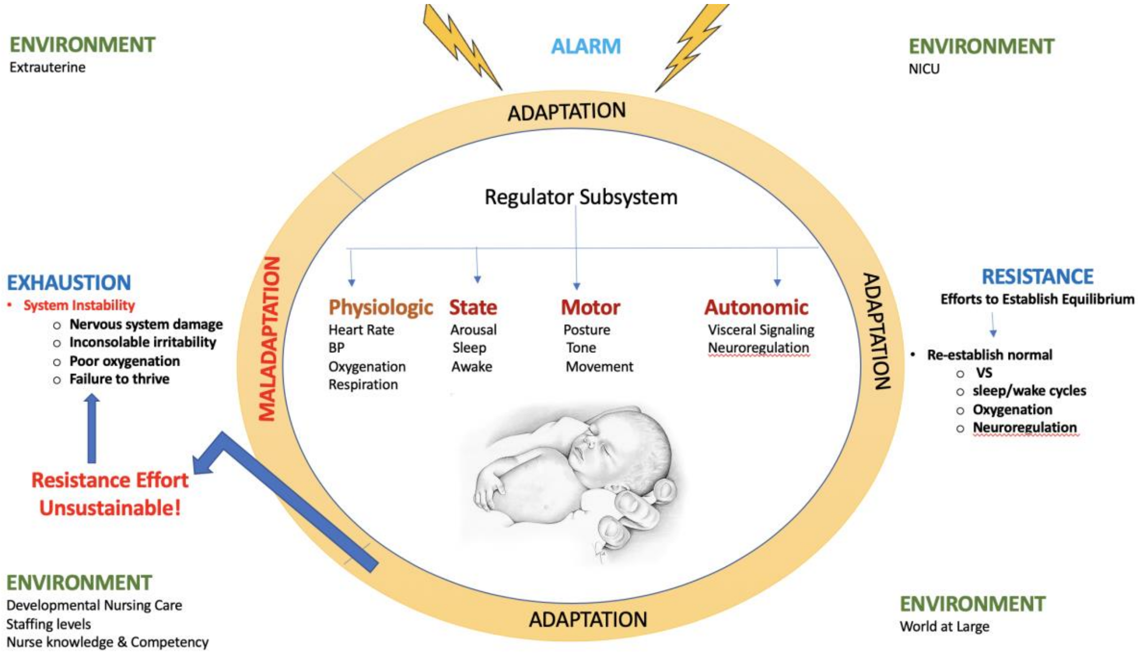
These systems are interdependent, and behaviors that communicate their stability are essential components in the assessment of neonatal care. Stress caused by neonatal handling and the invasiveness of the environment can destabilize the neonate’s internal systems that are called upon to thrive in the extrauterine environment. The NICU environment calls on the infant to challenge its ability to maintain a state of organization among its systems (Maltese et al., 2017), and facilitation to do so is crucial.

Conceptual Model

The general adaptation syndrome, Roy's adaptation model and the synactive theory of development all contain concepts that are adaptable to the study of interest, as they focus on how the individual infant appears to handle the experience of the world around them. For this study, a compilation of these three frameworks contributed to the foundational framework. These frameworks had components that were informative, for example, GAS informed this study by providing a pathway of adaptation, the RAM provided insight regarding internal systems that are initiated during the adaptation process, responses, and stimuli experienced. Lastly, STD guided the evaluation of the environment as well as an overview of infant responses to stimuli. The conceptual framework is depicted in a circular process of responses and adaptation with the neonate at the center (Figure 2).

Figure 2.

Postnatal Synactive Adaptation Model



The Neonate

In this framework, the neonate is in the center and is seen as a biophysical organism whose internal functioning is continuously interacting with the environment (Als, 1982; Rogers & Keller, 2009). In looking at this organism's functioning within the environment, the infant must be assessed for its capacity to adapt and organize its behavior to cope with the stimuli (Als, 1986). Infants are equipped with varying levels of capacity depending on their stage of development and may exhibit their capacity in different ways.

In this model, the responses to stimuli portrayed by neonates include autonomic and physiologic, state-organization, and motor responses. Autonomic and physiological signs include changes in heart rate, blood pressure, oxygen saturation, respirations, and visceral signs such as hiccupping, gagging, and spitting up. By recognizing the individual infant's responses and cues, the environment can be manipulated to facilitate the achievement of balance. The results of this study show that with prolonged stimulation and multiple procedures completed in subsequent order infants are unable to maintain physiologic stability.

The Environment

The environment is a crucial component of the preterm organism's ability to maintain balanced stability and thrive. In the proposed framework the environment is characterized into different concepts, the environment as extrauterine, the environment as the NICU, the environment as an institutional system, and the environment as the world at large.

This framework acknowledges Als (1986) statement that an infant has irreversibly left the intrauterine environment where an infant's protection, in addition, to its oxygenation, nutrition, waste clearance, infection protection, and sensory control once was. The extrauterine environment must meet the needs of infants born prematurely. The NICU, a vital component of a preterm organism's environment can be a harsh setting characterized by bright lights, noise, and medically necessary touch. A preterm infant's immature nervous system is not geared to the harshness of the NICU environment. The preterm neonate's survival in this new environment is dependent, in part, on the advances in technology, which attempts to simulate the maternal role in supporting respiratory, cardiac, digestive, and temperature control functions (Als 1982).

An infant in the NICU is exposed to a variety of stimuli. These stimuli may be focal, contextual, or residual (Roy, 1976). Focal stimuli, which is defined as stimuli that are immediately confronting the person (Roy, 1976), can be the direct touch or the handling event such as assessment, vital signs measurement, position change, and diaper change. Contextual stimuli are seen as all the other stimuli that contribute or influence the focal stimuli (Ursavaş et al., 2014). It could be seen as noise, bright lights, and manipulation of the infant's environment (i.e. opening/closing of incubator doors). This study revealed that infants are unable to maintain physiologic balance during the clustering of procedures. With minimal stimuli, as in a single procedure, infants are able to maintain physiologic balance effectively.

Other concepts in the environment include the institutional systems and the world at large. These can be seen as residual stimuli which are beliefs that affect the current process (Ursavaş et al., 2014). The world at large influences patient care through reimbursement practices and patient care policies. The institutional system affects patient care in the development of nursing care policies, staffing levels, and nursing knowledge and competencies. Als (1986) recognizes that the environment plays a critical role in an infants' mortality and morbidity and identifies the environment as an opportunity to help premature infants thrive. Nurses influence the infants' experience with the environment and have the capacity to facilitate a positive experience.

Adaptation

Als (1986) considers that many events experienced by the neonate in the environment can precipitate morbidity of various conditions, particularly those that affect brain development. During normal fetal brain development, the brain has fragile capillary beds and vascular autoregulation, which can be associated with intraventricular hemorrhage (IVH) (Als, 1986). IVH can also be associated with hypoxic events like asphyxia and apnea, to name a few, which lead to increase cerebral blood flow, impaired vascular autoregulation, and increased venous pressure (Als, 1986). This sequence lead Als to consider how to improve the use of technology and clinical aids, how to reduce these incidences by paying attention to the environment and caregiving routines, and to acknowledge an infant's adaption.

In the RAM and the STD, the infant's regulator subsystem serve as a coping mechanism to manage the stimuli. The regulator subsystem encompasses the physiologic mode of adaption, which responds to a given stimulus. Contained within the physiologic mode are nine components; oxygenation, nutrition, elimination, activity and rest, protection, senses, fluid-electrolyte and acid-base balance, neurologic function, and endocrine function (Ursavaş et al., 2014). Infants cope by attempting to maintain physiologic integrity.

As depicted in this framework and influenced by the general adaptation model, the infant can proceed through different levels of adaptation. The initial reaction to the environment can initiate an alarm response, where the organism responds to stimuli through physiologic/autonomic, state-organization, and motor responses. It is important to note that the environment/stimuli may not trigger an alarm response in all infants.

The alarm response may be seen, physiologically, as an increase in heart rate, blood pressure, and/or respirations, as well as changes in the oxygen saturation. Additionally, the infant may display state-organization distress cues such as irritability, motor distress cues like hypertonicity, and visceral signaling like hiccupping. During this time the caregiver must acknowledge the infant's responses and cease stimuli that are causing distress or adjust continued stimuli to facilitate the balance of the organism. If the organism can establish equilibrium, the infant is in resistance mode and will display normal physiologic parameters.

If the stimuli continue, it may become overwhelming and the organism can move into a state of exhaustion, this, in turn, can precipitate morbidity because the body's defenses are depleted (Selye, 1950). Exhaustion can be seen as a decompensation in physiologic/visceral, state-organization, and motor cues. Physiologically, an infant can become bradycardic, apneic, and hypotensive, which can lead to decrease systemic oxygenation. In state-organization, the infant may be inconsolable and unable to transition to sleep. Exhaustion in the motor responses may be seen as hypotonia or flaccidity. The regulatory subsystem in which the infant attempts to organize all the stimuli to maintain balance and stability encompasses interaction with the other systems, the physiologic/autonomic, motor, and state-organization. When the infant is unable to cope and regulate the stimuli, external facilitation is necessary. This was noted in the results of this study as infants who experienced multiple or clustered procedures were unable to maintain stability due to the repeated stimuli.

Nursing plays a pivotal role in the care of the preterm neonate and is at the forefront of improving care. When a premature infant meets its capacity to regulate or manage the stimuli, external facilitation should be employed. Several interventions in the physical environment and direct caregiving can be implemented to maintain stable functioning which can, in turn, improve oxygenation. Andrews and Roy (1986) point out that by adjusting the stimuli, instead of the patient, the nurse improves the patient interaction with the environment which can promote health.

Theoretical Rationale

The proposed theoretical framework demands a look at the infant and its process of adapting to the environment. The goal of this framework is geared toward identifying how the infant adapts to the stimuli it is subjected to and to validate responses to the environment in which the infant is attempting to not only survive but to thrive. This framework may also help in determining the threshold and magnitude of exposure to stimuli that cause an imbalance by identifying the point that an infant may experience exhaustion. The description of physiologic/autonomic, state-organization, and motor indicators and adaptation process is a source of nursing assessment observations. Therefore, this framework can be used as a basis to examine the effects of nursing care, nursing assessment, and subsequent responses.

