2018-05-26

The Association of Kangaroo Mother Care, Energy Conservation, and Bonding in Preterm Neonates

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Hahn School of Nursing and Health Science

DOCTOR OF PHILOSOPHY IN NURSING

THE ASSOCIATION OF KANGAROO MOTHER CARE, ENERGY CONSERVATION, AND BONDING IN PRETERM NEONATES

By

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A dissertation presented to the

FACULTY OF THE HAHN SCHOOL OF NURSING AND HEALTH SCIENCE

UNIVERSITY OF SAN DIEGO

In partial fulfillment of the
Requirements for the degree

DOCTOR OF PHILOSOPHY IN NURSING

May 2018

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UNIVERSITY OF SAN DIEGO

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Abstract

Purpose: To examine the association of kangaroo mother care (KMC) on energy utilization and bonding as evidenced by reduced biochemical markers of adenosine triphosphate (ATP) degradation, hypoxanthine (Hx), xanthine (Xa), and uric acid (UA), and (allantoin), a measure of oxidative stress in preterm infants 24-36 weeks gestation. A secondary objective was to compare specific physiological parameters using bedside monitoring and perfusion and oxygenation of the gut using near-infrared spectroscopy (NIRS) during 1 hour of KMC compared to incubator care.

Study design: A randomized controlled trial (RCT) examining the effects of 1-hour of KMC or 1-hour incubator care on urinary markers from samples collected 3-6 hours before and 3-6 hours after KMC. Preterm infants (n = 51) were assigned to intervention/control groups using stratified randomization based on weight. Urine concentrations of Hx, Xa, and UA, were measured using high performance liquid chromatography (HPLC) and allantoin was quantified using gas chromatography-mass spectrometry (GC-MS) methods. Bonding was measured using the Mother-to-infant Bonding Scale, a reliable 8-item self-assessment scale linking early maternal moods to difficulties in bonding. Psychometric properties have demonstrated a two-factor model, good predictive validity, a sensitivity of 0.90 and specificity of 0.80 for a threshold score ≥ 2, and acceptable internal consistency (a = 0.71). Physiologic measures were captured using bedside monitoring and abdominal NIRS to capture gut perfusion and oxygenation.

Results: There was a decrease in oxidative stress (p = 0.026) in the KMC group compared to incubator group. In both groups there were trending improvements in uric acid (p = 0.025) and xanthine (p = 0.042) over time, and in abdominal temperatures (p =

0.004) and perfusion index (p = 0.031) over time. No other physiologic or urinary measures showed statistically significant changes either between the groups or over time. A mixed model analysis of variance (ANOVA) was conducted with the use of unstructured covariance matrix adjusted using the Bonferroni method to assess the changes in the outcome measures of urinary purines and physiological measures. Mother–Infant Bonding scores were calculated using relative risk. The number and percentage of subjects who changed their MIBS scores from baseline to time 3 were measured, and the comparison of these changes between the KMC on DOL 3 and DOL 4 as measured by the Mother-Infant-Bonding-Scale (MIBS) in intervention and control groups were calculated. We found that scores showed KMC mothers exhibited a higher risk of bonding problems than those in the control group. Nineteen percent more mothers in the KMC group demonstrated an increase in MIBS score or a 26% increase relative risk for an increase of score (*RR*=1.26; 95% CI 0.97,1.63). However, the results were not statistically significant as the null value was included in the 95% confidence interval. Significance was set at an alpha of 0.05.

Conclusions: This is the first study to evaluate the association of KMC on biochemical markers of stress and physiological parameters of abdominal near-infrared spectroscopy (NIRS) and abdominal temperatures in preterm infants 24-36 weeks gestation. The results of this study suggest that stress and inflammatory processes are decreased in the presence of KMC. Further research is needed to understand the role of biochemical markers and KMC and its implications in nursing research in preterm neonates. This study has the potential to provide the physiological data to further support the benefits of energy conservation for recovery and growth in neonates.

Dedication

This is dedicated to my three beautiful children – Shana, Tony, and Kim. I love you more than you will ever know and I hope in some way, I have inspired you to dream big, and never give up on your dreams. The sky is the limit. Never let anyone hold you back from achieving your goals whether personal, academic, or spiritual. May God hold you close to His Heart, and fill your life with His love and tender care.

Acknowledgements

To my "Expert Team" Dissertation Committee: Dr. Fry-Bowers, Dr. Deming, and Dr. Barger - thank you for your patient guidance and wisdom over the past years. I am a nurse scientist today because of your kind leadership.

To all my professors - you all have taught me the meaning of teaching for success. You have inspired me to keep learning and growing each day and to lift others up as I climb the ladder of success.

To my wonderful PhD colleagues: Veronica, Rebecca, and Kathy - you have taught me what true love and dedication means as my classmates and friends. We are truly now family.

To my dear friend Susan: You have taught me that your love knows no bounds and far exceeds being a family member. Thank you for being there in good times, and challenging times, always encouraging me every day, in every possible way.

To my girlfriends: Tilly, Mel, Sheila and Angela – with every heartbeat… I know that I am alive because you dared to care.

To my attending neonatologists and fellows: You have been instrumental in my growth as a person, as a woman of color, and as a scientist.

To Nelia: You always told me I could do this……spurring me onward and upward.

To dear Wintley and Linda Phipps: I am so blessed that you choose to represent God's love to me as your loyal friend.

Dissertation Scholarships

5. 2018.02.05: First WIN CANS Doctoral Dissertation Grant, Western Institute of Nursing/ Council for the Advancement of Nursing Science Dissertation Award

4. 2017.09.28: CASMED Medical Systems, 50 Small adhesive probes for use with FORE-SIGHT ELITE Tissue Oximeter – Fall 2017

3. 2017.11.25: AMERICAN ASOCIATION OF COLLEGES OF NURSING, **Johnson and Johnson Campaign for Nursing's Future**- AACN –Fall 2017 Minority Nurse Faculty Scholar

2. 2016. 09.05: AMERICAN ASOCIATION OF COLLEGES OF NURSING, **Johnson and Johnson Campaign for Nursing's Future**- AACN –Fall 2016 Minority Nurse Faculty Scholar

1. 2016 .06.31 UNIVERSITY OF SAN DIEGO, Doris A. Howell Research Award

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Chapter One

Introduction

Premature infants enter the world facing two major disadvantages: being deprived of the time to neurologically and physically develop within their mother's womb and being physically separated from their mothers. Both of these can have a lifelong impact on an infant's health, putting them at higher risk for medical disabilities such as maladjusted cognition, damaged vision deteriorating to blindness, hearing loss, and varying degrees of cerebral palsy. Such impacts on preterm infants can also involve developmental problems related to emotional and psychological well-being, all of which can result in substantial treatment and follow-up care costs (Trasande, Malecha, & Attina, 2016). The physical separation between mothers and premature infants that is required for high-tech critical care has been associated with lifelong health consequences that burden families and society (Craig, Hartman, Owens, & Brown, 2016). Physical separation of infants from their mothers also contributes to poor infant–mother interaction, which is a strong predictor of chronic illness and behavioral problems in children (Mäntymaa, Puura, Luoma, Salmelin, & Tamminen, 2006). Chronic illness and behavioral problems have been linked to infant-parent attachment. Infant-parent attachment describes an aspect of the relationship between a child and a parent/caregiver that is dependent on the quality of the interaction. The quality of the interaction serves as a powerful predictor for the four types of attachment. Organized attachment is categorized as secure, insecure-avoidant, and insecure-resistant, and the one disorganized attachment is categorized as insecure-disorganized. Social and psychological researchers posit that disorganized attachment is a reliable predictor for serious psychopathology and

maladjustment in children. For example, adolescents who had disorganized attachment with their primary caregiver during infancy had higher levels of general psychopathology at age 17 (Mäntymaa et al., 2003). Those classified as disorganized between 5-7 years of age, have impaired formal operation skills such as lower mathematics attainment stemming from low self-esteem, low self-confidence, and can also suffer rejection by peers (Mäntymaa et al., 2003). Children that are diagnosed with disorganized attachment have a higher vulnerability to altered states of mind, such as dissociation in young adulthood. A meta-analysis of 12 studies (n=734) addressed the association of disorganization and externalizing behavior problems and found effect sizes that ranged from 0.17 to 0.54 with a mean correlation coefficient of 0.29. The negative findings demonstrate that the relationship is not straightforward (Mäntymaa et al., 2003).

Attachment is different from "bonding." "Bonding" is described as the strong attachment of an infant to the mother and vice versa that develops shortly after birth. It is a strong emotional, spiritual, behavioral, and biological connection between mother and infant. It is an instinctual glue that connects the mother to her baby, and enables the mother to accomplish with an expression of enjoyment the complexity of selfless tasks resulting from motherhood (Madrid, 2007). In the first hours postpartum, the mother and baby move through an intimate dance with sequenced behaviors such as gazing, fondling, kissing, nuzzling, and touching, activating bonding processes (Klaus et al., 1972).

This early puerperium period is considered a "sensitive period" as observed in mammal studies where 50% of ewes separated from their lambs for 4 hours, rejected them. If the separation continued for 12 to 24 hours, 75% of ewes rejected their lambs. However, if the 24-hour separation did not start until 2-4 days postpartum, all the ewes

reaccepted their lambs (Poindron & Neindre, 1980). Likewise, in humans, a parallel concept is drawn making an argument that close contact with mother and infant during this sensitive period is important for bonding (Kennell & Klaus, 1998).

The terms “bonding” and “attachment” appear in the literature as interchangeable words that may be used to convey the same meaning of emotion. However, “bonding” refers to the emotional connection that exists in the mother towards her child and “attachment” refers to the instinctual feelings that exist in the child towards the parent/caregiver (Kennell & Klaus, 1998). Attachment results from conscious/unconscious maternal actions that are activated by the initial bond and continues to adapt to the needs of the child throughout infancy and lifetime (Madrid, Skolek, & Shapiro, 2006).

This initial bond is termed maternal-infant bonding and was introduced with the work of Rubin in 1967 and highlighted in the publication by Martin Klaus and John Kennell in 1976, pediatricians from Case Western Reserve (Madrid, 2007). Klaus and Kennell (1976) posit that close physical contact between the mother and her infant immediately after birth enhances a rich secure infant attachment (Crouch, 2002). The intricacy of mother’s intimate response to her offspring is described as the foundation of emotional and cognitive development in the infant and can also significantly impact the child’s ability to form and maintain attachments throughout the life span (Madrid, 2007). Psychologists describe a “hardwiring” in humans for maternal attachment that is natural and spontaneous unless something directly hinders it.

Two most common obstacles to bonding are physical and emotional separation. Physical separation often comes from the common inpatient practice of separation of

mother and infant for nursery care immediately post-birth. Emotional separation can occur during pregnancy, birth, or early in puerperium and is caused by a traumatic event in the mother's life, calling into play strong emotions that are incompatible with infant bonding (Madrid, 2007). Both physical and emotional separation, if prolonged, have serious consequences to the complexity of mother and infant interaction and introduces chronic stress so severe that it can impact the physical and psychological health of mother and child, and the entire family system (Madrid et al., 2006).

Separation of mothers and their infants post-birth began in the 1900s with the use of general anesthesia, which made both newborns and mothers incapable of interaction for 24–48 hours (Lawrence & Norris, 2016). Such early mother–infant separation may result from critical illness or serious health problems for mother and infants, which are both significant stressors (Samra, El Taweel, & Cadwell, 2013). A developmental approach that maximizes interactions between premature infants and mothers in order to minimize the consequences of physical separation is kangaroo mother care (KMC) (Conde-Agudelo & Díaz-Rossello, 2014). In KMC, a parent must hold their infant skin-to-skin against their bare chest for extended periods of time. This behavior has been shown to reduce mortality and morbidity among premature infants (Conde-Agudelo & Díaz-Rossello, 2014). The direct effects of skin-to-skin contact include stabilization of breathing, improved oxygen saturation, regulation of heart rate, and improved breastfeeding in infants, along with improved milk production in the mother. Together, these effects contribute to better parent-infant bonding (Bergman & Bergman, 2013). While the neurobiological mechanisms of KMC have not been well described, it is possible that the benefits of KMC are related to energy conservation in infants.

Energy conservation in premature infants allows them to recover and repair from the impact of preterm parturition, supporting their healing, growth, and maturation (Ludington, 1990). One of the most crucial factors related to the recovery from preterm illness is an infant's ability to meet its physiological energy needs. The three main factors that negatively influence an infant's ability to meet its energy needs are inadequate glycogen stores, decreased glucose production, and increased glucose demand. These factors result from physiological immaturity and illness, interfering with the clinical goals of providing adequate nourishment for growth and development (Anderson, 2002). High energy demands due to illness and immature digestive and absorptive systems are a challenge to neonatal practitioners who must provide adequate macro- and micronutrients to meet the metabolic rates necessary for an infant's optimal growth, healing, and maturation (Anderson, 2002).