The environment can facilitate normal brain development by maintaining and promoting improvements in oxygenation. Als (1986) learned that with the use of technology that monitors transcutaneous oxygen changes, an infant's oxygenation was affected by changes in infant behavior and changes to the environment leading to an exacerbation or improvement in arterial oxygen saturation. Moreover, it was noted that sleep (part of the state-organization system) plays an important role in an infant's vulnerability to hypoxemia. It is recognized that infants frequently interrupted during rest spend more time in light rather than deep sleep, leading to lower arterial oxygen saturation (Als, 1986). Lastly, Als noted that ambient noise, such as laughter, door and drawers closing, and other extraneous sounds can be disruptive and reduce arterial oxygen saturation. There are several factors to consider to promote health in the preterm organism.

The use of this framework may help in identifying the vulnerability of the infant's system as it interacts with the environment. Als (1986) proposes that infant behavioral changes and environmental changes around the infant can worsen or improve arterial oxygenation. This framework can facilitate further examination that neonatal care has on infant oxygenation at the tissue level.

It has been studied that nursing provides approximately 85% of care received by preterm infants yet areas of research and advances in neonatal care have been traditionally geared toward medicine, technology, and pharmacology (Peters, 1992). Since nursing is the primary caregiver in the neonatal care environment, they hold a strong influence over this environment. This research sought to gain further knowledge of the effects of nursing caregiving procedures on moderate to late preterm infants. This framework is appealing for this research due to its approach to examining the care an infant receives. Nursing is the advocate for the neonate and is at the forefront of providing education and care that is individualized and cognizant of infant behaviors. This framework lays the foundation for acknowledging the effects of the environment. Recognizing these signals allows caregivers to change course and restructure care to facilitate proper balance. These theories provide an opportunity for caregivers to work together to provide an environment that promotes optimal growth and development.

In the next chapter, the research design of this study will be examined. A detailed description of the study methods, including the setting, participant information, sources of data and measurement concepts, the procedure, and the analysis plan. The following chapter provides the assumptions of this study, the research questions, aims, and hypotheses.

CHAPTER THREE

METHODOLOGY

The purpose of this chapter is to introduce the research design for the study regarding the effects of handling on an infant's regional oxygenation. The purpose of this study is to explore the relationships between routine caregiving procedures and renal and cerebral regional oxygenation (deep tissue oxygen supply and demand) in hospitalized preterm infants between 32-36 $^{6/7}$ weeks gestational age (moderate to late preterm infants). A quantitative approach, utilizing a prospective observation method was used to explore relationships between the variables over time. The following sections in the research design describe the methodology, study setting, sample criteria, data sources and data collection procedure, instruments used, and data analysis and limitations.

Research Questions

1) How is cerebral and renal oxygenation affected by routine procedures, monitored by near infrared spectroscopy (NIRS), in hospitalized moderate to late preterm infants (32-36 $^{6/7}$ weeks gestation)? 2) How do participant characteristics affect cerebral and renal oxygenation in response to commonly performed routine procedures measured via NIRS in hospitalized moderate to late preterm infants?

Research Design

The study is descriptive and used a prospective observational method to collect quantitative data seeking correlations. This method was used to explore the relationship between the independent variable of routine caregiving procedures that encompass both single stressful, clustered stressful, and clustered tissue-damaging procedures and the dependent variable of renal and cerebral regional oxygenation in infants ranging from 32-36 $^{6/7}$ weeks. The goal was to observe, describe and document relationships between specified variables, like regional oxygenation and neonatal handling events, specifically routine care such as (included but not limited to) assessment, diaper change and position change, and participant characteristics such as gestational age, birth weight, hemoglobin, and risk of mortality. This research method does not infer a causal connection but identified correlations between handling and regional renal and cerebral oxygenation, observing any changes in the regional oxygenation during handling events. The prospective method was utilized because the researcher was interested in specific outcomes of handling and therefore gathered data as the study progressed. The observation method was structured with predetermined variables to be evaluated.

Assumptions

In the context of this study, it was assumed that environmental factors can initiate an autonomic, physiologic, and behavioral response in infants. Although not all environmental factors will cause distress in every infant, this assumption notes that potential environmental factors, such as various types of infant handling, can produce a stress response in preterm infants. Infants, similar to adults, have a threshold of stimuli that is tolerable and when the threshold is exceeded, potentially detrimental effects can occur. The stress responses exhibited by infants may not be visible in current monitoring instruments such as heart rate, respiratory rate, or oxygen saturation monitors; therefore, this study observed regional oxygenation through the use of NIRS.

Hypotheses

Hypothesis 1: Commonly performed NICU procedures have no impact on cerebral and renal oxygenation in preterm infants.

Hypothesis 2: Cerebral and/or renal oxygenation is not affected by gestational age, birth weight, hemoglobin, or risk of mortality during commonly performed routine procedures.

Aims

The aims of this research study are two-fold.

Aim 1: Describe the impact of single care procedures, clustered care procedures, and clustered care procedures with tissue damaging procedures on cerebral and renal oxygenation in moderate to late preterm infants as measured by NIRS.

Aim 2: Describe the relationship between cerebral and renal regional oxygenation and gestational age, birth weight, hemoglobin value, and risk of mortality value during commonly performed routine procedures in moderate to late preterm infants as measured by NIRS.

Methods

The methods for this study included determining sample population and size, establishing a procedure, evaluating measurement concepts, description of data preparation, and methods of analysis. This was a descriptive study using prospective observation methodology allowing for the assessment of the relationship between handling events and regional oxygenation.

Study Setting

The study was conducted in a Neonatal Intensive Care Unit (NICU) at a Magnet® designated level 1 trauma acute care hospital in Southern California. The NICU is a level IV tertiary care, 84-bed facility with an average daily census of 78 in 2019 (H. Seto, personal communication, July 29, 2020). This institution had approximately 1600 patient admissions in 2019 (M. Culata, personal communication, August 7, 2020), both inborn and those transported into the facility from other institutions for a higher level of care.

Study Participants

The sample for this study was drawn from the population of preterm infants at the study site NICU. All healthy preterm infants without chronic disease born at or transported into the study site NICU who were born between 32 and 36 $^{6/7}$ weeks gestation were considered for this study. Additional inclusion criteria included availability of maternal history and parent availability for consent signature. The following characteristics are study exclusion criteria. Infants having:

- congenital anomalies
- received analgesics or sedatives
- mothers that reported illicit drug use during pregnancy
- hemodynamic instability
- surgical intervention at the time of the observation,
- necrotizing enterocolitis or intraventricular hemorrhage

The rationale for selecting this setting and population is accessibility due to the researcher's relationship with the unit leadership, medical staff, and current employment.

Determining sample size was done by utilizing Power Analysis and Sample Size (PASS) software version 19.0.3 and standard criteria, such as alpha of 0.05, power of .80, and an effect size of 0.5. A minimum sample of 34 was determined, an additional 10% was added as an attrition rate.

Infants were recruited by daily analysis of admissions to the NICU through communication with institutional leadership and monitoring by the researcher. Infants meeting the inclusion criteria were assessed for study eligibility. After participants were selected, consent was obtained from a parent or legal guardian by the researcher. The primary researcher/data collector is bilingual and was able to communicate with the Spanish-speaking parents or legal guardians for informed consent, which was translated into Spanish. Consent was obtained before study observation, with observation occurring between days three to seven of life. Consenting parents were approached face to face.

Protection of Human Participants

The researcher completed all training through the Collaborative Institution for Training Initiative (CITI) and institutionally required human subject protection training. The researcher obtained approval from the Institutional Review Board of the study site hospital. Informed consent was obtained from the parents or legal guardians of participants after a thorough explanation of the risks/benefits of the study and any questions/concerns of parents/guardians were addressed.

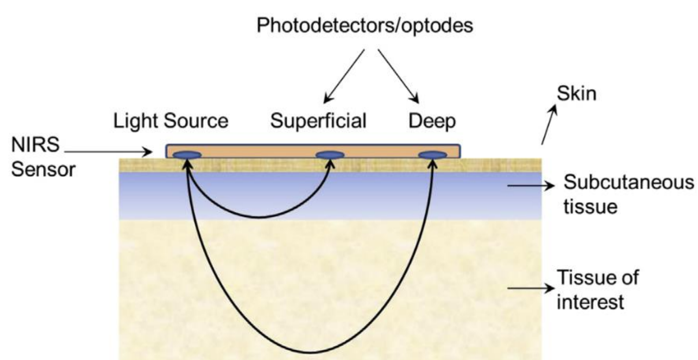
Data Source

The data used to answer the research question included regional renal and cerebral oxygenation data using the near infrared spectroscopy (NIRS) and arterial oxygenation and heart rate using pulse oximetry. Regardless of study status, infants at this institution are continuously monitored for heart rate, respiratory rate, arterial oxygenation via pulse oximetry and cardiorespiratory monitors, NIRS monitoring is not a routine monitoring practice in moderate to late preterm infants.

To measure renal and cerebral regional oxygenation via NIRS, the Foresight Elite™ (Edwards Life Sciences, Irvine, CA) was used and was continuously recording during the study period. This is a non-invasive device used to detect regional changes in oxygen delivery and extraction (Miller et al., 2017). Tissue (renal and cerebral) oxygenation is determined by the ratio of oxygenated hemoglobin to total hemoglobin at the microvascular level which includes arterial, venous, and capillary components (Sood et al., 2015). NIRS primarily reflects the venous saturation of the blood in the tissue to a depth of approximately 2 cm (Hyttel-Sorensen et al., 2015), the Foresight Elite™ reflects a depth of 2.5 cm (Figure 3). According to McNeill et al. (2011) acceptable baseline ranges for stable preterm infants are 66-83% for cerebral and 64-87% for renal.

Figure 3.

IN Vivo Optical Spectroscopy (INVOS) system (Covidein)



Note. Sood et al. (2015, p. 165)

Pulse oximetry technology became a standard for its low cost, simplicity, and ability to measure the oxygen saturation of hemoglobin via pulsatile arterial blood (Vesoulis et al., 2016). For this study, the Masimo™ device (Irvine, CA) was used to measure pulse oximetry readings and heart rate data. An additional pulse oximetry sensor was attached to an available limb to record data. Additionally, demographic, and maternal information was obtained utilizing the institution's electronic medical record, EPIC®. The research devices, NIRS and pulse oximetry, are calibrated at least every 6 months. Prior to commencing research observations, all equipment was checked to assure that calibrations were current and that monitors were in optimal working order by the institution's clinical engineering department.

Potential Risks

The risks associated with this study were minimal and included skin irritation. Applying the sensor to delicate skin could reduce circulation and/or cause skin deterioration. An infant could also experience discomfort with the removal of the sensors as they are removed from the skin. To ensure safety and measurement reliability the manufacturer recommended inspection of skin every 12 hours to assess for proper adhesion, skin integrity, and circulation. For this study, however, the maximum application time was approximately seven hours. Except for the placement of the NIRS and pulse oximetry probe, no additional procedures were performed. During the data collection, no risks became evident in any of the subjects.

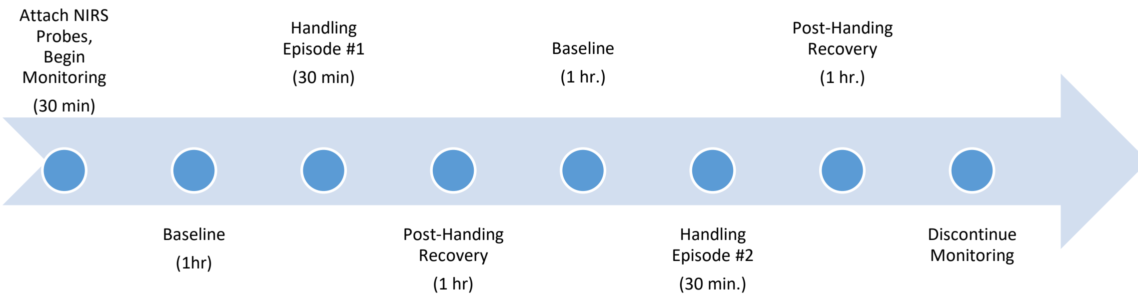
Procedure

All data was collected at the infant’s bedside in the NICU. The participant observation was conducted by the researcher who was positioned close enough to observe the nature of the caregiving event. The procedure included an approximate six-hour observation and data collection period. This facility typically provides routine nurse caregiving every three hours. Each infant was observed for two routine caregiving episodes during the six-hour observation period. Observations were conducted during the night and/or morning shifts. Despite the variability of care periods, the researcher was able to capture two consecutive care periods for each participant. To avoid risk to the infant, the scheduled caregiving was not changed for this study.

The researcher applied the NIRS sensors one hour before the first scheduled care period (Figure 4). A NIRS cerebral sensor was placed midline on the forehead and the right or left flank area at approximately T12-L2 for renal monitoring. The research pulse oximetry sensor was attached to any available wrist or foot. Monitoring consisted of a baseline period, the handling care sequence, and recovery period. More than three minutes between caregiving events counts as another episode. This is delineated as multiple providers may perform a handling event. The timeline represents the scheduled care periods. Although it appears to combine procedures into two handling episodes, most infants had multiple handling episodes during the study period. Many handling episodes began with a baseline period, the handling episode, and the recovery period. Only one participant was observed during the given six-hour period. The researcher did not interfere with usual care, procedures, protocols, or frequency of interruptions by various providers. During the study period, some participants were interrupted between handling episodes.

Figure 4.

Study procedure



Observations occurred between days three to seven of life. This time frame was selected as infants were more likely to have made the successful transition to extrauterine life, recovered from birth stress, have lessened impact from maternal medications, and had fewer scheduled procedures (Zeiner et al., 2016). Infants were observed 1 hour before scheduled handling episodes, throughout the handling sequence, and 1 hour after handling as the recovery period, so long as the observation did not exceed the six-hour periods. The handling event sequence included but was not limited to vital signs measurement (including blood pressure and temperature check), assessment (including auscultation), diapering, feeding, and positioning. Some infants experienced tissue-damaging procedures (e.g. skin puncture, tape removal) or other noxious stimuli. All interactions and procedures were noted including additional contact with parents, medical residents, or nurse practitioners who initiated patient contact. The caregiving sequence of each handling episode was noted.

NIRS data was automatically recorded every two seconds; heart rate and pulse oximetry data were also recorded every two seconds using the research Masimo™

device. The researcher manually documented in an observation procedure log, the time and event performed to log more detail regarding the event. The pulse oximetry recorded data was time and date stamped. The researcher ensured that time stamping on NIRS, pulse oximetry, and the Microsoft® Excel procedure log spreadsheet were synchronized. In addition, the researcher noted persons involved in care.

Measurement Concepts

To operationalize the physiologic responses, cerebral and renal regional oxygenation were measured, additionally, heart rate and oxygen saturation were obtained for trends. Continuous recording of cerebral and renal regional oxygenation was done by Foresight Elite™ near infrared spectroscopy. The accuracy and precision of this Foresight Elite™ are delivered at a variation range of +/- 3.05%, accounting for the variation of tissue and skin tone. This data was continuously recorded every two seconds. Oxygen saturation and heart rate were recorded every 2 seconds and recorded via Masimo™ device.

The risk of mortality was assessed by utilizing the Score for Neonatal Acute Physiology-Perinatal Extension II (SNAPPE II) to adjust for confounding variables related to illness acuity (Appendix 2). This risk of mortality scoring tool was originally developed by Richardson in 1993 as the score of neonatal acute physiology (SNAP) which was later modified due to its cumbersome 34 item tool. The modified SNAP tool was reduced to 6 physiologic items becoming the SNAP-II, and later three perinatal items, were added making it a nine-item tool, becoming known as SNAP-Perinatal Extension-II (SNAPPE-II). The SNAPPE-II includes an assessment of mean blood pressure (MBP), temperature, partial pressure of oxygen (PO_2)/fraction of inspired oxygen (FIO_2) ratio, lowest serum pH, seizures, urine output, birth weight, small for gestation age (points given in <3rd percentile) and Apgar score at 5 minutes assessed using data during the first 12 hours of life (Richardson et al., 2001). A higher SNAPPE-II indicates a higher mortality rate (Shivanna Sree & Banur Raju, 2015).

The SNAPPE-II underwent validation procedures to review its discrimination and goodness for fit. The primary measure of discrimination is the receiver operating characteristics (ROC) curve used to assess optimal level for maximum sensitivity and optimal specificity (Muktan et al., 2019). Once sensitivity and specificity are plotted to create the ROC curve, the area under the ROC curve (AUC) is further analyzed (Muktan et al., 2019). An AUC of 1.0 indicates perfect discrimination where a 0.50 would be random discrimination (Richardson et al., 2001). The goodness for fit analysis (Hosmer-Lemeshow) was used to assess deviations between observed and expected values, as its *P*-value approaches one, it indicates an extremely good fit (Richardson et al., 2001).

In the original validation procedure of this tool, Richardson et al. (2001) determined an AUC of .91 + 0.01 and a goodness for fit *P*-value =.90. Other studies showed similar results AUC .933 (James et al., 2009), AUC .846 (Shivanna Sree & Banur Raju, 2015), and .917 (Muktan et al., 2019). These results validate that SNAPPE-II is a good indicator of infant mortality (Muktan et al., 2019). The goodness of fit from the original validation was similar to another study from *P*-value =.97 (James et al., 2009). This result indicated that the use of SNAPPE-II is indicated for this study.

Demographic data collected included infant gestational age at birth, day of life or postnatal age at the time of study observation, birth weight, gender, race, Apgar score, ventilation mode and amount of oxygen (if any), birth order if twins, respiratory support at birth, and last hemoglobin lab value. Additional information was collected to determine the SNAPPE-II score. Data was collected via electronic health records.

The handling sequence was operationalized as starting when the nurse/provider first initiated direct contact and was complete when the nurse/provider had not been in direct contact with an infant for three minutes. A three-minute interval between handlings events was considered a new episode or sequence. The three-minute gap was based on our experience and preliminary data which showed that clustered procedures are usually performed consecutively, with less than a three-minute gap between procedures (Levy et al., 2017). To ensure accuracy in the three-minute interval, procedures were time-stamped in the Microsoft® Excel spreadsheet procedure log.

Analysis Plan

The data management plan included the utilization of Microsoft® Excel. Data from NIRS and Masimo™ was downloaded to an Microsoft® Excel spreadsheet. Patient NIRS and Masimo™ data were logged with participant numbers. Protected health information was not recorded via NIRS or Masimo™. A log was kept with patient name, date of birth, and medical record number and associated participant number in a separate locked location. NIRS and pulse oximetry recordings occurring every two seconds were compiled with the time-stamped procedure log.

Data Preparation

Data preparation is a crucial component before data analysis can begin. For this study, the procedure log data was cleaned and evaluated for consistency throughout the log. The NIRS and pulse oximetry data were assessed for motion artifact, sensor issues, out-of-range, and missing values. When preparing the data for analysis, procedures and their baseline periods were determined.

Procedure log

In this study, neonatal handling, or neonatal handling event, is equated with a routine caregiving procedure and was classified as a single, clustered, tissue-damaging procedure, and/or stressful care procedure. A single procedure is defined as one that is completed by itself with no other procedure occurring within 3 minutes of the start or end of the procedure. Moreover, a clustered procedure is defined as several procedures occurring consecutively with a gap no greater than 3 minutes. End times, where listed, were used for determining the classification of procedures as singlets or clusters; when end times were not listed, start times were used. We defined a tissue-damaging procedure as those invading the neonate's bodily integrity, causing skin or mucosal injury (Carbajal et al., 2008). Lastly, stressful care procedures are defined as direct or indirect procedures that cause physical uneasiness or annoyance or disrupt the balance between the neonate and its environment (Carbajal et al., 2008). It is important to note that a procedure's degree of stress is not found in the procedure itself, but in how the infant responds to it (Viner, 1999).

In this study, the procedure log was reviewed by two researchers independently to ensure appropriate classification of single versus clustered procedures, stressful care procedures, and tissue-damaging procedures. All procedures were classified as either single stressful care procedures (SCP_S), clustered stressful care procedures (SCP_C) or clustered stressful care procedures and tissue-damaging procedures (Both_C).

When the procedure log was compiled with NIRS and pulse oximetry data, baseline periods were assessed. This was done to ensure that every single or clustered procedure, had a preceding baseline period of at least 30 seconds. Upon review, three procedures, one single and two clustered procedures were removed for lack of a baseline period.