Although KMC benefits have been attributed to both mother and infant, the neurobiological mechanisms of KMC remain relatively unknown. Only one study to date has examined the relationship between KMC and energy conservation in premature neonates (Ludington, 1990). We hypothesize that the physiological and psychological benefits of KMC that have been documented in observational studies are due to the conservation of energy in infants.

This chapter provides background information on the field of study, introduces the proposed conceptual framework to guide the study, and considers the significance of the proposed study. The chapter also considers the problem addressed by this research as well as the purpose of the study and explores the assumptions of the study. Finally, it offers an overview of the dissertation structure.

Background and Significance

Premature infants spend their days in the neonatal intensive care unit (NICU) adapting to extrauterine life by learning to breathe, eat, and grow, while developing neurologically and physiologically. However, they also spend a significant part of their hospitalization fighting illness and coping with the complexity of survival (Ramel, Brown, & Georgieff, 2014). A major challenge during the first few days of postnatal life is infant weight maintenance. Maintaining an infant's weight is particularly challenging because they are physiologically unstable. Close attention must be paid to their energy requirements to prevent cascading catabolic processes during this period.

Energy requirements are calculated as the sum of oxygen consumption rates for all of the organs in the body, each of which has a different energy requirement. For example, the neonatal brain consumes 60% of the total body metabolism and is highly dependent on glucose and oxygen to support its high metabolic rate (Ramel et al., 2014). Diseases that affect organs with high metabolic demands increase the total body oxygen consumption, thus increasing the total energy requirement of an infant. Moreover, most diseases associated with prematurity, such as thermoregulation, respiratory distress syndrome, apnea, and bradycardia, affect respiratory centers of the brain and greatly increase the total energy demand (Ramel et al., 2014).

The stress induced from an increased demand for energy causes the breakdown of proteins, which are then recycled through the liver as a source of carbon for gluconeogenesis. This process is more likely to occur when limited glycogen stores have been overutilized in response to the persistent demand for more energy (Ramel et al., 2014). Due to both illness and prematurity, infants have increased energy expenditure,

higher metabolic needs, diminished fat absorption, and an inability to utilize nutrients provided during this time (Ramel et al., 2014). Furthermore, preterm disproportionate growth and poor weight gain can have long-term effects because they are risk factors for worsened neurodevelopmental outcomes (Ramel et al., 2014). Given the notable risks of energy expenditure for preterm infants, conserving neonate energy is critical to ensuring positive health outcomes. The following proposed conceptual framework for this study thus focuses on energy conservation to promote infant health.

Conceptual Framework

Energy conservation in critically ill patients is at the very foundation of nursing care. In the 19th century, Florence Nightingale focused on the importance of a nurturing, healing environment for the patient (McCarthy, Ouimet, & Daun, 1991). She proposed that nursing's major role in patient care was to bring the patient to a state of mind and body conducive to healing through responsible management of the patient's environment, assuring the patient received adequate rest, comfort, nutrition, and hygiene (McCarthy et al., 1991). Recent research on the psychobiology of the stress response on cell metabolism supported Nightingale's belief that the patient care environment affects individuals' healing and recovery (McCarthy et al., 1991).

Levine (1967) described four principles of energy conservation that theoretically encompass a holistic view of the patient. She purported that, since disease processes depleted energy, nursing care should try to conserve and restore the patient's energy for healing and well-being. Levine's theoretical model guided nursing care by examining the patient's environment in two parts: external and internal. The internal environment encompassed pathophysiological activity and the external environment had three

components: perceptual, operational, and conceptual. Together, the internal and external components comprised the first conservation principle: conservation of patient energy. Her second conservation principle described nursing care to conserve the function of structural integrity. The third conservation principle focused on the patient's personal integrity, giving credence to the personal activities which established their personal identity. The fourth conservation principle guided nursing interventions that promoted the social integrity of the patient by encouraging the maintenance of human relationships (Levine, 1967).

Mefford's theory of health promotion for preterm infants (2004) is a new, middle-range theory based on the aforementioned four conservation principles described by Levine that specifically applies to the care of premature infants. This theory outlines principles meant to guide nursing interventions that address the unique challenges facing preterm infants during their adaptation to extrauterine life (Mefford, 2004). Mefford's thesis was built on Levine's four principles, promoting a process of adaptive change by conserving the energy, structural, personal, and social integrity of the infant and mother as a whole unit. According to this theory, nursing interventions should be centered on keeping the mother–infant dyad together as much as possible as a single unit that is complemented by healthcare participation from the extended family members (Mefford, 2004).

Application of the theory of health promotion for preterm infants

As indicated in Levine's (1967) model, theoretical linkages can be made between the internal and external environments of a preterm infant. Environmental challenges originate from premature birth because of the disruption of intrauterine development

(internal environment) and the psychosocial stress and adaptation that confronts the family (Mefford, 2004). Premature birth abruptly disrupts the wholeness that the mother–infant dyad experienced in utero (internal environment) and thrusts the preterm infant into a harsh, extrauterine environment that is unsuited to the optimal development of their immature physiological systems. It also complicates the parents' adjustment to the parental role because they are faced with the crisis of childbirth before the expected time and the critical illness of the new family member (Mefford, 2004).

Furthermore, the external environment is influenced by perceptual, operational, and conceptual components (Mefford, 2004). The perceptual environment is related to the NICU and the complex sensory stimuli within it, including bright lights, noise, equipment, and people. An infant must respond to this environment with underdeveloped senses, and often the environment overwhelms them. The operational environment is related to the microorganisms, gravity, and radiation that can damage an infant without the protective barrier of the womb. Again, the infant has only their immature integumentary and immune systems with which to mount a response to these environmental threats. Gravity in particular has a direct effect on the reduced muscle mass of a preterm infant and can cause generalized hypotonia in response to hyperextension and abnormal movement patterns. A full-term infant develops a balanced, physiological flexor tone during the 9 months of conception due to the confinement of the womb and the increasing muscle mass of the growing fetus; however, this is impossible for a preterm infant. Lastly, Mefford (2004) explained that the conceptual environment includes the psychosocial, cognitive, and spiritual experiences of life. The central nervous system (CNS) is underdeveloped in both structure and function in a preterm infant,

challenging the infant's ability to have learning experiences in this environment. The younger the infant is according to gestational age, the greater the conceptual learning challenges will be for the infant and, in turn, the less competent their CNS.

Mefford (2004) asserted that the wholeness explained as the oneness with the mother in a symbiotic relationship that guided the developmental and maturation processes each day in utero until term gestation is disrupted by preterm birth and physiological immaturity, which is a threat to the balance of energy. Energy balance is contingent upon multiple bodily processes functioning correctly, many of which are immature in a preterm infant. Cellular processes that create energy in the body rely on oxygen to function. A preterm infant is often unable to get enough oxygen because of their immature lungs, specifically due to the decreased production of surfactant in the lungs that limits adequate gas exchange at a cellular level. This immature pulmonary system is, therefore, a great threat to the energy balance of preterm infants (Mefford, 2004). Similarly, energy balance requires adequate nutrition, but the structural immaturity of the preterm infant's gastrointestinal system is inadequate to handle digestion and nutrient absorption. According to Mefford, the immaturity of the CNS also challenges an infant's ability to coordinate sucking, swallowing, and breathing, compounding the difficulty of the oral intake of nutrients (Mefford, 2004).

Due to the complexity of immature systems, premature infants are thrust into an energy-deprived state due to disease processes that result from physiologic immaturity, inadequate caloric nutrition, and the increased energy demands of extrauterine life. Thus, it is important to identify the nursing interventions that can specifically impact energy

conservation in premature infants. However, prior to developing such interventions, more accurate measurements of infant energy expenditure/conservation are needed.

Current Measurements of Energy Expenditure

The importance of having an accurate measurement of infant energy expenditure cannot be overstated. Studies have shown that measuring energy expenditure in preterm infants in the clinical setting is difficult and is only completed in rare instances for nutritional evaluation (Adams, Nelson, Bell, & Egoavil, 2000). Both indirect calorimetry (IC) and direct calorimetry (DC) have been employed to measure infant energy expenditure, but the methods are time consuming and the instruments frequently need to be calibrated (Adams et al., 2000). Direct calorimetry (DC) is a measure of energy expenditure dependent on the determination of heat loss from the body, while indirect calorimetry (IC) is a method that calculates heat production of the oxidative metabolism by measuring oxygen consumption (VO_2) and carbon dioxide production (VCO_2). In three large studies, similar results were found when DC and IC measurements were compared (Adams et al., 2000).

Infrared thermographic calorimetry (ITC) is a method that has been tested in conjunction with IC that calculates mean body surface temperature using heat theory. It calculates heat losses from the body through radiation, convection, conduction, and evaporation to determine the total heat loss, which can be translated to energy expenditure (Adams et al., 2000). In a study performed by Adams et al. (2000), 10 preterm infants with comparable demographics, characteristics, and anthropometric measures were measured concurrently with IC and ITC for 4.7 hours (Adams et al., 2000). There was no significant difference between the two methods. Although ITC, IC,

and DC are all reliable, noninvasive methods to quantify energy expenditure, they can be very tedious and labor intensive.

Vazquez Martinez, Martinez-Romillo, Diez Sebastian, and Ruza Tarrio (2004) conducted a study to identify the major formulas and calculations used to estimate energy expenditure in critically ill children. They found that the equations used to calculate energy expenditure during the phases of injury and critical illness do not accurately predict true energy expenditure in critically ill children, and especially those that are ventilated or in the early post-injury phase. Of the metrics analyzed, the researchers found that IC was the most accurate measure of energy expenditure during these critical periods (Vazquez Martinez et al., 2004). To identify potential downstream targets that mediate positive effects on metabolism and immunity purine measurements could serve as a secondary strategy when positive energy balance cannot be fully achieved. The identification and validation of biomarkers and bioindicators of cellular and mitochondrial energy balance is needed. Waiting weeks and months for the emerging growth patterns to identify short- and long-term morbidities may be too late. An alternate method for measuring infant energy expenditures that has the potential to provide more accurate data is the measurement of purines through measurements of ATP degradation at the intracellular level.

Urinary Purines as Biochemical Markers of Energy

As early as 1963, purines were studied as markers of hypoxic episodes in animals through identification of elevated levels of inosine and hypoxanthine in organ tissues. Calderon, Boskovic, Sowers, and Angeles (2008) reviewed several different studies that investigated purines and xanthine as markers of hypoxia and suggested their possible

usefulness in the neonatal clinical setting. These authors asserted that oxygen depletion in tissues leads to anaerobic metabolism and results in the rapid depletion of adenosine triphosphate (ATP). Lactic acid accumulates due to the reduction in ATP and decreases the ability to maintain cellular function. ATP produced by oxidative phosphorylation is also reduced and only partially compensated for by an increase in glycolysis. Overall, this leads to a significant decrease in steady-state ATP levels by the continued need to use ATP for energy (see Figures 1 & 2). The unreliable and unsteady levels of ATP are insufficient to meet energy demands, leading to a buildup of free adenosine that subsequently degrades to inosine, hypoxanthine, xanthine, and uric acid. Thus, researchers have asserted that purine measurements are reliable biochemical markers that can be helpful as a non-invasive and a more accurate measurement of energy at the cellular level.

Holden et al. (2014) conducted a study with 82 late-preterm infants using urinary hypoxanthine as a measure of ATP utilization. Markers of ATP breakdown were measured on day of life (DOL) 3 and 6 using high-performance liquid chromatography (HPLC). The infants were grouped and defined according to their diagnoses: poor nippling only (n = 8), hyperbilirubinemia plus poor nippling (n = 21), early respiratory disease and poor nippling (n = 26), and respiratory disease only (n = 27). Researchers found that infants diagnosed with respiratory disease alone had significantly higher urinary hypoxanthine concentrations, indicating that specific disorders can change ATP metabolism and increase purine breakdown (Holden et al., 2014). This research showed that hypoxanthine is stable in urine and that it can be used to evaluate ATP metabolism in the infant population. It is well documented that late-preterm infants have lower energy

stores and higher energy demands compared to full-term infants (Holden et al., 2014). If purine biomarkers are reliable and stable measures of ATP utilization, then purines should be reliable indicators of energy conservation in preterm neonates (see Figure 1; Holden et al., 2014).

Many causes of morbidities in preterm infants are linked to increased oxygen and metabolic needs. However, there are few studies that evaluate interventions intended to decrease these metabolic needs or advance nursing interventions that support practices that minimize infant energy demands. Based on the available data, measurements of purine levels in urine may be a relatively noninvasive method to reliably quantify the biochemical markers of energy metabolism. Researchers report findings that support the value of using urinary concentrations of purines and allantoin as early markers of ATP utilization and cell injury (Holden et al., 2014). With improved metrics of energy expenditure/conservation such as purine and allantoin measurements, promising nursing interventions like KMC could be tested more accurately for their effectiveness. This proposed intervention to reduce preterm infant energy expenditure is detailed in the following section.