NIRS Criteria

Although some studies, like Hyttel-Sorensen et al. (2015) did not remove artifacts in the regional oxygenation (StO_2) data, we chose to clean the data based on NIRS research studies by Alderliesten et al. (2016); Terstappen et al. (2018). We cleaned the data based on the following criteria a) if two consecutive StO_2 data points differed by 30% or greater with no accompanying changes in SpO_2, then the data points beyond a 30% difference were removed until the values returned to a difference of less than 30%, b) if the consecutive data points differed by 30% or greater with accompanying changes in SpO_2 and/or missing data, then the StO_2 values were removed from the start of the 30% difference until there were no more missing data points. Utilizing these criteria, only two instances of cerebral StO_2 data in two participants were removed totaling 34 seconds, of which 2 seconds would have been removed anyway due to value $\geq$95%.

If a NIRS sensor issue was indicated in the procedure log, the data was assessed from the beginning of that procedure's baseline period until the end of the procedure, and all existing data points between the first and last missing values were removed. Cerebral sensor issues constituted a total of 144 seconds removed, of which 114 would have been removed anyway due to values $\geq$ 95%. For renal sensor issues, a total of 316 seconds were removed, of which 80 sec would have been removed due to $\geq$ 95%.

Additionally, all StO_2 values above 95% were removed because, considering that StO_2 depends on the balance of oxygen delivery and oxygen use, and the volume ratios reflecting StO_2 in are 70-80% in veins, 5% in capillaries, and 15-25% is arteries, values of 95% or greater are implausible since regional StO_2 is 70-80% venous (Hessel et al., 2014; Urlesberger et al., 2011). StO_2 readings are mainly obtained from venous blood, which represents oxygen utilization of the tissue, therefore StO_2 measurements tend to be close to venous saturation. This justifies the removal of data above 95% (Urlesberger et al., 2011). The data solely removed for these criteria is an additional 1076 seconds removed for cerebral StO_2 and an additional 290 seconds removed for renal StO_2.

Pulse Oximetry Criteria

Pulse oximetry data was assessed for removal if the raw data indicated "low perfusion", "sensor off patient", or "interference detected". The region adjacent to the indication was analyzed and determined to be erroneous if a decrease occurred in SpO_2 to $\leq$ 90% that was considered by use of the procedure log and clinical reasoning to be artifactual, as evidenced by a lack of correlation with or a drastic change in heart rate (Malviya et al., 2000). If pulse oximetry was deemed artifactual, its corresponding HR data was also removed. With these criteria, a total of 858 seconds of data was removed of which 48 seconds would have been removed due to missing values in heart rate or SpO_2 values.

Additionally, if a pulse oximetry sensor issue was noted in the procedure log, then the data was assessed from the beginning of that procedure's baseline period until the end of the procedure, and all existing data points between the first and last missing values were removed if the procedure description and SpO_2/HR tracings provided clinical reason to believe the readings were inaccurate. Under these criteria a total of 334 seconds was removed, however, 16 seconds would have been removed due to missing values in heart rate or SpO_2 values. If only one of the SpO_2 or HR tracings were missing, the other was also removed at the corresponding time point, since both variables utilize the same sensor, this constitutes an additional 2022 seconds of SpO_2 data and 34 seconds of heart rate data solely removed due to these criteria.

Statistical Analysis

Descriptive statistics are presented in the form of mean ± standard deviation if the variables are normally distributed and median with minimum and maximum values if the variables are not normally distributed. Analysis of variance (ANOVA) was used to compare the means among the three procedures while Kruskal Wallis test was used to compare the medians. Multiple comparisons tests were used for post hoc tests if the overall ANOVA were significant. Bonferroni adjustment was used if the variances were equal while Tamhane's tests were to adjust for alpha if Levene's test were significant. Multiple linear regression was used to assess the association of the outcome variables with the age of gestation, birth weight, hemoglobin, and risk of mortality (SNAPPE-II). Assumptions of linearity, normality, homoscedasticity, and no multicollinearity were met. SPSS version 27 (IBM SPSS, Inc., Armonk, NY) was utilized to analyze the data with the level of significance set at $\alpha = 0.05$.

Limitations

There are several limitations worth noting in this study. Limitations related to the use of NIRS included loss of data due to detachment of sensor during handling event and possibly sensor interference with light exposure. A limitation with SpO_2 data was the loss of participant data due to the data retrieval process, for the eight participants. The project's final sample size of 37, is a small sample size which may limit the generalizability of findings. Variations in caregiving sequences and methods may have differed among caregivers further limiting generalizability. Some participants did not include start and end times of procedures early in the study. Lastly, the presence of the researcher at the infant bedside may have caused nurse caregivers to change how they usually provide care.

Summary

In this study, exploration of the relationship between caregiving handling events and end-organ perfusion was measured by NIRS. This study utilized a prospective observation design and was conducted at a Neonatal Intensive Care Unit (NICU) of a level 1 trauma center at a Magnet® designated acute care hospital in Southern California. The study included a maximum six-hour observation period, which was comprised of two prescheduled handling sequences. Data collection was done by continuous recording via the NIRS and Masimo™ devices and manual entries into a time-stamped Microsoft® Excel spreadsheet. Data collection included regional oxygenation in renal and cerebral areas, oxygen saturation, procedure information, and demographic information. Descriptive and inferential statistics were completed by utilizing repeated-measures ANOVA, Kruskal Wallis test, and multiple linear regression models.

In the following chapter, chapter four, the results of this study will be discussed, including enrollment information, demographic data, and statistical analysis.

CHAPTER FOUR

RESULTS

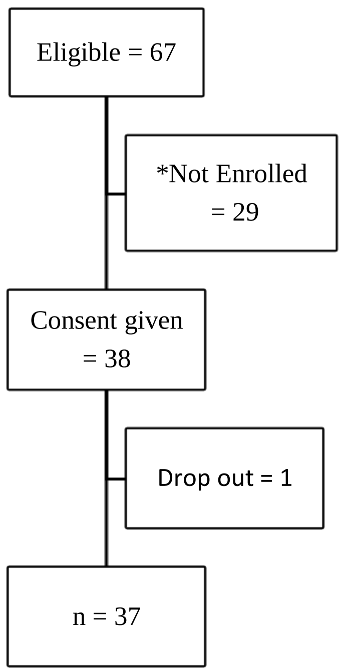
Although research was previously conducted on the effects of care on various physiologic variables on preterm infants, more knowledge can be discovered with the advances in technology. The researcher used a quantitative prospective descriptive design to observe the effects of care on cerebral and renal oxygenation. This chapter discusses study findings through an evaluation of the participant demographics, descriptive analysis, and inferential analysis.

Enrollment

A total of 67 participants were eligible for this study during the study period of February 2021 to May 2021. Of the eligible infant participants, six parents declined to allow their infant to participate, 13 infants were excluded because the observation window closed, and ten infant parents were not available for consent. The final sample was 37, one infant participant who provided consent was transferred to another facility before study observation. The final sample size of 37 is above the minimum of 34 obtained by the PASS software (Figure 5).

Figure 5

Enrollment Flow Chart



Note. *Infants not enrolled due to parent declined (n=6), observation window closed (n=13), parents not available for consent (n=10).

Demographics

The participants for this study were obtained from a level IV NICU and were born between 32 and 36 $^{6/7}$ weeks gestation. For this study, the mean observation time was 5.8 hours, with observations occurring at a mean of 4.8 days of life. The risk of mortality was assessed by utilizing the SNAPPE-II score. The SNAPPE-II score is used to determine the risk of mortality in infants. A score of 0-20 represents a mild mortality risk, 20-40 a moderate mortality risk, and >40 severe mortality risk (Rachuri et al., 2019). In the study, the participants had a mean SNAPPE-II of 6.3, representing a mild mortality risk.

In this study, 35% of participants were moderate preterm (32-33 $^{6/7}$ weeks gestation), while the majority, 65%, were late preterm (34-36 $^{6/7}$ weeks gestation). The participants had a mean birth weight of 2263 grams, 76% were born by cesarean section, and 62 % were male. In this study, 86% of infants had an Apgar score of ≥8 and 97% of participants did not require any type of respiratory support (Table 2).

Table 2

Study characteristics

	Mean ± SD (or %)
Duration of Study (hrs.)	5.8 ± 0.30
Day of Life (at time of study)	4.8 ± 1.35
SNAPPE-II	6.3 ± 9.6
Birthweight (g)	2263 ± 602.8
Hemoglobin (g/dL)	17.2 ± 3
Gestational Age (wks.)	34.2 ± 1.1
Moderate Preterm	35%
Late Preterm	65%
Birth Method	
Cesarean	76%
Vaginal	24%
Gender	
Male	62%
Female	38%
Apgar 5 min	
≤7	14%
≥8	86%
No respiratory support at time of study	97%

Analysis

For this analysis, a total of 231 procedures were captured in 37 participants, according to the following breakdown: single stressful care procedures (n=60), clustered stressful care procedures (n=128), and clustered stressful care procedures containing at least one tissue-damaging procedures (n=43). We did not observe any tissue damaging procedure performed on its own.

In total, 37 participants were enrolled in this study. Demographic variables of participant's gestation age, birth weight, hemoglobin, and risk of mortality score were assessed in all three groups; single stressful care procedures (SCP_S), clustered stressful care procedures (SCP_C), and clustered stressful care procedures combined with tissue-damaging procedures (Both_C). Gestational age, birth weight (BW), hemoglobin (Hb), and risk of mortality were not significantly different between the three procedures assessed, SCP_S, SCP_C, and Both_C (Table 3).

Table 3

Descriptives between group

	SCP_S	SCP_C	Both_C	P-value
Gestational Age	34.2 ± 1.1	34.1 ± 1.1	34.1 ± 1.2	0.89
BW	2249.2 ± 666.2	2247.3 ± 560.5	2311.9 ± 707.2	0.83
Hb	16.4 ± 3.6	17.2 ± 3	16.7 ± 3.2	0.25
SNAPPE-II	5.8 ± 9.5	6.9 ± 9.8	3.1 ± 5	0.06

Association of Demographic Variables

Significant associations were observed between physiological outcome measures and participant demographic variables during procedures. Mean cerebral StO_2 is significantly associated with gestation age ($p=0.007$), birth weight ($p<0.001$), hemoglobin ($p<0.001$), and the SNAPPE-II ($p=0.007$) (Table 4). Mean renal StO_2 is significantly associated with hemoglobin ($p<0.001$), while heart rate is significantly associated with gestational age ($p<0.001$), birth weight ($p<0.001$), and hemoglobin ($p=0.002$). The mean SpO_2 is not associated with any demographic variables.

During procedures the maximum percent reduction from baseline in cerebral StO_2 is significantly associated with gestational age ($p=0.024$), while the SpO_2 is significantly associated with hemoglobin ($p=0.008$) (Table 5). The minimum value in cerebral StO_2 is significantly associated with birth weight ($p<0.001$), hemoglobin ($p<0.001$), and SNAPPE-II ($p=0.002$) (Table 6). Hemoglobin is significantly associated with minimum values in cerebral StO_2 ($p<0.001$), renal StO_2 ($p<0.001$), SpO_2 ($p=0.018$), and heart rate ($p=0.016$). The maximum value in cerebral StO_2 is significantly associated with gestational age ($p=0.025$), birth weight ($p=0.007$), and hemoglobin ($p<0.001$) (Table 7). Maximum renal StO_2 ($p<0.001$) and SpO_2 ($p<0.001$) are also significantly associated with hemoglobin, while heart rate is significantly associated with gestational age ($p<0.001$) and birth weight ($p=0.003$). Lastly, the maximum reduction in cerebral StO_2 is significantly associated with hemoglobin ($p=0.048$) and SNAPPE-II ($p=0.028$), while SpO_2 is significantly associated with hemoglobin ($p=0.010$) (Table 8).

Table 4

Mean Values

	Cerebral_StO_2		Renal_StO_2		SpO_2		HR	
	Slope	P-value	Slope	P-value	Slope	P-value	Slope	P-value
Gestational Age	-0.883	0.007*	0.516	0.167	0.111	0.537	4.211	<0.001*
BW	0.003	<0.001*	-0.001	0.389	0.000	0.468	-0.007	<0.001*
Hb	0.944	<0.001*	0.714	<0.001*	-0.081	0.173	-0.900	0.002*
SNAPPE-II	-0.088	0.007*	-0.025	0.501	-0.035	0.103	0.075	0.466

* Indicates significance at an alpha of 0.05

Multiple linear regression

Table 5

Maximum Percent Reduction from Baseline

	Cerebral_StO$_2$		Renal_StO$_2$		SpO$_2$		HR	
	Slope	P-value	Slope	P-value	Slope	P-value	Slope	P-value
Gestational Age	-0.900	0.024*	-0.492	0.354	0.415	0.558	0.458	0.645
BW	0.001	0.317	0.002	0.097	-0.002	0.200	-0.002	0.404
Hb	0.087	0.464	0.000	0.999	-0.621	0.008*	0.355	0.276
SNAPPE-II	0.075	0.063	0.064	0.233	-0.020	0.811	-0.094	0.419

* Indicates significance at an alpha of 0.05

Multiple linear regression

Table 6

Minimum Value

	Cerebral_StO$_2$		Renal_StO$_2$		SpO$_2$		HR	
	Slope	P-value	Slope	P-value	Slope	P-value	Slope	P-value
Gestational Age	-0.605	0.172	0.589	0.273	-0.427	0.538	2.991	0.054
BW	0.003	<0.001*	-0.001	0.314	0.001	0.317	-0.005	0.060
Hb	0.782	<0.001*	0.719	<0.001*	0.539	0.018*	-1.221	0.016*
SNAPPE-II	-0.143	0.002*	-0.072	0.186	-0.014	0.861	0.226	0.213

* Indicates significance at an alpha of 0.05

Multiple linear regression

Table 7

Maximum Value

	Cerebral_StO$_2$		Renal_StO$_2$		SpO$_2$		HR	
	Slope	P-value	Slope	P-value	Slope	P-value	Slope	P-value
Gestational Age	-0.844	0.025*	-0.126	0.669	0.000	0.997	3.942	0.001*
BW	0.002	0.007*	0.000	0.404	0.000	0.267	-0.007	0.003*
Hb	1.096	<0.001*	0.542	<0.001*	-0.056	0.015*	-0.441	0.265
SNAPPE-II	-0.025	0.509	0.030	0.319	-0.016	0.062	0.041	0.773

* Indicates significance at an alpha of 0.05

Multiple linear regression

Table 8

Maximum Reduction

	Cerebral_StO_2		Renal_StO_2		SpO_2		HR	
	Slope	P-value	Slope	P-value	Slope	P-value	Slope	P-value
Gestational Age	-0.240	0.650	-0.715	0.195	0.427	0.542	0.951	0.633
BW	-0.001	0.214	0.001	0.154	-0.001	0.269	-0.001	0.713
Hb	0.314	0.048*	-0.177	0.285	-0.595	0.010*	0.780	0.230
SNAPPE-II	0.118	0.028*	0.102	0.069	-0.001	0.987	-0.185	0.429

* Indicates significance at an alpha of 0.05

Multiple linear regression

Cerebral Regional Oxygenation (StO_2)

The effects of single stressful care procedures, clustered stressful care procedures, and clustered stressful care procedures combined with tissue-damaging procedures on cerebral StO_2 were assessed. We found no statistically significant difference in mean cerebral StO_2 between the three procedure groups, p = 0.836 (Table 9). However, when we calculated the maximum percent reduction in cerebral StO_2 from baseline, there was a significantly lower reduction in StO_2 when a single procedure was performed (SCP_S) versus when procedures were performed consecutively or in clusters (SCP_C and Both_C), 2.3% (min -3.3%-max 15.6%), 5.1% (min -3.4%-max 36.7%), and 4.8% (min -0.6%-max 36.9%) respectively, p<0.001 (Table 9). The lowest cerebral StO_2 in response to procedures did not differ among the three procedure groups p=0.076. However, the maximum cerebral StO_2 in response to procedures was 87.8% (SD 6.1) for SCP-C and 87.9% (SD 7) for both-C, which is significantly higher than 84.5% (SD 6.1) for SCP_S (p<0.002). There was no statistically significant difference in the duration of time the subject spent on the lowest cerebral StO_2, 11 (min 2-max 86) seconds for SCP_S, 12 (min 2-max 126) seconds for SCP_C, and 10 (min 2-max 254) seconds for Both_C (p=0.831).

Renal Regional Oxygenation (StO_2)

There was no significant difference in mean renal StO_2 among the procedure groups SCP_S, SCP_C, and Both_C (Table 9). Similar to cerebral StO_2, when we calculated the maximum percent renal StO_2 reduction from baseline, there was a significantly lower reduction in renal StO_2 when a single procedure was performed (SCP_S) versus when multiple procedures were performed consecutively or in a cluster (SCP_C and Both_C), $p<0.001$. In response to procedures, there was a significantly larger percent reduction in renal StO_2 compared to cerebral StO_2 in all three groups (Table 9). The lowest renal StO_2 observed in response to procedures was 76% (SD 6.8) (SCP_C) and 76% (SD 8.2) (Both_C), which is significantly lower than 81% (SD 7.6) observed in the SCP_S group ($p<0.001$). However, the maximum renal StO_2 observed in response to procedures was not significantly different among the three groups ($p=0.133$). Similar to cerebral StO_2, the maximum reduction in renal StO_2 was smaller in the SCP_S than in the SCP_C and Both_C groups, $p<0.001$. Among the three procedure groups, there was no statistically significant difference in the duration of time the subject spent on the lowest renal StO_2: 8 (min 2-max 182) seconds for SCP_S, 6 (min 2-max 290) seconds for SCP_C, and 6 (min 2-max 14) seconds for Both_C ($p=0.071$).

Oxygen Saturation (SpO_2)

Unlike cerebral and renal StO_2, SpO_2 mean values were significantly higher in the SCP_S group than in SCP_C and Both_C groups ($p<.021$) (Table 9). Similar to cerebral and renal StO_2, procedures performed singly (SCP_S) resulted in the maximum percent reduction from baseline for SCP_S 3.4% (min 0.1%-max 32.7%), SCP_C 9.7% (min 0.9%-max 59.7%), and Both_C 8.6% (min -5.8%-max 49.2%), ($p<0.001$). The lowest

SPO_2 value observed in response to procedures was 87% (min 37%-max 98%) (SCP_C) and 86% (min 49%-max 98%) (Both_C), which is significantly lower than 94% (min 65%-max 99%) (SCP_S) $p<0.001$). The maximum SpO_2 observed in response to procedures was not significantly different across the procedure groups ($p=0.715$). The lowest SpO_2 observed in response to procedures in the SCP_C and Both_C groups are below the recommended values for preterm infants. Similar to cerebral and renal StO_2, the total duration spent at the lowest SpO_2 value was not statistically significant between the three procedure groups ($p=0.145$) (Table 9).

Heart Rate

Similar to the cerebral and renal StO_2, the mean heart rate was not significantly different among the three procedure groups, SCP_S, SCP_C, and Both_C. Unlike cerebral and renal StO_2 and SpO_2, the maximum percent reduction in heart rate compared to baseline was not significantly different between the three groups ($p=0.255$) (Table 9). The lowest heart rate observed in response to procedures was not significantly different in all three procedure groups ($p=0.125$). However, the maximum heart rate in response to procedures was observed in Both_C (183±16.5), which is significantly higher than the heart rate response in the SCP_S group (169.9±14.1) ($p<0.001$). The heart rate response from the SCP_C group is not significantly different from the Both_C groups. The total duration of time spent at the lowest heart rate was not statistically significant between the three procedure groups ($p=0.347$) (Table 9).

Chapter 5, the final chapter, includes the discussion and conclusion of the study findings.