Kangaroo Mother Care

Kangaroo mother care (KMC) is the concept of skin-to-skin contact (SSC) between a parent or surrogate and a newborn or infant child. This term has many synonyms, including kangaroo, kangaroo method, kangaroo position, kangaroo intervention, and maternal/parental-infant skin-to-skin contact. The defining attribute of KMC is skin-to-skin contact between parent and infant (Chan, Valsangkar, Kajeepeta, Boundy, & Wall, 2016).

The World Healthcare Organization (WHO) recommends KMC to improve neonatal mortality and morbidity in infants in both low-income and affluent settings that have low birth weight or that weigh less than 2,000 grams (Nyqvist et al., 2010a). Highlighted in these guidelines are some of the direct effects of KMC on the infant, which include stabilization of several physiological parameters such as breathing, oxygen saturation, heart rate, and improved breastfeeding in infants, as well as improved milk production for the mother. Together, these effects appeared to lead to better parent–infant bonding (Boundy et al., 2016).

Operational definition of KMC

For the purposes of this study, kangaroo mother care (KMC) is defined as the intervention of maternal–infant skin-to-skin contact characterized by the infant being placed in an upright, frog-like position directly on the skin of the mother's chest, between the mother's breasts (Charpak & Ruiz, 2011). This intervention should employ a method that should be standardized and protocol based upon the resources of the hospital unit so that there is consistency in the way it is performed. Researchers defined the KMC program as all the activities necessary for the implementation of KMC intervention, including a well-trained interdisciplinary healthcare team that is supported by physical and administrative structures (Charpak & Ruiz, 2011).

This definition of KMC is most appropriate to the conceptual context of this study proposal (Walker & Avant, 2011). Key antecedents and consequences of the KMC paradigm are (a) maternal–infant nonseparation, (b) impact on infant self-regulation, (c) maternal–infant contact, (d) neuromaturation in infants, (e) the effect of KMC on maternal mood and lactation, and (f) the KMC experience and how it relates to mother–

infant and family relationships (Feldman, 2004).

The concept of skin-to-skin contact (SSC) is central to KMC, but the timing of when to initiate KMC, the length of time necessary for optimal benefits, the position of the infant, the necessary equipment, and the measurement indicators all vary widely in the literature (Chan et al., 2016). These variabilities are due to the lack of evidence in scientific processes that lead to a clear theoretical definition (Lawrence & Norris, 2016). Measurements of the initial timing, quality, and quantity of time spent in skin-to-skin contact with the mother are important variables that still need to be considered (Anderson, Radjenovic, Chiu, Conlon, & Lane, 2004). Despite the inconsistencies in current KMC application methods, the model was developed around three key components: breast milk, warmth, and love (Nyqvist et al., 2010a). The two different KMC application methods that are currently used in the context of clinical practice are continuous KMC (CKMC) and intermittent KMC (IKMC). In low-income settings, mothers are expected to do skin-to-skin care for 24 hours each day, with short breaks for self-care. This is an example of CKMC. In more affluent settings, mothers practice skin-to-skin care for different amounts of time ranging from 1-2 hours at intermittent periods during the 24-hour day; this is an example of IKMC.

Benefits of KMC for infants

It is not fully understood why KMC has such significant benefits for preterm infants when compared to term infants. One early school of thought was that it stimulated the parasympathetic nerve fibers in an infant and improved gastric functions, stabilized physiological functions, and diminished stress responses (Nelson & Panksepp, 1998). More recently, researchers have posited that KMC causes the secretion of oxytocin,

which acts as a neurotransmitter that specifically targets the parasympathetic nuclei, enhancing sedative and analgesic effects. Oxytocin (OT) is synthesized in the hypothalamus, and specifically, in the paraventricular and supra optic nuclei. In the biochemical realm, it is a neuropeptide that is involved in cognitive domains, social behavior, parental care behavior, socioemotional processing, bonding and attachment behaviors, and generosity in humans (Francis, Kirkpatrick, de Wit, & Jacob, 2016). However, there is some evidence that OT plays a role in some psychiatric disorders that are involved with social dysfunction including autism spectrum disorders (ASD), depression drug abuse, anxiety, and schizophrenia.

There are numerous challenges as researchers seek to understand its neurobiological role in modulating both normal and abnormal behaviors. Since it is synthesized in the brain, it would be risky and invasive to measure OT in cerebrospinal fluid; so many experimental and observational studies measure peripheral levels as a proxy for oxytocin released from the hypothalamus. In studies done in animals and humans, peripheral OT levels have been found to be positively associated with behavioral outcomes, such as less anxiety in children, and positive communication and social interaction between parents and their infants, which further suggests the peripheral measure may be an indicator of OT functioning in the brain (Francis et al., 2016).

While the neurobiological controls behind KMC are not well understood, it has become increasingly clear the mechanisms that provide the basic needs of attachment and survival are an organized system of energy balance, thermoregulation, place-attachment, and social presence mechanisms that are engaged in a timed, integrative modulation of neurobiological environments (Nelson & Panksepp, 1998).

Ludington-Hoe (2011) presented five main categories of KMC benefits: physiological, behavioral, breastfeeding, psychosocial, and neurobehavioral. Kangaroo mother care contributed to the physiological stabilization of the infant through direct effects on heart and respiratory rates, oxygenation, and temperature control. Researchers asserted that changes in infant heart rate measured at different levels of activity gave a dependable estimate of energy demands (Bergh, Charpak, Ezeonodo, Udani, & van Rooyen, 2012; Ludington, 1990). Behaviorally, KMC soothed and calmed infants, producing an analgesic effect. It also provided an opportunity for further energy conservation during quiet sleep. Quiet sleep helped to minimize both the alert active and the quiet alert states, during which energy expenditure increased and was costly to the premature infant. Activity fluctuations in infants were responsible for 7% to40% of daily energy consumption (Bergh et al., 2012; Ludington, 1990). When initiated early after parturition, KMC facilitated breastfeeding for a longer duration, with better milk production in the mother and increased prevalence of exclusive breastfeeding (Bergh et al., 2012; Charpak et al., 2005; Ludington, 1990). Psychosocially, KMC facilitated improved maternal infant attachment and increased interactions between mother and infant. By reducing maternal stress, KMC increased maternal satisfaction (Bergh et al., 2012; Bergman, 2014; Ludington, 1990). Theoretical models of patient satisfaction have been used to define maternal satisfaction. From these models a multidimensional concept has emerged which is influenced by many factors. A definition of “positive evaluation of distinct dimensions of childbirth” has emerged (Srivastava, Avan, Rajbangshi, & Bhattacharyya, 2015). On a neurobehavioral level, infants who underwent KMC

exhibited improvement in their overall developmental scores. Both mental and motor improvements were observed in infants that had KMC (Bergh et al., 2012).

As discussed previously, an important indicator of well-being in infants is healthy growth and weight gain. Studies have demonstrated that infants exposed to KMC showed improved weight gain compared to traditional care methods (Dodd, 2005). Kambarami, Chidede, and Kowo (1999) found a significant difference in infant weight gain after implementation of KMC in a pilot study conducted in Zimbabwe (Tooten et al., 2012). Seventy-four infants were consecutively allocated to receive either KMC or routine NICU care in the incubator once they were considered stable enough for the study. The KMC group seemed to have an advantage over the control group because they were larger in size and a few days older. However, infants who received KMC gained twice as much weight per day (20.8 g vs. 10.2 g, $p = 0.0001$) after adjusting for age and weight on admission to the study. In another study, Cattaneo et al. (1998) conducted a randomized control trial in three tertiary academic hospitals in Addis Ababa, Ethiopia; Yogyakarta, Indonesia; and Merida, Mexico with 185 low birthweight infants. The intervention group received KMC in a kangaroo ward for approximately 20 hours per day and the control group received conventional care, including daily contact with their mothers but not KMC. Infants who received KMC had a higher mean daily weight gain of 21.3 g vs. 17.7 g ($p > 0.001$); however, significant differences were noted in chronological age and gestational age at the time of enrollment. These studies suggest that KMC contributes in some way to infant weight gain, but the caloric intake and different amounts of time that infants were held was not considered in these studies and could have affected the reported results.

Benefits of KMC for mothers

Many studies have shown compelling evidence that KMC optimizes the environment of the mother–infant dyad, leading to enhanced intimacy (Oras et al., 2016). It has been hypothesized that skin-to-skin contact signals the release of oxytocin in the mother, making it a biochemically-mediated event that promotes a strong emotional instinct to keep an infant close and increases maternal responsiveness to infant needs (Johnson, 2013). The oxytocin release was thought to have synergistically decreased maternal cortisol levels and lowered maternal stress as well (Johnson, 2013; Young, 2013). To date, only one study has documented a change in maternal oxytocin levels with the use of KMC (Cong et al., 2015).

Previous studies have found that KMC increased maternal sensitivity, defined as a mother's ability to recognize and respond to her infant's needs (Johnson, 2013). In turn, maternal sensitivity increased maternal synchrony described as the infant's and mother's degree of social engagement, improves the mother's ability to bond with her infant, and develop recuperative measures related to early birth (Johnson, 2013). While maternal stress and anxiety associated with premature births have been shown to interfere with this bonding process, KMC has also been shown to decrease maternal stress levels as evidenced by lower cortisol levels (Johnson, 2013; Pineda et al., 2014). Although further research is needed into the specific hormonal benefits of KMC for mothers of preterm infants, the extant studies nevertheless suggest that it has a significant impact on maternal-infant bonding. When combined with a family integrated care model in lieu of a family-centered care model, KMC may prove even more effective for health promotion of preterm infants.

Family-Centered Care Model Sets the Stage for KMC

Family-centered care (FCC) is an approach to planning, delivering, and evaluating healthcare that is grounded in mutually beneficial partnerships among healthcare providers, patients, and families. It defines relationships in healthcare by recognizing the vital role that families play in the well-being of the patient, particularly for infants and children. In FCC, there is mutual collaboration between families and healthcare providers that acknowledges the emotional, social, and developmental support of parents and families as an integral component of patient care. The knowledge, values, beliefs, and cultural background of the patient's family are incorporated into the delivery of healthcare, with the goal of achieving a partnership that allows the family to effectively participate in the patient's care. Families are encouraged to play an active role in the care and decision making of the patient (O'Brien et al., 2015).

Family-centered care is very important in the NICU due to the complexity of patient care delivery and the fragility of the infants. Although physicians and nurses in the NICU readily attest to the importance of FCC, the official clinical practices and NICU care processes frequently do not reflect this philosophy. Family-centered care models in practice tend to be based on an underlying premise that healthcare professionals are the experts in the care of the NICU patient, while parents are peripheral consultants who can only be accommodated to a certain extent. The extent of that accommodation is often left to the discretion of the bedside nurse, the medical team, and the organization. In particular, nurses have expressed frustration because they perceive themselves as clinical experts, while the parents as visitors or intruders hinder the care of

the sick infant (O'Brien et al., 2015). Many families are left frustrated, disenfranchised, isolated, and separated physically and emotionally from their infants because of the way that FCC is currently practiced in the United States.

Additionally, parents report feeling anxious, stressed, and unprepared to care for their infants after discharge (O'Brien et al., 2015). Although many FCC initiatives are intended to make parents central to the care of their infant, paradoxically, these programs are frequently instrumental in the displacement of parents to the periphery of care. This occurs because parents are not fully integrated into standard infant care practices at the bedside. This potential disruption to the parent–infant interaction processes has been shown to lead to adverse consequences for both parents and infants (Tooten et al., 2012). A family integrated care model, in contrast, offers a more inclusive approach that actively involves the family in infant care during NICU treatment.

Family Integrated Care Model Facilitates Increased Opportunities for KMC

The family integrated care (FICare) model that was introduced in Canada and Australia attempts to bridge the gaps that the FCC model fails to address by removing some of the frustration between the parents and nursing staff. Family integrated care extends the FCC concepts by stipulating that parents must agree to be present at their infant's bedside for a minimum of 8 hours a day. During this time, the parents are coached in the clinical setting to provide as much daily care as possible to their infant, with full support from the interdisciplinary team. The FICare model expands on the FCC model so parents do not feel disconnected from their infant's care and instead feel integral to the care of their infant (Pelletier & Stichler, 2013).

The FICare model embraces the mother–infant dyad by requiring the parent to provide all basic care to the infant, with the aid of special support and training, while healthcare professionals administer the advanced and more complex medical care. The training and support that come with FICare addresses the individual's preferences by reading the infant's cues as well as the autonomy and needs of the parents, while enhancing optimal survival outcomes for the infant. Family integrated care has been shown to enhance the involvement of families in the NICU by increasing parent–infant engagement, increasing opportunities for KMC to decrease maternal stress, and improving both short and long-term outcomes for infants and their families. Family integrated care may also affect the incidence of nosocomial infections, resulting in decreased length of stay (LOS). Overall, improved long-term outcomes may correlate with the enhanced caring and confidence of the parents once the infant is discharged and decrease both parental stress and interdisciplinary caregiver stress (O'Brien et al., 2015).