Table 9

Clinical comparisons between the three groups

	Stressful Care Procedure_Single (SCP_S)	**Stressful Care Procedure_Cluster (SCP_C)**	**Stressful Care Procedure + Tissue-Damaging Procedure Cluster (Both_C)**	**P-value**
Mean_Cerebral_StO2; *(Mean ± SD)*	82.4±6.5	82.7±5.5	83.1±6.2	0.836
Mean_Renal_StO2; *(Mean ± SD)*	86.2±6.5	86.1±5.1	86.2±4.9	0.994
Mean_SpO2; *(Mean ± SD)*	97.6±2.2	96.5±2.2	96.4±2.4	0.021*
Mean_HR; *(Mean ± SD)*	155.2±13.8	158.3±12.2	159.4±12.4	0.329
Percent_Cerebral_StO2_reduction_from_baseline; *Median (Min. , Max.)*	2.3(-3.3,15.6)	5.1(-3.4,36.7)	4.8(-0.6,36.9)	<0.001*
Percent_Renal_StO2_reduction_from_baseline;; *(Mean ± SD)*	5.1±4.6	11.4±6.7	12.0±8.3	<0.001*
Percent_SpO2_reduction_from_baseline; *Median (Min. , Max.)*	3.4(0.1,32.7)	9.7(0.9,59.7)	8.6(-5.8,49.2)	<0.001*
Percent_HR_reduction_from_baseline; *Median (Min. , Max.)*	7.8(-5.3,50.7)	11.6(-1.8,72.5)	9.7(-4.4,60.4)	0.255
Min_Cerebral_StO2; *Median (Min. , Max.)*	81(62,90)	78(50,90)	77(54,90)	0.076
Min_Renal_StO2; *(Mean ± SD)*	81.8±7.6	76.9±6.8	76.6±8.2	<0.001*
Min_SpO2; *Median (Min. , Max.)*	94(65,99)	87(37,98)	86(49,98)	<0.001*
Min_HR; *Median (Min. , Max.)*	144(87,179)	133(58,162)	130(61,170)	0.125
Max_CerebralStO2; *(Mean ± SD)*	84.5±6.1	87.8±6.1	87.9±7	0.002*
Max_Renal_StO2; *Median (Min. , Max.)*	92(75,94)	93(77,100)	93(84,100)	0.133
Max_SpO2; *(Mean ± SD)*	99.4±0.9	99.5±0.8	99.4±1	0.715
Max_HR; *(Mean ± SD)*	169.9±14.1	180.1±14.5	183±16.5	0.001*
Maximum reduction of cerebral StO2; *Median (Min. , Max.)*	4(1,14)	8(1,41)	8(1,34)	<0.001*
Maximum reduction of renal StO2; *(Mean ± SD)*	7.6±4.9	14.8±6.6	16±9	<0.001*
Maximum reduction of SpO2; *Median (Min. , Max.)*	6(1,35)	13(2,63)	14(2,51)	<0.001*
Maximum reduction of HR; *Median (Min. , Max.)*	27(10,104)	45(13,157)	43(12,144)	<0.001*
Total_seconds_of_min_value_of_Cerebral_StO2; *Median (Min. , Max.)*	11(2,86)	12(2,126)	10(2,254)	0.831
Total_seconds_of_min_value_of_Renal_StO2; *Median (Min. , Max.)*	8(2,182)	6(2,290)	6(2,284)	0.071
Total_seconds_of_min_value_of_SpO2; *Median (Min. , Max.)*	4(2,46)	6(2,38)	2(2,14)	0.145
Total_seconds_of_min_value_of_HR; *Median (Min. , Max.)*	2(2,12)	4(2,16)	2(2,10)	0.347

CHAPTER FIVE

DISCUSSION

Moderate to late preterm infants are admitted to the NICU due to their systemic immaturity. During hospitalization, infants undergo a variety of necessary care procedures. The purpose of this research study is to assess the effects of routine care on cerebral and renal oxygenation in hospitalized preterm infants. Routine procedure is described as non-tissue-damaging care performed singly, non-tissue damaging multiple care procedures performed consecutively or in clusters or tissue-damaging and non-tissue-damaging multiple care procedures performed consecutively or in cluster. The research questions guiding this study are 1) How is cerebral and renal oxygenation affected by routine procedures, monitored by near infrared spectroscopy (NIRS), in hospitalized moderate to late preterm infants (32-36 $^{6/7}$ weeks gestation)? 2) How do participant characteristics affect cerebral and renal oxygenation in response to commonly performed routine procedures measured via NIRS in hospitalized moderate to late preterm infants?

To answer the research questions, a prospective observation method was used. Preterm infants born between 32-36 $^{6/7}$ weeks gestation were recruited. Infants were observed for approximately 6 hours. This time frame was selected to capture two scheduled care periods. Several findings emerged based on the research questions. In this chapter, a summary of the results and implications for practice will be discussed.

Summary of Findings

The results of this study show significant results regarding the effects of routine NICU care on moderate to late preterm infants. To our knowledge, this is the first study identifying the effect of routine handling procedures, performed singly or in cluster, on cerebral and renal StO_2. The results of this research study show a greater percent change reduction when clustered care procedures are performed than when single care procedures are performed. Although some of the clustered procedures contain tissue-damaging procedures (TDP) (Both_C), the results indicate a similar response irrespective of the presence or absence of a TDP.

Our study results show that reductions in cerebral StO_2, renal StO_2, and SpO_2 are greater in clustered procedures than single procedures. Additionally, results show that the maximum reduction in cerebral StO_2, renal StO_2, SpO_2, and heart rate is almost twice as great in clustered procedures than in single procedures. We could not locate similar studies reporting percent changes in StO_2 concerning routine care procedures; however, we did identify studies assessing different aspects of this study.

A recent study reported effects of care on heart rate and SpO_2 in percent change but not in StO_2. A study by Donia and Tolba (2016) assessed the percent change in heart rate and SpO_2 before, during, and after procedures in two groups. In this study, group one was exposed to painful procedures, and group two was not exposed to painful procedures. Although the percent change was greater in group one, both groups had a significant percent change in heart rate and SpO_2 during procedures compared to baseline (Donia & Tolba, 2016). In this study, the number of procedures significantly predicted the percent change in SpO_2 during and after the procedure. This is similar to our research, where the percent change in SpO_2 was significantly greater in clustered procedures than in single procedures.

Our results show that infants have a significantly higher heart rate when exposed to clustered procedures than with a single procedure. This result suggests that during clustered procedures, infants had a higher heart rate, potentially indicating stress. This is similar to the response of subjects studied by Zeiner et al. (2016), whose heart rate was significantly higher during procedures when compared to baseline. This research also found that preterm infants responded with similar signs of stress in procedures with and without a painful stimulus. In our study, clustered procedures that contained a potentially painful tissue-damaging procedure produced near identical results to clustered procedures that did not include a potentially painful procedure.

The results also demonstrate a difference in StO_2 values between cerebral and renal. The percent reduction from baseline in renal StO_2 is more than double the cerebral StO_2 in all three procedure groups (single stressful care procedures (SCP_C), clustered stressful care procedures (SCP_C), and clustered stressful care procedures with tissue-damaging procedures (Both_C) The maximum reduction from baseline is twice as high in renal StO_2 than in cerebral StO_2. The mean renal StO_2 is higher than cerebral mean StO_2 in all three procedure groups; likewise, the maximum value is higher in renal StO_2. However, in minimum values, the renal StO_2 is slightly lower than cerebral StO_2 values. In response to the procedure, there is a significantly greater fluctuation in renal StO_2 values than in cerebral values in all three groups, suggesting a brain-protecting systemic effect. This is similar to preliminary data by Mousselli et al. (2019), where cerebral StO_2

was inclined to remain steady during most caregiving procedures in extremely preterm infants.

Limitations and Strengths

This study had several notable limitations and strengths. A limitation of this study is the small sample size which may limit generalizability. Secondly, NIRS and pulse oximetry data were lost or removed due to sensor issues noted in the procedure log and in the raw data. Additionally, pulse oximetry data was lost due to problems in downloading the data in the first 8 participants. Another limitation was the lack of procedure end times for participants early in the study. Lastly, the presence of the researcher may have caused a potential change in caregiving methods.

The results of this study were strengthened by the direct observation and real-time documentation of procedures. An effort was also made to ensure synchronized time stamping with NIRS, pulse oximetry devices, and procedure log. Additionally, the adherence to strict inclusion and exclusion criteria ensured that participants were homogenous.

Implications

As a result of this study, there are several implications for practice, nursing, theory, and future research to consider. Practice that guides the care of neonates requires an understanding of neonatal physiology. The effects of stress in a neonate can produce acute changes in physiologic variables like heart rate and potentially reduce cardiac output and further decrease tissue perfusion, which can increase the damage due to ischemia (Slater et al., 2012). An examination of infant caregiving patterns may decrease potentially detrimental effects of stress. In addition, using soothing intervention strategies, like facilitated tucking and containment, for handling and positioning can minimize undue stress and pain (Gomes Neto et al., 2020; Schiavenato & Holsti, 2017). However, the practice of caring for preterm infants is influenced by institutional policies, procedures, and staffing. This study provides some initial data that can prompt institutions to examine the effect of policies, procedures, and staffing on the care of infants. This includes the utilization of an individualized care schedule that is based on infant cues and physiologic responses.

As primary health care providers, nurses play a pivotal role in patient care. These findings are helpful to neonatal nursing practice because they demonstrate the effects of clustering procedures on infant tissue perfusion. These results may prompt nurses to change methods of routine care by allowing the infant to rest between intrusive procedures. Nurses may also be able to communicate with the multidisciplinary team on the optimal times to perform procedures.

Theory may be impacted by the results of this study in the development of neonatal-specific theories. The conceptual framework presented implies that infants reach a threshold of stress before decompensation begins. The results of this study confirm that infants who experience multiple repeated stimuli experience a greater negative effect than those who have a single stimulus. The development of neonatal-specific theories prompts a closer look at the impact of neonatal care and the environment.

As a result of this study, additional research is needed in assessing biomarkers of hypoxia and stress. It was demonstrated in the study results that infant experience greater fluctuations in renal StO_2 than cerebral StO_2, which prompts a closer look at kidney decompensation. Additionally, research assessing biomarkers of hypoxia in this population during individual and cumulative procedures can provide a deeper look at the effects of care. Utilizing NIRS in intervention studies with randomization can assess different methods of providing care on tissue oxygenation, bringing to question of the adequacy of current standard monitoring.

Conclusions and Future Directions

It is evident from the results of this research that infants are impacted more by the quantity or length of procedures, as in clustered procedures, than they are by single procedures. Study infants exhibited similar physiologic responses to handling, whether the handling episode had a painful procedure included or not. The conceptual framework composed for this study is appropriate. It emphasized the effect of stimuli and the adaptation process. The study results reveal that when exposed to multiple stimuli, as what occurs during clustered procedures, preterm infants are unable to maintain body-wide homeostasis thus increasing the risk for decompensation. It is during exhaustion where infants sustain potentially detrimental changes in tissue perfusion. If the results of this study are ignored, detrimental effects may be exhibited by preterm infants. Caregiving to preterm infants requires knowledge, collaboration, and sensitivity to provide care that is not damaging to infant health.