Statement of the Problem

Due to the negative, long-term consequences of postnatal separation for both the preterm infant and mother, it is imperative to identify the biological and biochemical mechanisms of KMC and its influence on infant growth and development (Johnson, 2013). Although there is clear evidence of the benefits of KMC in the literature, it is important to gain further insight into the specific effects of KMC on the physiological mechanisms of bonding between the neonate and mother. These mechanisms include the natural biochemical mediation affecting maternal–infant attachment and how it relates to the empowerment of the mother in her new maternal role. Studies have shown compelling evidence that KMC optimizes the mother–infant dyad and leads to intimacy,

highlighting positive neonatal outcomes as the main focus and ignoring the maternal outcome benefits.

Despite the evidence that KMC benefits both mothers and infants, in the United States it is not standard practice in all clinical settings. Kangaroo mother care has yet to be consistently incorporated into NICUs and its use is generally left up to the nurses' discretion (Charpak et al., 2005). Individual institutions often struggle to implement KMC in a sustainable way despite efforts to educate and train healthcare providers worldwide (Nyqvist et al., 2010a). Thus, the ability to measure and critically evaluate nursing interventions designed to promote mother–infant togetherness is vital to the consistent operationalization of the KMC concept (Waltz, Strickland, & Lenz, 2017). Addressing the gap in knowledge from concept to actual practice by measuring the effects of KMC is integral to the effective implementation of such nursing interventions that optimize mother–infant outcomes (Lawrence & Norris, 2016).

Mothers of preterm infants are particularly at risk for attachment problems and increased psychological symptoms leading to postnatal depression and decreased responsiveness (Evans, Whittingham, & Boyd, 2012). The increased risk is due to a combination of factors including the disruption of the normal physical contact between mother and infant and the enforced separation because of the NICUs intense medical environment. This may present an opportunity for the mother to withdraw from her infant because her desire to provide protection in this environment is unrealized (Evans et al., 2012). Given the prevalence of disruptions to the developing maternal–infant relationships, timely and early intervention is crucial to identify problems and effectively

treat them. Accurate measurement that can detect disruption in bonding processes are needed to provide meaningful assessment for clinical evaluation and research.

Purpose of the Study

Because premature infants have minimal energy stores, we hypothesize that the positive infant outcomes associated with KMC are a result of decreased energy expenditure from dissociative stress, evidenced by increased heart rate, crying, flailing, and uncoordinated movements. The conserved energy can be channeled towards infant healing, maturing, and growing. This study will be the first to directly link biochemical data to the physiological benefits of KMC reported in control trials and meta-analyses. This study will examine the association of KMC intervention on stress reduction, more efficient infant energy utilization, and maternal bonding through direct measurements of biochemical markers in an effort to optimize the application of the KMC method. First, the effect of KMC on stress reduction and infant energy utilization will be measured using markers of adenosine triphosphate (ATP) degradation including hypoxanthine (Hx), xanthine (Xa), uric acid (UA), and oxidative stress (allantoin). Second, the effect of KMC on maternal bonding will be measured using The Mother-to-Infant Bonding Scale (MIBS). It is a self-report mother-to-infant bonding scale that has been validated in the general and NICU populations. It was devised to screen the general population for postnatal difficulties relating to the maternal emotional behavior towards her baby in the first days 48 to 72 hours postpartum. The instrument has 8 words (adjectives) describing feelings mothers have toward their babies in the first weeks after they are born and is a simple questionnaire to administer. Psychometric testing in the NICU population of MIBS satisfactorily detected difficulties in mother–child bonding; the area under the

ROC curve was 0.93 with a sensitivity of 0.9 and a specificity of 0.8 for a threshold score ≥2. The positive predictive value for this threshold was 40.9% (IC95% (20.36-61.45) and the negative predictive value was 98.1% (IC 95% (89.93-99.95) (Bienfait et al., 2011). This is a reliable instrument that demonstrates valid data in the NICU population. Intervention and control groups will be given the MIBS self-rating instrument 48 hours after delivery.

Research Aims

This stratified, randomized control study seeks to measure the biologic effects of KMC on mothers and infants. Due to the negative and long-term consequences of postnatal separation for the infant and mother, it is imperative that we study the biological mechanisms of KMC and its influence on bonding (Johnson, 2013). Psycho-neuro-biological studies have shown that early interaction and bonding can impact the growth and organization of the developing brain and can positively affect physiological and psychological development (Mäntymaa et al., 2003). However, biological documentation of energy conservation of KMC is lacking. This study aims to link biochemical data to the physiological benefits of KMC to add further evidence to the science of early dyad interaction.

Specifically, the current study aims to quantitatively correlate ATP levels with KMC and ATP utilization markers as an exploratory step towards understanding the mechanism of energy conservation. Ultimately, energy conservation aims to sustain energy homeosatasis in premature infants, which can contribute to growth and neuromaturation in the preterm infant. This study will examine whether short-term reductions in energy expenditure due to KMC have an impact on cellular function, weight

gain, and other logical sequelae of energy conservation. Moreover, it will quantify how much energy is conserved at the cellular level during and after KMC. Energy conservation will be examined using concentrations of ATP degradation indicators measured pre- and post-KMC in order to understand how best to demonstrate cellular decrease in energy needs in this population.

The specific aims of this study are to:

Specific Aim 1: To examine the association of KMC and biochemical markers of ATP degradation and oxidative stress in urine of premature infants 24-36 weeks on DOL 3. We will measure urinary concentrations of hypoxanthine (Hx), xanthine (Xa), uric acid (UA), and allantoin in human premature neonates randomized to receive KMC on day of life 3 compared to those randomized to no KMC until day of life 4 or receiving standard incubator care on DOL 3.

Hypothesis for specific aim 1: Preterm infants receiving KMC will have a significant decrease in urinary ATP utilization markers compared to babies in isolettes, measured at 3 and 6 hours after routine NICU care.

Specific Aim 2: To examine the association of KMC and mother-infant-bonding in premature infants 24-36 weeks in the early puerperium by DOL 3.

Bonding will be measured using the Mother-Infant-Bonding- Scale (MIBS) in intervention and control groups.

Intervention group: MIBS will be measured on Day of Life 2 after study consent and then on Day of Life 3 and 4, 3-6 hours after KMC.

Control group: MIBS will be given to mother on Day of Life 2 after study consent and then on Day of Life 3 and 4, 3-6 hours after incubator care and KMC intervention.

Hypothesis for specific aim 2: There will be a significant difference in the MIBS self-rating scale in mothers in the intervention group compared to mothers in the control group after KMC care intervention.

Specific Aim 3: To examine the association of KMC and abdominal near-infrared spectroscopy (NIRS) while the infant's abdomen is against the mother's chest.
We measured abdominal oxygenation and perfusion using the Fore- Sight II NIRS tissue oximeter monitor for splanchnic StO2. The NIRS–infrared probe (Casmed, Fore-Sight II Branford, CT, USA) was placed on the left lower abdominal quadrant immediately before KMC intervention or immediately before incubator care and NIRS data was collected for 1 hour. This is the first study to assess the infant's intestinal perfusion and oxygenation using abdominal near-infrared spectroscopy (NIRS) assessment during the KMC intervention vs. the incubator.

Hypothesis for specific aim 3: There will be increased perfusion and oxygenation in infants who are in the intervention group versus compared to the control group.

Research questions

This study will explore the following research questions: (1) Is there a relationship between kangaroo mother care and energy conservation in premature neonates? (2) Is there a correlation between KMC intervention and a decrease in physiological, and biochemical markers of ATP degradation and oxidative stress? (3) Can the results from this study be used to advocate and advance for the primacy of KMC in clinical practice? (4) Is maternal–infant bonding enhanced by KMC intervention? And (5) Does KMC increase intestinal perfusion and oxygenation, thereby increasing

nutritional absorption? By addressing these research questions, this study aims to evaluate the theoretical evidence of the effects of KMC and link behavioral and physiological benefits to the biochemical markers of ATP degradation. In doing so, the study intends to validate the effects of KMC on health outcomes and explore the potential for advocating for the primacy of KMC in clinical practice environments.

Assumptions

One assumption of this study is that KMC does in fact reduce the energy consumption of infants. Though a reduction in energy consumption can be inferred from the positive outcomes reported for infants treated with KMC, actual measurements of infant energy consumption using various methods to measure calorie expenditure have not been reported for infants treated with KMC. There is no biochemical data to support these theoretical assumptions. The emerging field of using bioindicators to examine energy utilization and conservation may get us closer to our goal of having empirical evidence.

Overview of Dissertation Structure

The current study will be presented in the traditional dissertation structure. This, the first of five chapters, is an introduction to kangaroo mother care and the benefits associated with this care. It also introduces the concept of energy conservation and bonding and the use of purines as biochemical markers of ATP degradation, which is presented as a valid measure of energy utilization/conservation. The second chapter will review the literature relevant to the physiological and theorized benefits of kangaroo mother care and how it is connected to energy conservation and bonding. Chapter 3 will outline and describe the methods involved with executing this study. Chapter 4 will

describe the study findings and analyze the data mined from study participants. Chapter 5 will describe the study strengths and limitations and will introduce future steps to advance the study of KMC implementation and energy conservation in premature infants and a short conclusive discussion to the current study.

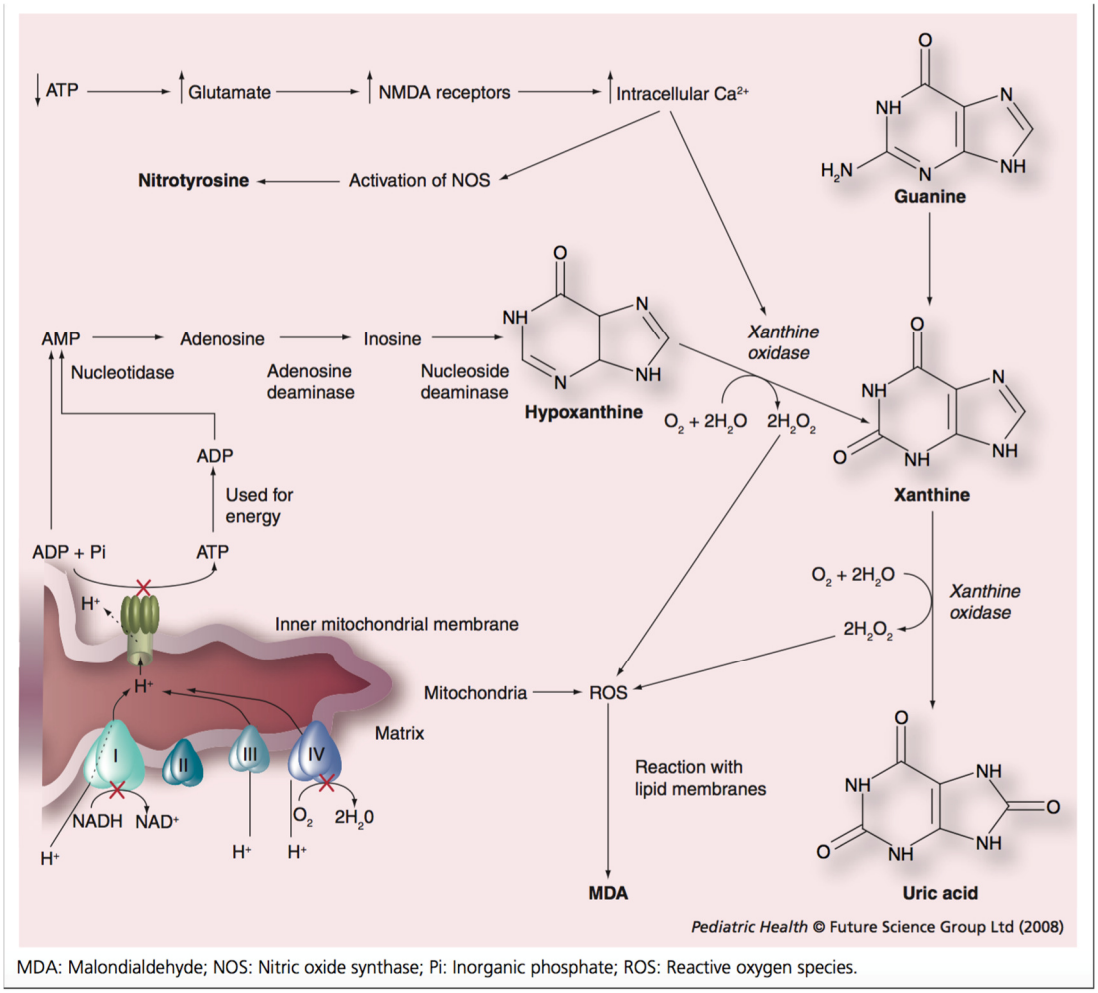
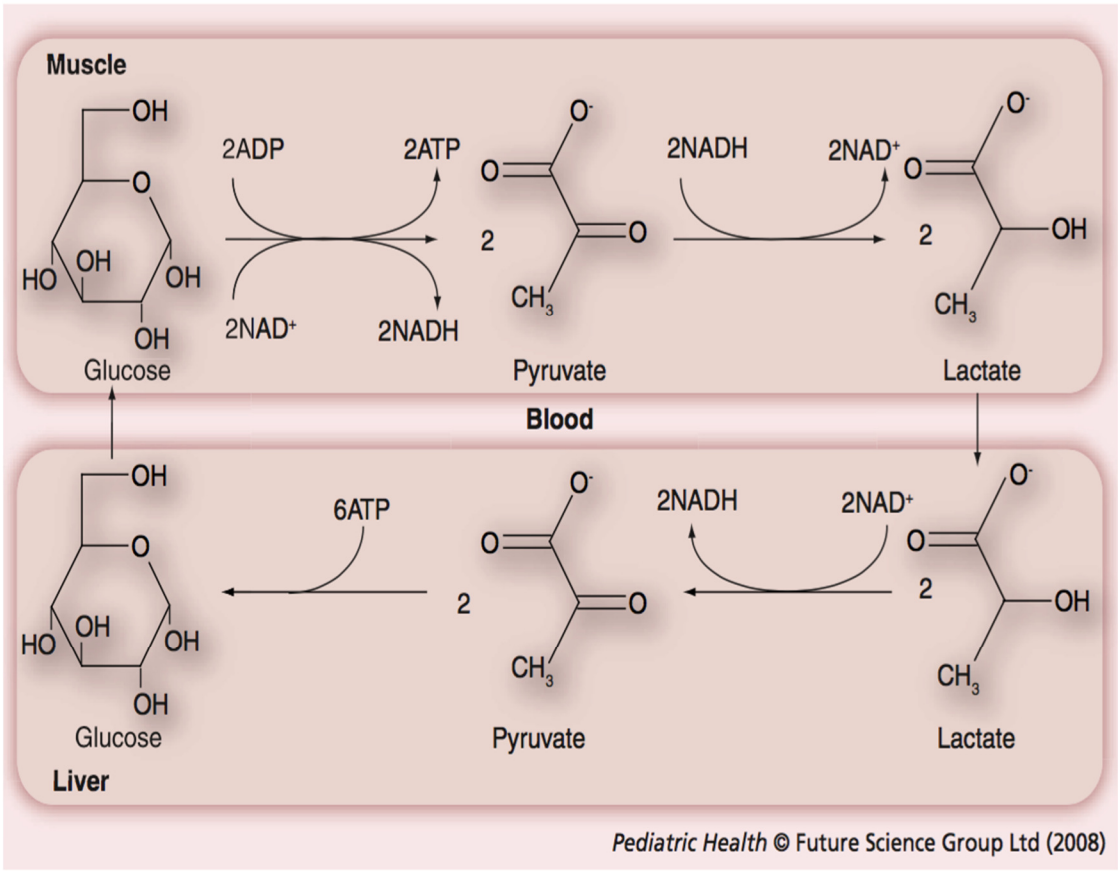