Although our results show significant alterations in StO_2, HR and SpO_2 in the clustered care groups, the effect of these changes on tissues is unknown. For future studies, questions such as “How long and how low does the StO_2, HR and SpO_2 need to be before tissue damage occurs” need to be answered. This study identified areas that need closer observation to provide care that promotes improved patient outcomes.

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Appendix A

Procedures	**Stressful Care Procedures (SCP)**	**Tissue Damaging Procedure (TDP)**
Accessories (adjusting, removing, or placing: cap, eye shields, linen, ID band)	✓	
Applying pressure	✓	
Assessing heel lance site	✓	
Assessing IV placement site	✓	
Assessing/Flusing IV site	✓	
Assessment	✓	
Auscultation	✓	
Blood collection	✓	
BP Measurement (includes cuff placement, cycling, cuff removal)	✓	
Burping	✓	
Changing IV site	✓	
Clothing change	✓	
Diaper change	✓	
Feeds NG	✓	
Feeds oral	✓	
Holding	✓	
Handling (moving up in bed, picking up, putting down, sitting up)	✓	
Heel blood collection	✓	
Heel lance		✓
IV puncture		✓
Medication	✓	
Nasal suction		✓
Oral care	✓	
Oral suction		✓
Patting	✓	
Placing heel warmer	✓	
Pulse ox placement	✓	
Removing bili bed	✓	
Removing heel warmer	✓	
Repositioning	✓	
Room change	✓	
Securing IV	✓	
Skin care	✓	
Swaddling	✓	
Securing NG	✓	
Tape removal (skin tape, pulse ox, skin temperature probe)		✓
Temperature measurement (axillary or temporal)	✓	
Tourniquet placement	✓	
Unswaddling	✓	
Venipuncture		✓
Verify GT placement	✓	
Weighing	✓	

Appendix B

Preterm Handling Study

Study Information

Participant #	Date	Start Time	End Time

Electrodes

aEEG	Pulse ox	NIRS Kidney	NIRS Cerebral
None		Flank	Forehead

Demographic Data

DOB	GA @ birth	Gender	Race	Birth Weight (g)	Birth Order	APGAR 5 min	APGAR 10 min	Primary Dx	DOL	Mat Subst Use	Mode of Birth	Vent @ Birth	Vent @ Study	O_2 Level (%)	Most recent Hgb

Severity of Illness

BP	Mean BP	Temp (ºC)	PO_2/FiO_2 Ratio	Lowest pH	Seizures	Urine output	Birth weight (g)	SGA < 3rd percentile	APGAR 5 min	Notes

Procedure Log

Time start	Time stop	Procedure	Comment

Appendix C

Parameter Range	Score Points
Mean blood pressure (mm Hg)	
>30	0
20-29	9
<20	19
Lowest temperature (°F)	
>96	0
95-96	8
<95	15
Po_2/Fio_2 ratio	
>2.5	0
1-2.49	5
0.3-0.99	16
<0.3	28
Lowest serum pH	
>7.2	0
7.1-7.19	7
<7.1	16
Multiple seizures	
No	0
Yes	19
Urine output (ml/kg/hr)	
>1	0
0.1- 0.9	5
<0.1	18
APGAR score	
>7	0
<7	18
Birth weight (gm)	
>1000	0
750-999	10
<750	17
Small for gestational age	
<3rd percentile	12

[Table/Fig-1]: Scale design
Score was awarded zero for a particular variable when the investigation was not ordered based on clinical assessment

Appendix D

LOMA LINDA UNIVERSITY
HEALTH

INSTITUTIONAL REVIEW BOARD
HUMAN RESEARCH & COMPLIANCE
24887 Taylor Street • Suite 201 • Loma Linda, CA 92350
(909) 558-4531 (voice) • (909) 558-0131 (fax)

Initial Approval Notice - Expedited ***IRB# 5210046***

To: **D'Errico, Ellen**
Department: **Nursing Graduate Programs**
Protocol: **Physiological effects of handling in moderate to late preterm infants receiving neonatal intensive care**

This study was reviewed and approved administratively on behalf of the IRB. This decision includes the following determinations:

Risk to research subjects: **Minimal**
Approval begins: **16-Feb-2021**
Stipulations of approval:
See attached list of items (if applicable).
See Appendix A for Conditions of Approval.

Adverse events and unanticipated problems must be reported in accord with the attached Adverse Event Reporting Matrix **A.**

All investigators are responsible for assuring that studies are conducted according to the approved protocol. Principal investigators are responsible for the actions of sub-investigators and staff with regard to this approval.

Please note the PI's name and the assigned IRB number, as indicated above, on any future communications with the IRB.

Direct all communications to the IRB c/o Human Research and Compliance.

Thank you for your cooperation in LLUH's shared responsibility for the ethical use of human subject in research.

Andrea O. Rayo ________________________ 02/17/2021 ____________
IRB Chair/Designee Date

Appendix E

LOMA LINDA UNIVERSITY
Nursing Research

February 5, 2021

To: Nancy Brashear, PhD-c
Ellen D'Errico, PhD

Dear Nancy,

On behalf of the Nursing Research Council (NRC), I have the pleasure of informing you that your dissertation entitled, "**Physiologic effects of handling in moderate to late preterm infants receiving neonatal intensive care"** has been recommended for acceptance. We feel that this is a well written, well developed worthwhile project and are excited to have you move forward. We look forward to hearing your results!

You may proceed to the LLU IRB for approval and once approval is received move forward. Please share this approval letter with the LLU IRB and email me a copy of the final IRB documents and approval so that I can update your file. Upon completion of your project the Nursing Evidence-based Practice and Research Council requests that you present your findings to the council.

Good luck with your project. If we can be of any further assistance, please contact me.

Sincerely,

Patti Radovich

Patti Radovich, RN, PhD, CNS, FCCM
Chair, Nursing Evidence-based Practice and Nursing Research Council
Director Nursing Research
909-558-3923 pager pradovich@my2way.com
pradovich@llu.edu

Appendix F

PHYSIOLOGIC EFFECTS OF HANDLING IN MODERATE TO LATE PRETERM INFANTS RECEIVING NEONATAL INTENSIVE CARE

Study Title

LOMA LINDA UNIVERSITY
School of Nursing

INFORMED CONSENT

TITLE:	**PHYSIOLOGIC EFFECTS OF HANDLING IN MODERATE TO LATE PRETERM INFANTS RECEIVING NEONATAL INTENSIVE CARE.**
SPONSOR:	__________
PRINCIPAL INVESTIGATOR:	Ellen D'Errico, PhD, RN 11262 Campus St. Loma Linda Ca, 92354 909-558-1000 ext. 83832

Key Information for You to Consider

- **Voluntary Consent**. You are being asked to allow your baby to participate in a research study. It is up to you whether you choose to permit your baby to participate or not. There will be no penalty or loss of benefits to which you or your baby are otherwise entitled if you choose not to participate or discontinue participation.
- **Purpose**. While in the NICU, babies experience a variety of procedures, some are routine care and some can be painful. This study is done to better understand the responses of babies to care. We want to conduct this study to see if routine care effects kidney and brain oxygen levels.
- **Duration.** It is expected that your baby's participation will last no more than 7 hours.
- **Procedures and Activities.** We will place a soft adhesive electrode on your baby's forehead and back and record your baby's use of oxygen in the brain and kidneys during the observation period. A researcher will be present to record care activities provided, and write down your baby's responses in a log.
- **Risks.** We do not anticipate any risks from the use of the electrodes. Some of the foreseeable risks include skin irritation.
- **Benefits**. Although your baby will not directly benefit from this study, we hope the results and the information learned from this study will help us learn how care effects a baby so we can improve clinical care.
- **Alternatives.** If you decide not to participate in this study, your baby will receive the standard care and treatment given to all babies in the NICU. Participation is voluntary.

PHYSIOLOGIC EFFECTS OF HANDLING IN MODERATE TO LATE PRETERM INFANTS RECEIVING NEONANTAL INTENSIVE CARE

PURPOSE OF STUDY

You are invited to participate in this study because your baby is premature and is a patient in our neonatal intensive care unit (NICU). While in the NICU, babies experience a variety of procedures, some are routine cares and some can be painful.

This study is done to better understand the responses of babies to care. We want to conduct this study to see if routine care effects kidney and brain oxygen levels. Our long-term goal is to improve clinical care and outcomes for premature babies.

Approximately 38 babies will take part in this study at Loma Linda University Children's Hospital.

DESCRIPTION OF PROCEDURE

For up to 7 hours, on day of life 3-7, we will record your baby's oxygen use using an electrode on your baby's back and forehead. The electrode has a soft adhesive and should not cause discomfort to your baby. We will record and keep track of your baby's vital signs such as heart rate, breathing, and oxygen saturation, as well as all medical procedures. We will also make note of your baby's behavior (like sleep/awake/crying, yawning, and hiccupping to name a few) before, during, and after routine care and procedures. We will also collect information from your baby's medical record including (but not limited to) gender, race, birth weight, vital signs, and treatments.

RISKS

The committee at Loma Linda University that reviews human studies (Institutional Review Board) has determined that participating in this study exposes your baby to minimal risk.
We do not anticipate any risks from the use of the electrodes. The manufacturer states that the risks are minimal and may include skin irritation. The manufacturer recommends checking skin every 12 hours, however, for this study; the electrodes will be on no more than 7 hours.

BENEFITS

Although your baby will not directly benefit from this study, we hope the results and the information learned from this study will help us understand how care effects a baby so we can improve clinical care.

PARTICIPANT RIGHTS

Participation in this study is voluntary. Your decision whether or not to participate or withdraw at any time from the study will not affect your baby's ongoing medical care and will not result in any penalty or loss of benefits to which you are otherwise entitled.

ALTERNATIVE TREATMENT

If you decide not to participate in this study, your baby will receive the standard care and treatment given to all babies in the NICU.

CONFIDENTIALITY

Efforts will be made to keep your baby's personal information confidential. We cannot guarantee absolute confidentiality. Your baby will not be identified by name in any publications describing the results of this study. We will de-identify data by labeling it with a unique participant number. Your baby's personal identifying information will be kept in a separate location, in a locked cabinet and room. Your rights regarding permission to use your health information are described on the attached "Authorization for Use of Protected Health Information" form.

COSTS

There is no cost to you or your insurance company for participating in this study.

REIMBURSEMENT

You will not be paid for participating in this study.

IMPARTIAL THIRD-PARTY CONTACT

If you wish to contact an impartial third party not associated with this study regarding any questions, you may contact the Office of Patient Relations, Loma Linda University Medical Center, Loma Linda, CA 92354, phone (909) 558-4647, e-mail patientrelations@llu.edu for information and assistance.

WHERE CAN I GET MORE INFORMATION?

You may call Nancy Brashear, PhD(c), RN during regular office hours at 909-558-1000 ext. 81764.

You will get a copy of the California Experimental Subject's Bill of Rights and this form.

MY INFORMED CONSENT STATEMENT

I have read the contents of this consent form and have listened to the verbal explanation given by the investigator. My questions concerning this study have been answered to my satisfaction. I hereby give voluntary consent for my baby to participate in this study. I have received a copy of the California Experimental Subject's Bill of Rights and this form for my records. Signing this consent document does not waive my rights nor does it release the investigators, institution or sponsors from their responsibilities. I agree that my baby's protected health information may be used for research purposes described in this form. As part of my baby's participation in this study, I authorize the release of information to Loma Linda University Institutional Review Board. I hereby give voluntary consent to participate in this study.

I understand I will be given a copy of this consent form after signing it.

Name of Subject	Date/Time
Signature of Parent/Guardian	Printed Name of Parent/Guardian

INVESTIGATOR'S/CO-INVESTIGATOR STATEMENT

I have reviewed the contents of the California Experimental Subject's Bill of Rights and the consent form with the person signing above. I have explained potential risks and benefits of the study.

Investigator/Co-Investigator Signature	Date/Time

PHYSICIAN'S STATEMENT

As the primary physician responsible for the care of this patient, I indicate having knowledge of this research and my patient's participation.

Primary Physician Signature	Date/Time
Physician Name Printed	

Page 4 of 4
Consent Version Date: _______

Appendix G

EFFECTOS FISIOLÓGICOS DEL MANEJO EN BEBÉS PREMATUROS MODERADOS A TARDÍOS QUE RECIBEN CUIDADOS INTENSIVOS NEONATALES

LOMA LINDA UNIVERSITY
School of Nursing

CONSENTIMIENTO INFORMADO

TÍTULO:	**EFECTOS FISIOLÓGICOS DEL MANEJO EN BEBÉS PREMATUROS MODERADOS A TARDÍOS QUE RECIBEN CUIDADOS INTENSIVOS NEONATALES**
PATROCINADOR:	
INVESTIGADORA PRINCIPAL:	Ellen D'Errico, PhD, RN 11262 Campus St. Loma Linda Ca, 92354 909-558-1000 ext. 83832

Información clave para su consideración
• **Consentimiento voluntario**. Se le pide que permita que su bebé participe en un estudio de investigación. Depende de usted si decide permitir que su bebé participe o no. Si decide que no participe o suspende su participación, no será objeto de penalización o pérdida de beneficios a los que de otra manera usted o su bebé tienen derecho. • **Propósito**. Mientras que en la Unidad de Cuidados Intensivos Neonatales (NICU, por sus siglas en inglés) los bebés experimentan una variedad de procedimientos, algunos son cuidados de rutina y otros pueden ser dolorosos. Este estudio se hace para entender mejor las respuestas de los bebés a tales cuidados. Queremos llevar a cabo este estudio para ver si los cuidados de rutina afectan los niveles de oxígeno renal y cerebral. • **Duración.** Se espera que la participación de su bebé dure no más de 7 horas. • **Procedimientos y actividades.** Colocaremos un electrodo adhesivo suave en la frente y otro en la espalda de su bebé y registraremos el uso de oxígeno en el cerebro y en los riñones de su bebé durante el período de observación. Un/a investigador/a estará presente para registrar las actividades de cuidados proporcionadas y anotar las respuestas de su bebé en un registro. • **Riesgos.** No anticipamos ningún riesgo por el uso de electrodos. Algunos de los riesgos previsibles incluyen irritación de la piel. • **Beneficios**. Aunque su bebé no se beneficiará directamente a causa de este estudio, esperamos que los resultados y la información obtenidos durante el mismo nos ayuden a saber cómo afectan al bebé los cuidados que recibe a fin de que podamos mejorar la atención clínica. • **Alternativas.** Si decide que su bebé no participe en este estudio, su bebé recibirá los cuidados y tratamientos habituales dados a todos los bebés en la NICU. La participación es voluntaria.

PROPÓSITO DEL ESTUDIO

Se le invita a participar en este estudio porque su bebé es prematuro y es paciente en nuestra Unidad de Cuidados Intensivos Neonatales (NICU, por sus siglas en inglés). Mientras están en la NICU, los bebés experimentan una variedad de procedimientos, algunos son cuidados de rutina y algunos pueden ser dolorosos.

Este estudio se hace para entender mejor las respuestas de los bebés a tales cuidados. Queremos llevar a cabo este estudio para ver si los cuidados de rutina afectan los niveles de oxígeno renal y cerebral. Nuestro objetivo a largo plazo es mejorar la atención clínica y los resultados para los bebés prematuros.

Alrededor de 38 bebés participarán en este estudio en el Loma Linda University Children's Hospital.

DESCRIPCIÓN DEL PROCEDIMIENTO

Durante un máximo de 7 horas en los días de vida 3 al 7, registraremos el uso de oxígeno de su bebé usando un electrodo en la espalda y otro en la frente de su bebé. Los electrodos tienen adhesivos suaves; no van a causarle molestias al bebé. Registraremos y realizaremos un seguimiento de los signos vitales de su bebé, tales como la frecuencia cardíaca, la respiración y la saturación de oxígeno, además de todos los procedimientos médicos. También —antes, durante y después de los cuidados y procedimientos de rutina— tomaremos nota del comportamiento de su bebé (según lo evidencia durante el sueño, o cuando despierta, llora, bosteza o tiene hipo, por ejemplo). Además, recopilaremos información del historial médico de su bebé que incluyen (pero no se limitan a) género, raza, peso al nacer, signos vitales y tratamientos.

RIESGOS

El comité de la Loma Linda University que revisa los estudios en humanos (Junta Examinadora Institucional) ha determinado que participar en este estudio expone a su bebé a un riesgo mínimo.

No anticipamos ningún riesgo por el uso de los electrodos. El fabricante afirma que los riesgos son mínimos y pueden incluir irritación de la piel. El fabricante recomienda revisar la piel cada 12 horas; con todo, para este estudio, los electrodos permanecerán no más de 7 horas.

BENEFICIOS

- Aunque su bebé no se beneficiará directamente de este estudio, esperamos que los resultados y la información obtenidos durante el mismo nos ayuden a saber cómo afectan al bebé los cuidados que recibe a fin de que podamos mejorar la atención clínica.

DERECHOS DE LOS PARTICIPANTES

La participación en este estudio es voluntaria. Su decisión de permitir la participación de su bebé en este estudio o de retirarla en cualquier momento no afectará la atención médica continua de su bebé y no resultará en ninguna penalización o pérdida de beneficios a los que de otra manera su bebé tenga derecho.

TRATAMIENTO ALTERNATIVO

Si decide que su bebé no participe en este estudio, su bebé recibirá la atención estándar y el tratamiento que se da a todos los bebés en la NICU.

CONFIDENCIALIDAD

Se harán esfuerzos para mantener confidencial la información personal de su bebé. No podemos garantizar la absoluta confidencialidad. Su bebé no será identificado por nombre en ninguna publicación que describa los resultados de este estudio. Anonimizaremos los datos etiquetándolos con un número de participante único. La información de identificación personal de su bebé se conservará en lugar aparte, en un archivo protegido en una habitación bajo llave. Sus derechos con respecto al consentimiento para usar la información médica de su bebé se describen en el formulario adjunto titulado «Autorización para el uso de información médica protegida».

COSTOS

No hay ningún costo para usted o su compañía de seguros por la participación de su bebé en este estudio.

REEMBOLSO

No se le pagará por la participación de su bebé en este estudio.

CONTACTO IMPARCIAL CON TERCEROS

Si con respecto a cualquier pregunta desea comunicarse con un tercero imparcial no asociado con este estudio, puede comunicarse con la Oficina de Relaciones con el Paciente, Loma Linda University Medical Center, Loma Linda, CA 92354, teléfono (909) 558-4647, correo electrónico patientrelations@llu.edu para obtener información y asistencia.

¿DÓNDE PUEDO OBTENER MÁS INFORMACIÓN?

Puede llamar a Nancy Brashear, PhD(c), RN, durante el horario de oficina regular, marcando el 909-558-1000 ext. 81764.

Usted obtendrá una copia de la Carta de Derechos del Sujeto Experimental de California y este formulario.

MI DECLARACIÓN DE CONSENTIMIENTO INFORMADO

He leído el contenido de este formulario de consentimiento y he escuchado la explicación verbal dada por la investigadora. Mis preguntas con respecto a este estudio han sido respondidas a mi entera satisfacción. Por la presente doy mi consentimiento voluntario para que mi bebé participe en este estudio. He recibido una copia de la Carta de Derechos del Sujeto Experimental de California y este formulario para mis registros. Firmar este documento de consentimiento no abroga mis derechos ni libera de sus responsabilidades a los investigadores, instituciones o patrocinadores. Estoy de acuerdo con que la información médica protegida de mi bebé se pueda utilizar para fines de investigación según se describen en este formulario. Como parte responsable de la participación de mi bebé en este estudio, autorizo la divulgación de información a la Junta Examinadora Institucional de la Loma Linda University. Por la presente doy mi consentimiento voluntario para la participación de mi bebé en este estudio.

Entiendo que se me dará una copia de este formulario de consentimiento después de firmarlo.

Nombre del sujeto experimental	Fecha / Hora
Firma del padre, madre o tutor/a	Nombre del padre, la madre o el (la) tutor/a en letra de molde

DECLARACIÓN DE LA INVESTIGADORA O DEL (DE LA) INVESTIGADOR/A CORRESPONSABLE

He revisado el contenido de la Carta de Derechos del Sujeto Experimental de California y el formulario de consentimiento con la persona que firma arriba. He explicado los riesgos y beneficios potenciales del estudio.

Investigadora / Investigador/a corresponsable	Fecha / Hora

DECLARACIÓN DEL MÉDICO

Como médico principal responsable de la atención de este/a paciente, indico tener conocimiento de esta investigación y de la participación de mi paciente.

Firma del médico principal	Fecha / Hora
Nombre del médico en letra de molde	

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Consent Version Date: _______