Figure 1. Formation of the biochemical markers of hypoxia. From "Biochemical Markers of Neonatal Hypoxia," by M. S. Plank, D. S. Boskovic, L. C. Sowers, and D. M. Angeles, 2008, *Pedatric Health, 2*(4), p. 486. Copyright 2008 by Future Medicine Ltd. Reprinted with permission.



During anaerobic metabolism, pyruvate is converted into lactate to regenerate NAD^+ in order to enable glycolysis to continue.

Figure 2. Formation of lactate. From "Biochemical Markers of Neonatal Hypoxia," by M. S. Plank, D. S. Boskovic, L. C. Sowers, and D. M. Angeles, 2008, *Pediatric Health, 2*(4), p. 487. Copyright 2008 by Future Medicine Ltd. Reprinted with permission.

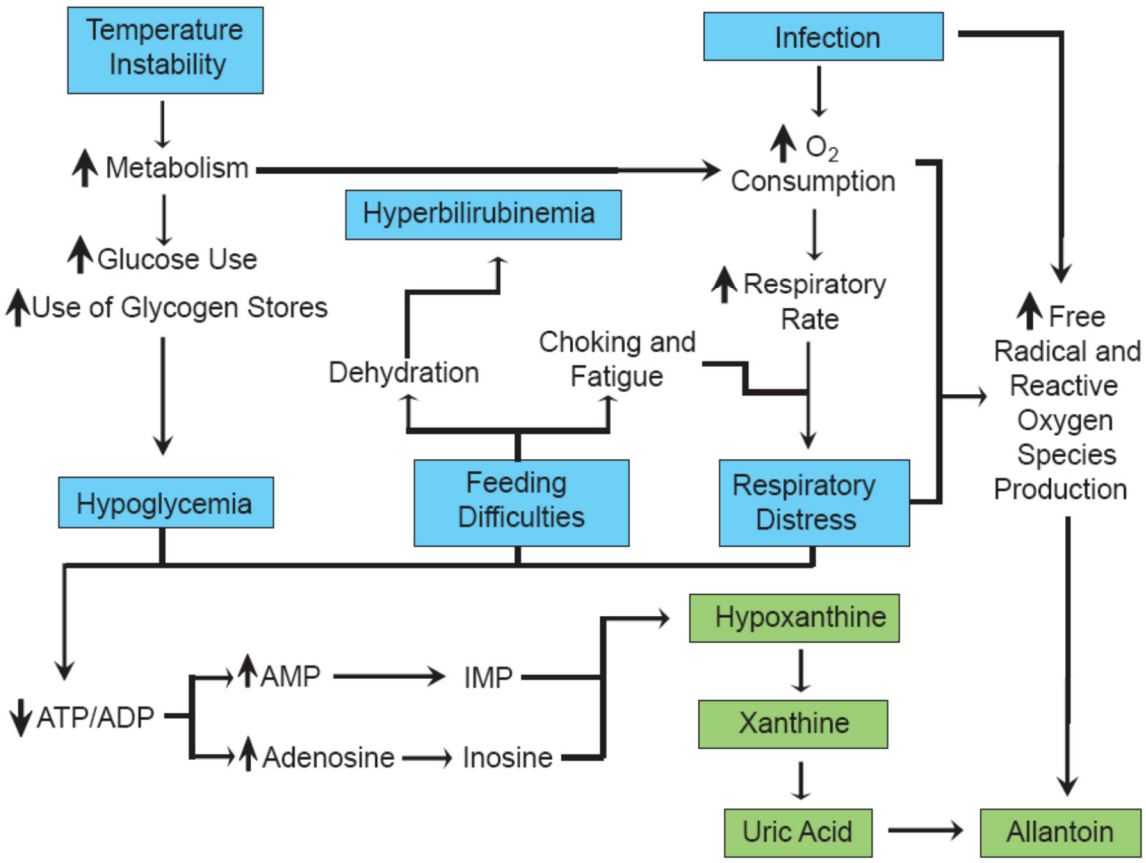


Figure 3. Stress Pathway. Pathway depicting the interrelationship between preterm morbidities and biochemical markers studied *Infant Child Adolesc Nutr*. 2014 August; 6(4) : 240-249.

Chapter Two

Introduction

Premature infants enter the world facing the dual disadvantages of being deprived of the ability to fully develop within their mothers' wombs and of being physically separated from their mothers. At this crucial under-developed stage, both of these factors can have lifelong impacts on their health. In particular, while physical separation is necessary in order to deliver the high-tech critical care that ensures the survival of premature infants, it is associated with lifelong health consequences that burden both the families of premature infants and society overall (Craig et al., 2016). Healthcare costs for caring for premature infants totaled $13.6 billion in the United States in 2014, and the cost to the state of California was $2.2 million. The pathophysiology and mechanism of preterm labor are not very well understood and the little understanding that we do have, does not guide effective treatment. Babies born prematurely face many challenges throughout their hospital stay with an increased risk of newborn health problems that can lead to long term disabilities and possible death (Mäntymaa et al., 2003).

Modern technology has increased the survival rates of premature infants and has pushed the boundaries of viability so babies as young as 23–24 weeks gestation can survive. However, this has also increased the burden of developmental outcomes among premature infants, making conditions such as cerebral palsy more prevalent and resulting in substantial costs for treatment and follow-up care (Trasande et al., 2016). Physical separation of infants from their mothers also contributes to poor infant–mother interaction, which has negative effects on both mothers and children and has even been

associated with child illness (Mäntymaa et al., 2003). While the impact of early physical separation is bidirectional, research specifically focusing on outcomes in infants has suggested an association between such premature separation and cerebral palsy, maladjusted cognition, damaged vision deteriorating to blindness, hearing loss, and developmental problems related to emotional and psychological well-being (Sutton & Darmstadt, 2013).

Kangaroo mother care (KMC) aims to maximize interaction between premature infants and their mothers in order to minimize the negative consequences of physical separation (Conde-Agudelo & Díaz-Rossello, 2014). Kangaroo mother care involves a parent holding their infant skin-to-skin on their bare chest for extended periods of time and research has shown that it can contribute to reductions in mortality and morbidity among premature infants (Conde-Agudelo & Díaz-Rossello, 2014). Some of the direct effects of KMC are stabilization of breathing, improved oxygen saturation and heart rate, and improved breastfeeding in infants, along with improved milk production in the mother (Bergman & Bergman, 2013). Although benefits to both mother and infant have been documented in observational studies, the neurobiological mechanisms of KMC remain unclear. For instance, only one study to date has examined the relationship between KMC and energy conservation in premature neonates (Ludington, 1990). The neuroscience is based on the direct skin-to-skin contact that connects sensory nerve pathways of the mother and infant. The physiological effects elicited from skin-to-skin contact suggest that energy is being synthesized and conserved in order to achieve these observed parameters of physiologic variable stability. The intimate contact of skin-to skin between mother and infant evokes neurobehaviors that ensure fulfillment of basic

biological needs (Moore, Anderson, Bergman, & Dowswell, 2012). Ludington, (1990) used proxy indicators of energy expenditure such as heart rate, activity level, and behavioral state to examine energy conservation in preterm infants. Whether these indicators translate into energy conservation still remains unknown.

Literature Search Strategy

This comprehensive literature review of over 100 sources covered a variety of study designs, including randomized control trials, cohort studies, case studies, meta-analyses, and review papers. Articles were drawn from the following research databases: CINAHL, PubMed, PsycINFO, Cochrane Review, and Ovid. Articles that were included examined the association of KMC with behavioral, physiological, cognitive, and developmental outcome indicators. The search terms used for the review were kangaroo care, skin-to-skin care, energy conservation, energy expenditure, maternal–infant attachment, maternal–infant bonding, preterm birth, preterm infant, morbidity and mortality in preterm birth, premature birth and kangaroo care, bonding and attachment, stress and preterm infant, measurement of energy, adenosine triphosphate (ATP) utilization, ATP degradation and urinary purines, and cell injury and oxidative stress in infants. Studies in languages other than English were excluded. This chapter will review the background of KMC, the association between KMC and maternal–infant bonding; the benefits of KMC, KMC and brain health, and a summary of the literature and conclusion will conclude the chapter.

Background

Research on KMC began in the 1970s with Peter de Chateau's work in Sweden described as "early contact" with mother and baby (Chateau & Wiberg, 1977). It is not

clear from reading his work whether he was specifically speaking of skin-to-skin care or just having contact, such as touch and holding and physical closeness with the mother. These early studies focused on full-term infants in the first one to two hours after birth and found the behavior of mothers towards their infants improved. Klaus and Kennell did some similar work in the United States describing early maternal–infant bonding (Klaus & Kennell, 1971). In 1979, the term "skin-to-skin contact" came into focus. Mary Ellen Thomson, a doctoral candidate in nutrition at McGill University in Montreal, Canada, conducted a study to answer the question whether early mother–newborn contact would significantly influence maternal breastfeeding behaviors. Mothers were given their unwrapped infant to hold against their bare chest for 15-30 minutes postpartum. The work of de Chateau was given as the rationale for this early contact (Thomson, Hartsock, & Larson, 1979).

The defining feature of KMC is skin-to-skin care between parent and newborn. The first report of skin-to-skin care appeared in the literature in 1983 when Dr. Edgar Rey Sanabria in Bogota, Colombia, introduced what he termed the "kangaroo mother" method to address the shortage of caregivers and resources in hospitals there in 1978 and 1979 (Whitelaw & Sleath, 1985). Dr. Nils Bergman, a Zimbabwean, has done a lot of work in South Africa and is considered to be one of the founders of the Kangaroo Mother Care movement. However, Gene Cranston Anderson and Susan Ludington were instrumental in introducing the KMC concept to North America. Even so, the specific term "kangaroo mother care" did not come about until 30 researchers and a representative from the World Health Organization met in Trieste, Italy, in 1996. This group became known as The International Network of Kangaroo Mother Care. Finally, in 2003, the

World Health Organization broadened the concept to set international standards and practical guidelines (Nyqvist et al., 2010b).

Ludington-Hoe (2011) asserted that the term "kangaroo mother care" includes maternal–infant contact, paternal–infant contact, and surrogate–infant contact, referring to any surrogate that stands in place of the biological parents including siblings, grandparents, or adoptive parents. Kangaroo mother care is defined as an infant placed in an upright position, prone, in a bare chest-to-chest, or bare skin-to-skin technique with the mother, father, or surrogate (Ludington-Hoe, 2011). Marsupials carry their offspring in a similar fashion, held in a pouch close to their bodies. Ludington-Hoe (2011) described this skin-to-skin contact as a pleasing sensation to the KMC provider and to the infant. It stimulates the C-afferent nerves to release oxytocin, a powerful hormone that is able to stimulate the brain and body to modulate to environmental changes and contributes to a sense of soothing and calmness. Emotional attachment to mothers also improved when infants and mothers were in skin-to-skin contact as soon as possible after birth. In spite of these important findings, evidence of adaptive nursing care in response to the promotion of KMC was absent at the time.

Kangaroo mother care is currently advocated for and approved by the American Academy of Pediatrics (AAP) and is promoted by the American Heart Association (AHA), the American College of Obstetricians and Gynecologists (ACOG), the National Association of Neonatal Nurses (NANN), the Association of Women's Health, Obstetric, and Neonatal Nurses (AWHONN), the World Health Organization (WHO), and the U.S. Centers for Disease Control and Prevention (CDC) (Ludington-Hoe, 2011). There is ample evidence that the effects of KMC are overwhelmingly positive, resulting in calls

for professional nursing to establish a new paradigm of nonseparation of infant and mother during the neonatal period (Ludington-Hoe, 2011). However, nursing policies and protocols have been slow to integrate KMC into practice (Ludington-Hoe, 2011).

Despite the well-documented benefits of KMC for premature infants, it is still a relatively infrequent practice in the United States at the bedside in NICUs. Ludington-Hoe (2011) noted that moving forward, newborn and neonatal foundations and nursing organizations could encourage KMC by publishing strong position statements supporting KMC and by publicizing scientific findings on the routine use of KMC. A poignant observation is that although behavioral and physiologic benefits may be observed during the time of KMC, the developmental and social benefits outlive the span of the actual intervention. Indeed, benefits have been observed from one to 16 years later (Ludington-Hoe, 2011).

Maternal-Infant Bonding and Kangaroo Mother Care

Kangaroo mother care (KMC) is essential to maternal sensitivity, which has been described as a mother's ability to recognize and respond to her infant's needs (Johnson, 2013). Maternal sensitivity increases maternal synchrony in both the mother's and infant's ability to bond and develop recuperative measures related to early birth. Maternal synchrony is the mutual behavior of mother and infant with their biological rhythms harmoniously emerging in playful syncopated interactions (Johnson, 2013). The amount of stress and anxiety in the mother is intrinsic to bonding processes and can negatively affect the process. There is a sequential set of pre-feeding behaviors that the newborn gradually enters immediately after birth. This begins with the birth cry, followed by a period of relaxation, then an awakening, crawling, finding the breast, and finally suckling

or simulation of suckling at the breast (Nyqvist, et al., 2010b). Maternal–infant skin-to-skin care during these first hours sets the stage for enhanced maternal sensitivity by preventing disruption of these pre-feeding behaviors (Nyqvist et al., 2010b).

Maternal bonding is described as a mother's love, affection, and concern, which translate into actions of protection and providing a safe environment for her infant (Johnson, 2013). Fundamentally, it relates to the position that the infant holds in the mother's world (Johnson, 2013). Bonding and attachment have been documented as crucial to an infant's well-being (Johnson, 2013). The release of oxytocin in the mother promotes a strong emotional instinct to keep her infant close to her body and signals a biochemically mediated event that increases maternal responsiveness to the needs of her infant. Kangaroo mother care increases the release of oxytocin in the mother and infant and decreases plasma cortisol in mother, in turn signaling a decrease in maternal stress. This gives support to the logic that the more skin-to-skin contact the mother has with her infant, the more maternal sensitivity is stimulated by oxytocin and the more she will be able to appropriately handle stress to meet the needs of her infant. Maternal stress and anxiety associated with having a premature infant has been shown to interfere with this bonding process. Kangaroo mother care has been shown to decrease maternal stress levels as evidenced by lower cortisol levels (Cong et al., 2015). Close and sustained contact between mother and infant establishes and reinforces healthy biological bonding behaviors with the mother and enhances secure attachment with mother and infant (Feldman, 2004). However, close contact is hindered by the baby's prematurity and critical disease process, which leads to the physical separation of mother and infant (Feldman, 2004). It is hypothesized that skin-to-skin contact signals the release of

oxytocin in the mother, which promotes a strong emotional instinct to keep her infant as close as possible. As such, it functions as a biochemically mediated event that increases maternal responsiveness to the needs of her infant. Oxytocin release may also act synergistically to decrease maternal cortisol levels cogent to lowering of maternal stress. However, to date only one study has documented a change in parental oxytocin levels with the use of KMC (Cong et al., 2015).

Kangaroo Care and Neurological/Neurodevelopmental Outcomes

Kangaroo mother care has been known to facilitate maternal–infant bonding, which can be interrupted due to early and persistent maternal separation associated with prematurity. Existing evidence strongly suggests that KMC can help the infant's body physiologically regulate to the external demands of premature birth. The stress during birth is significant and essential to activate the brain and the lungs (Lagercrantz & Bistoletti, 1977). However, there is a paucity of knowledge regarding KMC and its effect on infant brain health. Further research into its potential as a preventative measure for such conditions as cerebral palsy in premature infants is warranted.

Premature infants born at less than 33 weeks gestation are at a very high risk for neurological impairment such as cerebral palsy (CP), which can have a profound effect on their neurodevelopment in early childhood. Cerebral palsy is a general term that is used to describe malformation or damage to motor areas in the brain, which disrupts the ability of the brain to control movement and posture (Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007). Children with cerebral palsy are three times more likely to need early intervention and specialized education. In the past 40 years, neonatal care has focused on saving the lives

of babies by investing in sophisticated technological equipment that has improved lung and heart function, but infants who have survived the battle for life with just these techniques have been at high risk for short-term and/or long-term neurologic sequelae after they were discharged from the hospital (Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007).

Feldman, Rosenthal, and Eidelman (2014) conducted one of the first studies showing the benefits of KMC well into childhood. This research tested KMC as an intervention to promote better cognitive outcomes among premature infants. Using a prospective, longitudinal, randomized controlled trial design, researchers enrolled 146 Israeli mothers and their premature infants in two comparable hospitals. Psychologists who tested mental cognition at different stages of assessment were blinded to whether the infant was in the intervention group or the control group. The study began with 146 subjects, with 73 in the intervention group and 73 in the control group. At the 10-year assessment the total number decreased to 117, with 55 remaining in the intervention and 62 in the control. Both groups were case-matched for demographic and medical conditions that included gender, birth weight, and gestational age; the Clinical Risk Index for Babies was used to quantify medical risk. The standardized intervention consisted of infants being taken out of the incubators and undressed, then placed between their mother's breasts for 1 hour daily for 14 consecutive days. The control group infants received all of their care in the incubators. Cognitive development and executive functions across the first 10 years of life were measured by trained psychologists at discharge/term, then at 3, 6, 12, and 24 months (age corrected) and at 5 and 10 years. The instruments that were used to measure the outcomes demonstrated strong validity and

reliability, as these tools were well established and had been tested before. The two measures had an interrater reliability average of 93% and intraclass reliability of .94.

Preterm birth has been known to have a high risk for intraventricular hemorrhage, or periventricular hemorrhagic infarction, owing to the disruption of brain development and damage to the immature brain. Feldman et al. (2014) posited that KMC during this sensitive period targets maturation on the autonomic nervous system but specifically works at the parasympathetic branch, which provides brainstem-mediated support. Researchers hypothesized that infants who received KMC would show more optimal physiologic functioning, autonomic functioning, sleep organization, hypothalamic-pituitary-adrenal axis activity (HPA), mother–child interactions, and improved cognitive skills across childhood with improved physiology of executive functions. The study results indicated significant improvements for those in the intervention group on many important outcomes. At age 10, premature infants who received KMC showed attenuated stress response, more autonomic functioning, organized sleep, better cognitive control, and more reciprocal mother–child relationship. At 6, 12, and 24 months, the KMC group scored higher on the Mental Developmental Index compared to the control group (96.09 ± 6.75 vs 93.25 ± 8.26; $p = .047$, 91.33 ± 8.13 vs 84.96 ± 10.59; $p = < 0.0001$, and 95.62 ± 12.94 vs 89.30 ± 12.29; $p = < 0.001$ respectively). Feldman et al. (2014) also noted that it has been unclear whether touch-based interventions, such as KMC, can result in lasting effects on a child's development beyond infancy. The researchers hypothesized that infants who received KMC would show improved executive functions at age 10 when compared to those who did not receive KMC. When the researchers measured along developmental epochs, they found that cognitive and executive function were indeed

higher at 6, 12, and 24 months. This substantiated not only the short-term benefits of KMC but also the long-term benefits. Although there is growing evidence supporting the use of KMC, the impact of KMC on energy conservation in premature infants is unclear.

Conceptual Model Underpinning Energy Conservation

Energy conservation in critically ill patients has been at the very foundation of nursing care throughout the history of nursing. In the 19th century, Florence Nightingale focused on the importance of a nurturing, healing environment (McCarthy et al., 1991). She proposed that nursing's major role in patient care is to bring the patient to a state of mind and body conducive to healing by responsible management of the patient's environment and to assure the patient receives adequate rest, comfort, nutrition, and hygiene (McCarthy et al., 1991). Recent research on the psychobiology of the stress response on cell metabolism supports Nightingale's belief that the patient care environment may affect healing and recovery (McCarthy et al., 1991).

Myra Levine, a nurse theorist whose work framed the foundation for energy conservation, described four principles that theoretically encompass a holistic view of the patient. She emphasized that disease processes can deplete energy and that nursing care should utilize knowledge and resources that are available to the patient to conserve and restore energy for healing and well-being (Levine, 1967). Levine's theoretical model informs nursing care by examining the patient's environment in two parts, externally and internally. According to Levine, the internal environment encompasses pathophysiological activity, and the external environment has three components: perceptual, operational, and conceptual. The internal and external components comprise the first conservation principle: conservation of patient energy. Her second conservation

principle describes nursing care as using healing to conserve the function of structural integrity. The third conservation principle focuses on the patient's personal integrity, giving credence to personal activities that provide meaning to personal identity. The fourth conservation principle guides nursing interventions that promote the social integrity of the patient by encouraging the maintenance of human relationships (Levine, 1967). Mefford's Theory of Health Promotion for Preterm Infants applies Levine's Four Conservation Principles to premature infants and focuses on addressing their unique needs (Mefford, 2004).

Nursing Care to Conserve Energy

Mefford (2004) has outlined critical nursing interventions that can promote conservation of energy specifically among premature infants. She asserted that nurses must support the pulmonary and cardiovascular systems during extrauterine transition to assure adequate oxygenation and cellular life processes. Mefford (2004) has also noted that nursing interventions should maintain airway integrity, monitor breathing and circulation, and assure adequacy of oxygenation and ventilation to facilitate optimal pulmonary function and comfort. She has argued that the use of nursing interventions that balance energy demands and supply are necessary, particularly during acute phases of illness. According to Mefford (2004), measures that keep the infant calm, promote rest, and manage pain and thermal instability are essential. Energy conservation must also include the appropriate intake of nutrients either parenterally or enterally through nasal gastric or transpyloric tubes, which should be carefully monitored (Mefford, 2004). Ultimately, the achievement of energy conservation is health and wholeness, as reflected by physiologic stability and growth (Mefford, 2004).

Nursing Care to Conserve Structural Integrity

Multiple threats to structural integrity are dangerous for a preterm infant and include bronchopulmonary dysplasia from barotrauma and oxygen toxicity from supplemental oxygen and ventilation. Supplemental oxygen is also a risk factor for retinopathy of prematurity. Conversely, insufficient oxygen can result in hypoxic episodes, which can in turn cause brain injury. As a result, nursing care should be centered on optimizing oxygenation while minimizing the need for supplemental oxygen (Mefford, 2004). Notably, the immature brain has an impaired ability to autoregulate cerebral blood flow manifested by fluctuations in systemic blood pressure, which can result in serious complications including periventricular–intraventricular hemorrhage and periventricular leukomalcaia (Mefford, 2004).

Nursing interventions that promote blood pressure stabilization and cardiovascular stabilization while minimizing noxious environmental stimulation and promoting comfort may help to decrease neurologic sequelae associated with prematurity (Mefford, 2004). Careful handwashing is imperative to protect immature immunity, and aseptic techniques with central lines and careful attention to interventions that protect skin integrity is essential to prevent systemic infection. Close monitoring of feeding intolerance to reduce infection and necrotizing colitis is also necessary. Moreover, particular attention to facilitating an infant's flexed posture and midline positioning is important to counteract the effects of gravitational pull on the body and the infant's weak muscles. Nursing care should also focus on developing an infant's pre-feeding competence by encouraging hand-to-mouth and hand clasping movements (Mefford, 2004).

Nursing Care to Conserve Personal Integrity

The primary role of nursing care for premature infants should be to care for the infant in a developmentally supportive manner, particularly due to premature infants' immature central nervous system (CNS). Mefford (2004) has endorsed Als' synactive theory of development, which provides a foundation for developing neurodevelopmental competence based on interpreting the behavior of preterm infants. Als (1982, 1986), a child psychologist, provided a framework of preterm infant behavior that conceptualizes a network of five behavioral subsystems: autonomic, motor, state, attention interaction, and self-regulation. Each of these subsystems are in constant interaction with each of the other four subsystems and the environment, and they can be observed by the nurse when assessing the behavior of the infant and can then be modulated to the infant's individuality and personal uniqueness (Mefford, 2004). Mefford has embraced these subsystems as a way for the nurse to communicate with the infant by reading these behaviors as calming or stressful. Moreover, behaviors are identified as avoidance behaviors or stable approach behaviors. In addition to interpreting physiologic cues like vital signs and physical assessment findings, nurses need to be able to interpret infant behavior cues in order to promote and conserve personal integrity (Mefford, 2004).

Nursing Care to Conserve Social Integrity

In addition to personal integrity, nursing care should conserve social integrity. This should focus on helping parents to grieve the loss of a healthy newborn by having a premature baby and supporting parents as they cope with the stress of a preterm infant and the NICU environment. Nursing care should also foster parent–infant attachment and bonding by helping parents to understand the physiologic challenges their infant faces

and by providing guidance to facilitate parents' understanding of their infant's behavioral cues. Given the evidence that mother–infant interactions begin well before birth Johnson, (2013), supports the coming together of mother and infant immediately after birth as necessary to conserve social integrity for both mother and infant (Johnson, 2013). Parents should be an integral part of caring for the infant in the NICU. A primary goal of nursing care should be to encourage an intact family system, with the family ready to assume total care of the infant by the time the infant is discharged (Mefford, 2004).

Consensus on Kangaroo Mother Care

Preterm has been defined by the World Health Organization (WHO) as all live births before 37 completed weeks (whether singleton or multiple) (Bick, 2012). It is further subdivided into extremely preterm (< 28 weeks), very preterm (28- < 32 weeks), and moderate preterm (32- < 37 weeks). The latter group includes late preterm birth (34- < 37) completed weeks (Bick, 2012). The WHO has endorsed KMC as a life-saving intervention that can be used in low- or high-income settings and can empower parents, especially mothers, in the care of their newborns (World Health Organization, 2015). "Born Too Soon" was a call to action for lifesaving interventions for premature infants released by a global team of leading international organizations, United Nations agencies, and academic institutions. They highlighted the strong evidence that interventions such as KMC, can reduce the rates of death and disability among premature infants and are cost-effective (Bick, 2012). In fact, the WHO sponsored the Global Action Report in "Born Too Soon" on death from preterm birth complications and they noted a 75% reduction of death in low-income settings when KMC and breastfeeding interventions were used effectively and efficiently (March of Dimes, Partnership for Maternal, Newborn, and

Child Health (PMNCH), Save the Children, & WHO, 2012). As a result, the WHO has advocated for KMC as a safe intervention for healing, especially for infants that are preterm and weigh ≤ 2,000g (Bick, 2012).

Notably, the International Expert Group at the 7th International Workshop on Kangaroo Mother Care distinguished between intermittent (IKMC) and continuous (CKMC). They noted that KMC should involve a progression from short periods of skin-to-skin care eventually leading to more continuous skin-to-skin contact—up to 24 hours per day, 7 days per week—until time of discharge and full breastfeeding is achieved (Nyqvist et al., 2010b). Additionally, the committee report from the conference defined KMC as "early, continuous, and prolonged mother–infant skin-to-skin contact, with ideally exclusive breastfeeding" (Nyqvist et al., 2010b). They also noted that KMC is an integral element of newborn care in high-tech NICUs (Nyqvist et al., 2010b). Conclusions from the conference report support scientific evidence that KMC can provide a neutral thermal environment and can contribute to optimal thermal regulation for premature infants (Nyqvist et al., 2010b).

The practice of separating mothers from their infants is disruptive to the bonding process, but KMC has been found to decrease maternal depression and increase maternal sensitivity, which promotes and strengthens the bonding process (Nyqvist et al., 2010b). Kangaroo mother care is also noted to have positive effects on the psychological and social development of the mother–infant dyad, thereby reducing maternal stress and contributing to favorable family environments (Nyqvist et al., 2010b).

Benefits of Kangaroo Mother Care

In Western cultures, post birth mother–infant separation has been the standard of care in early postnatal and perinatal care. However, guidelines from the 7th International Workshop on KMC support the view of preterm infants as external fetuses, indicating parental skin-to-skin care or KMC as the optimal environment for further development of preterm infants. Skin-to-skin contact between mother and infant is the foundation and architecture of KMC. National guidelines indicate that maintenance of the physical relationship between mother and infant is crucial and all postpartum and intrapartum care should adhere to the paradigm of nonseparation of infants from mothers. This makes all postnatal arrivals to the nursery or NICU candidates for KMC as a preferred routine place for further care (Nyqvist et al., 2010b).

In 2016, Chi Luong and colleagues conducted a randomized controlled trial with low birth weight (LBW) infants weighing from 1,500–2,500 grams (Chi Luong, Long Nguyen, Huynh Thi, Carrara, & Bergman, 2016). They replicated a previous study that took place in Cape Town, South Africa, and measured the physiological stability achieved by skin-to-skin contact compared to the incubator during the transition period for newborns (Bergman, Linley, & Fawcus, 2004). The Chi Luong (2016) study tested the hypothesis that the environment provided by mother–infant skin-to-skin contact can improve neonatal thermoregulation and cardiorespiratory physiology during the extrauterine transition to life when compared to incubator care. In the earlier study, Bergman et al. (2004) reported that skin-to-skin contact accomplished stability in all experimental subjects, whereas it did so in less than half of the control (incubator) subjects.

Chi Luong et al. (2016) aimed to replicate Bergman's 2004 study with a larger participant group and in a different context (Bergman et al., 2004; Chi Luong et al., 2016). The study was conducted in Ho Chi Minh City, Vietnam, which is a lower-middle-income country with 9% low birth weight, and KMC is not widely practiced there. The study was conducted at a large birthing center with nearly 60,000 deliveries per year and 1,200 obstetric beds. The neonatal unit consisted of 180 beds and admitted 16,200 cases in 2012 at the time of the study. The hospital's protocol was that all babies under 2.5kg or less than 37 weeks gestation had to be transferred to the NICU for observation, which resulted in separation from the mother during that period. The aim was to compare care methods of skin-to-skin contact and the conventional way of separating infants from mothers for incubator care on the stabilization of newly born low birthweight infants.

In order to test the hypothesis a randomized controlled trial was conducted. The study population consisted of mother–infant dyads with infants weighing between 1,500 and 2,490 grams. Infants were randomized using block randomization at birth (n =50) to skin-to-skin contact and (n=50) to routine care in the incubator. Exclusion criteria included mothers who tested positive for human immunodeficiency virus and hepatitis B, severe malformation or chromosomal abnormalities, or any life-threatening disorders or severe asphyxia at birth, neonatal convulsions, or multiple births. Blinding was not carried out due to the nature of the intervention. Infants in the control group were separated from the mother immediately after birth for resuscitation efforts and examination, given routine transitional care and medication, and then transferred to the neonatal department about 30 minutes after birth. The intervention group was placed on a

clean cloth on the mother's abdomen immediately after birth and was then cleaned, covered with a new cloth, and the cord was cut. Vital signs and demographic information were recorded while the infant was on the mother's chest, with a 3-minute interruption for measurements and medication administration.

Researchers measured infant response using the Stability of Cardio-Respiratory in Preterm Infant (SCRIP) instrument as well as a modified version of SCRIP that includes late preterm infants called the Stability of Cardio-Respiratory system in Late Preterm (SCRIL). The total SCRIP and SCRIL scores were composite measures of stability over the first 6 hours of extrauterine life measured in 5-minute epochs and recorded at 30-minute intervals. Heart rate, oxygen saturation, and temperature were measured at the first minute. At the second and third minutes an accurate count of respirations was measured, and in the fourth and fifth minutes of the 5-minute epoch the length and number of apneic episodes and periodic breathing were recorded.

The SCRIP score was a maximum of 6 defined as follows: score of 2 for normal heart rate (HR) 100–160 bpm; score of 1 for HR between 80–100 bpm; score of 0 for HR < 80 or >200 bpm; score of 2 for normal respiratory rate (RR) not defined in breaths per minute; score of 1 for apnea < 10 seconds or periodic breathing; score of 0 for apnea ≥ 10 seconds or tachypnea >80 breaths per minute; score of 2 for oxygen saturation of > 89; score of 1 for a fall to 80–89%; and a score of 0 for a fall below 80%. The SCRIL score was a maximum score of 6 defined as score of 2 for HR 120–159.9 bpm; score of 1 for HR 100–119.9 bpm or 160–169.9 bpm; score of 0 for < 100 or >170 bpm; score of 2 for 40–59.9 breaths per minute, score of 1 for 30–39.9 or 60–69.9 breaths per minute or apnea < 6 secs or periodic breathing; score of 0 for < 29.9 or > 70 breaths per minute or

apnea ≥ 6 seconds, and oxygen saturation scores defined as 2 for > 97%; score of 1 for 94 - 97% oxygen with cannula; and score of 0 for any fall < 94% nasal continuous positive airway pressure (nCPAP)/ ventilation. The SCRIL was an attempt by the researchers to develop a more sensitive instrument that captured the limitations of respiratory support, which was not captured in the original SCRIP score.

The SCRIP and SCRIL scores indicated that infants in the skin-to-skin contact group achieved physiologic stability in one hour compared to infants in the incubator who showed respiratory instability during the first 3-4 hours of life followed by heart rate instability for up to six hours (Chi Luong et al., 2016). The total SCRIP score out of 6 was 5.66 ± 0.72 in the skin-to-skin contact group and 4.72 ± 0.83 in the maternal-infant separation groups at 120 minutes ($p = 0.0001$) and 5.82 ± 0.66 for skin-to-skin contact and 5.24 ± 0.72 maternal–infant separation group at 360 minutes ($p = 0.0001$) with a significant temperature stability trend over the 6 hours ($p = 0.02$) in the intervention group. The SCRIP scores in this study support the hypothesis by Bergman et al. (2004) that skin-to-skin autonomic regulation and support protects the newborn from becoming unstable. See Table 1.

Table 1.

Stability of Cardio-Respiratory System in Preterm Infants (SCRIP) Score Showing Skin-to-Skin Autonomic Regulation: Chi Luong Study: KMC Intervention vs Incubator

Time in minutes	Skin-to-Skin	Incubator	p
120	5.66 ± 0.72	4.72 ± 0.83	$p = 0.0001$
360	5.82 ± 0.66	5.24 ± 0.72	$p = 0.0001$
720	9 /50 infants	26 /50 infants	$p = < 0.001$
IV fluid support			
720	9 /50 infants	26 /50 infants	$p = 0.004$
Antibiotic use			

Note. Data in table from "Randomized Controlled Trial of Skin-to-Skin Contact From Birth Versus Conventional Incubator for Physiological Stabilization in 1200- to 2199-Gram Newborns" by N. J. Bergman, L. L. Linley, and S. R. Fawcus, 2004, *Acta Paediatrica, 93*(6), p. 779–785. Copyright 2004 by N. J. Bergman, L. L. Linley, and S. R. Fawcus. Reproduced with permission.

Results from this study demonstrated that the incubator infants had respiratory instability in the first 3–4 hours. Bradycardia, respiratory instability, and lower body temperatures were attributed to dissociation stressor response (Chi Luong et al., 2016). Dissociation stressor response is a result of separation from the mother early in postpartum hours. It is described as a separation distress cry that is ignored and so the infant disengages from his environment as a result of the discomfort of acute isolation distress. This lends support to the hypothesis of separation stress or dissociation stressor response in infants that are separated from the mother or surrogate. The absence of maternal warmth for thermogenesis caused an increase in consumption of energy and a cascading decrease in blood glucose, measured at 180 and 360 minutes (Chi Luong et al., 2016). This contributed to the overall temporal decline and hypoglycemia at 4 hours post birth.

The study also suggested that the separation of mother and infant mirrors the negative physiological outcomes in mammalian research separation (Hofer, Shair, & Murowchick, 1989). In a study examining mammalian research and the implications for growth and development after maternal separation, a study by Hofer and colleagues (1989) examined 2-week-old rat pups in which maternal–offspring separation in very young rat pups evidenced poor growth, poor weight gain, poor development, and failure to thrive. In the Chi Luong (2016) study, separation in the early transition period resulted in delayed physiological stabilization in the incubator group, with a subsequent need for medical interventions and intravenous fluid support (9/50 in the skin-to-skin group vs 26/50 in the incubator group, $p = < 0.001$), and more antibiotic use in the incubator group when compared to the skin-to-skin group, (9/50 skin-to-skin group) vs (26/50 incubator group, $p = 0.004$) (Chi Luong et al., 2016). The Chi Luong study showed decreased morbidity in the skin-to-skin contact group relative to the incubator group, which substantiates the findings from Bergman (Bergman et al., 2004). Stabilization achieved in the early transition period (the first 6 hours of life) was an important predictor of the continuing clinical course of the infant (Chi Luong et al., 2016). There was also evidence that hypercortisolemia reported in all incubated premature infants can be lowered rapidly by skin-to-skin intervention (Chi Luong et al., 2016).

Chi Luong et al. (2016) briefly alluded to the increased consumption of energy for thermal regulation and hypoglycemia in the incubator group. Preterm neonates' ATP or energy stores are limited and susceptible to cell injury due to ATP depletion (Esiaba et al., 2016). Kangaroo mother care has the potential to alter biochemical markers of ATP utilization, oxidative stress, and cell injury. However, the difference in energy costs at the

cellular level is currently unknown. The evidence of the cumulative effect of destabilization in cardiorespiratory parameters can lead to ATP depletion and could result in potentially dangerous metabolic dysfunction and cell injury (Esiaba et al., 2016). Furthermore, dissociative stress with resulting hypercortisolemia was associated with maternal–infant separation (Chi Luong et al., 2016). A measure of oxidative stress in allantoin could explore the level of cellular protection of KMC having a protective mechanism from the exposure of chronic or dissociative stress in premature infants. Understanding the conservation of energy among preterm infants who experience KMC versus those who are cared for in incubators is crucial, because the difference in energy costs at the cellular level is currently unknown.

Kangaroo Mother Care and Benefits of Weight Gain

One of the most crucial factors related to premature or critically ill term infants is the infant's ability to meet its physiological energy needs (Hay, Brown, & Denne, 2014). Three main factors that negatively influence the infant's ability to meet energy needs are inadequate glycogen stores, decreased glucose production, and increased glucose demands. Carbohydrates, primarily glucose, are principal sources of energy for the brain and heart until lipid oxidation develops over the several weeks following birth (Hay et al., 2014). Energy conservation in premature infants allows for recovery and repair, growth, and maturation, and promotes positive reaction to the mother (Ludington, 1990). In a randomized control trial in Hyderabad, India, researchers compared the efficacy of early initiation of kangaroo ward care (KWC) to intermediate intensive care (IIC). They reported a significant increase in weight gain (gm/day; 24.4 $\pm$ 6.9 vs. 21.5 ± 5.4g; p = 0.01) in the KWC group, but on other secondary outcomes measurements were similar in

both groups (Sharma, Murki, & Pratap, 2016). They concluded that KMC was an essential component to the care of stable very low birth weight infants (VLBW) and stable extremely low birth weight infants (Sharma et al., 2016).

Kangaroo Mother Care and Energy Expenditure

Peng et al. (2014) conducted an exploratory secondary analysis examining the mainstream NICU environment as a source of stress for the immature neurological system of premature infants. Bright lights, noise, care interactions from touch stimulation, and handling of the infant are all sources of environmental stress. Indeed, the environment necessary for an infant's survival may play a role in increasing an infant's energy requirements for physiological well-being and for the processes of healing, growth, and recovery. Peng et al. (2014) examined energy expenditure in 37 infants by measuring their heart rates during environmentally stressful periods. Their operational definition of physiological stress signals was based on (a) heart rate < 100 beats per minute and >160 beats per minute or an increase in baseline of 5 beats per minute or more; (b) irregular respirations or respiratory rate < 40/min or > than 60/min or an increase in baseline of more than 7/min or more; and (c) oxygen saturation < 90 or a decrease of more than 2.5%.

They found that energy expenditure (EE) that was based on heart rate was an accurate estimate of total EE. Energy expenditure in preterm infants was calculated using the following equation: EE per heart beat (Cal/kg x beat) = mean metabolic rate x duration of study (min)/ accumulated heart beats) (Peng et al., 2014). A photometer was used to measure light in foot candles (TES-1336) and a phonometer (NL-10A) was used to measure sound levels in decibels. A Likert-type scale was used to measure the degree

of stimulation of nursing interventions as follows: level 0 – no intervention; level 1 – interventions that include light or noise stimulation; level 2 – interventions that include noise and light; level 3 – interventions that include light or noise and handling; level 4 – interventions that include light + noise + handling; and level 5 – any intervention that caused pain. As the intervention levels increased, there was significant correlation in energy expenditure. After adjusting for demographic factors there was a significantly positive relationship between EE and different levels of nursing intervention (intervention level 2, $p = 0.01$; intervention level 3, $p = <0.0001$; intervention level 4, $p = <0.000$; intervention level 5, $p = 0.02$). Specifically, the EE for nursing levels 2 (average 0.94 units; mean, 40.68cal/kg averaged over a time frame), level 3 (average 2.05 units; mean, 41.45 cal/kg averaged over a time frame), level 4 (average, 2.42 units mean, 42.5 cal/kg average over a time frame), and level 5 (average, 3.07 units; mean 43.96 cal/kg averaged over a time frame) were significantly higher than for level 0 (no intervention status).

Based upon the findings described in the above paragraph, these researchers suggested that heart rate was an accurate estimate of EE during stressful activity (Peng et al., 2014). This assumption is based on the Fick principle, where cardiac output (heart rate x stroke volume) is defined as the ratio of oxygen consumption to arteriovenous oxygen difference. Based on these results, increased EE from environmental stressors may negatively impact growth and developmental outcomes in premature infants. Researchers concluded that interventions such as KMC can optimize energy conservation in preterm infants, thereby improving developmental outcomes (Peng et al., 2014).

Kangaroo Mother Care and Energy Conservation

Ludington (1990) conducted a small pilot study (*n*=8) of energy conservation in stable preterm infants during KMC using indicators of infant heart rate, activity level, and behavioral state as proxy measures for state-related energy expenditure. Infants included four boys and four girls, all at 34–36 weeks gestation and within four days of being discharged home. The study tested four hypotheses: (a) heart rate will be reduced during skin-to-skin (SSC); (b) a greater percentage of time will be spent in quiet sleep states versus awake states during SSC; (c) the duration of sleep state bouts will be longer during SSC intervention; and (d) activity level over all states as well as within each state will be reduced during SSC.

Ludington (1990) suggested that once the postnatal recuperative energy demands have been met, nursing measures that support minimal demands for energy expenditure should be encouraged. Moreover, she asserted that the least amount of energy demands occur in the quiet sleep state, whereas premature neonates are mostly in the active states of sleep or awake activity. Ludington noted that activity level, behavioral state, and heart rate are valid indicators that were used to test the effectiveness of the KMC intervention. The assumption was that infants are soothed during KMC. However, whether these soothing effects translate into energy conservation is unknown.

The study's dependent variables were heart rate, behavioral state, and activity level. The energy balance framework guided the study (Ludington, 1990). Ludington argued that an increase in energy expenditure is met by an increase in oxygen demands and then by an increase in heart rate. Changes in heart rate were used as reflections of energy demands with estimates of energy expenditure calculated by Woodson's method

based on the Fick principle (Woodson, Field, & Greenberg, 1983). Using this estimation, Ludington found that heart rate measures obtained at different levels of physical exercise were a reliable measure of energy expenditure. (Ludington, 1990).

The behavioral states of infants' sleep and wakefulness were examined in relation to KMC. Wakeful states were determined to cost more energy in terms of oxygen consumption than sleep states. Activity level was shown to account for as much as 40% to a low of 7% of daily energy expenditure. The activity level scale was used for measuring activity. The interrater measurement of the scale was 0.85. The Anderson Behavioral State Scale was used as an instrument to measure state. The scale is a nominal scale of 12 states: regular quiet, irregular sleep, active sleep, very active sleep, drowsy, quiet alert, quiet awake, active awake, very active awake, fussy, cry, and hard cry. The observed state of the infant was determined using criteria that accompanied the measures for the instrument. Interrater agreement was 0.89.

A Pearson product moment correlation using weighted heart rate and behavioral state means to control variation in the number of observations between subjects highlighted strong correlations during pre- SSC (p = 0.007), SSC (p = 0.004), and post-SSC periods (p =0.01). A collapse of the data from all three periods rendered a robust linear relationship (p = 0.0001) with little variability in the slope of the regression line. Repeated-measures analysis of variance revealed significant differences across the three periods of SSC for behavioral state and activity level but not for heart rate.

Findings from this study suggested that energy expenditure decreased for infants on behavioral and activity level variables during SSC but not for heart rate (Ludington, 1990). Activity level during SSC was significantly lower than during pre- (p = 0.0042)

and post- periods ($p = 0.0027$) ($p = 0.0002$). Activity during active sleep was significantly reduced during SSC. A significantly greater amount of time was spent in quiet sleep during SSC than in pre-SSC ($p = 0.0101$) and post-SSC ($p = 0.0079$). The mean duration of quiet sleep time increased during SSC and was twice as long in SSC than in pre-SSC ($p = 0.0002$) and post-SSC periods ($p = 0.0001$).

The findings of this study add support to the body of literature that shows positive effects from the sensory experience of SSC. Activity level was significantly reduced, which can be interpreted as energy conservation (Ludington, 1990). Heart rate did not drop as expected during SSC, although a linear correlation of oxygen assumption was shown. The authors attributed this to the increase in body and skin temperature from SSC. The sample size and the maturity of these subjects prevent generalization of these results. Additionally, this study was carried out using only one episode of skin-to-skin care which could have had confounders in measurements including wellness and parent bonding. Authors did not describe whether this intervention was the first experience in KMC position or if there were several daily sessions before these measurements were taken. Ludington purported that more precise and longitudinal measurements of energy expenditure and conservation are needed in order to generalize these conclusions.

Kangaroo Care and Thermoregulation

Knobel-Dail, Tanaka, Holditch-Davis, & White (2017) investigated thermal stability by measuring central and peripheral temperatures in premature infants. Abdominal skin temperature was used as a proxy for central temperature and foot temperature as a reporter of peripheral temperature. Infants with less than 29 weeks' gestational age were found to have poor autoregulation. Developmental circulation

changes influenced abdominal temperatures to remain sub-optimal up to the first two weeks of life while in the incubator, despite recorded optimal core and peripheral foot temperatures (Knobel-Dail et al., 2016). It seems reasonable to expect that placing the infant skin-to-skin with the mother would likely increase neonatal abdominal temperature over time due to the frog-like position of the infant's abdomen against the mother or caregiver. Additionally, the more upright position of the baby during KMC appears to be favored. These factors may have an influence on better digestion and are important reasons to assess intestinal perfusion and oxygenation during KMC intervention. Premature infants are poikilothermic and normothermia is a driving goal for preterm infants demanding constant nursing and medical surveillance with engagement of strategic and mechanical measures to keep body temperature optimal.

Stress and Kangaroo Mother Care

The birth and arrival of a preterm infant has been found to be stressful for both mother and infant (Cho et al., 2016). The infant's unexpected arrival has been reported to cause high levels of stress in parents, affecting both their parenting behaviors and parenting competence (Cong et al., 2015). Furthermore, physical separation and placement in a high technological unfamiliar environment like a NICU contributes to increased maternal and infant stress (Cong et al., 2015). The infant's inability to readily adjust to extrauterine life increases dissociative stress, guilt, and anxiety in parents. In addition to the extensive physiological and behavioral benefits of KMC cited previously, it has been found to decrease parental stress and anxiety and reduce dissociative stress in infants, which in turn can enhance a bonding phenomenon that is not yet scientifically understood.

Studies have shown that infants in incubators experience hypercortisolemia, which can be rapidly reduced by KMC (Chi Luong et al., 2016). Many studies have reported cortisol levels in both mothers and infants as being lowered after KMC intervention (Neu, Hazel, Robinson, Schmiege, & Laudenslager, 2014). Currently, there are no biochemical biomarkers of stress signaling a reduction in inflammatory processes in the presence of KMC. Esiaba et al. (2016) conducted a study using urinary allantoin as a marker of oxidative stress in germinal matrix intraventricular hemorrhage (IVH) in preterm newborns. Allantoin is produced in humans by free radicals of nonenzymatic oxidation of uric acid following oxidative stress associated with inflammatory processes (Esiaba et al., 2016). The measurement of allantoin has been validated in adults and in neonates, and elevated allantoin concentrations have been found in connection to increased ATP utilization and necrotizing enterocolitis.

Esiaba et al. (2016) enrolled infants at less than 34 weeks gestation (n=44) and categorized them based on the presence of IVH as diagnosed by head ultrasound and/or magnetic resonance imaging. Demographic variables were homogenous for gestational age, birth weight, and 1-minute Apgar Scores. The 5-min Apgar score for the severe IVH group (3.86 ± 2.54; p = 0.002) was significantly lower than the scores in the no IVH (6.82 ± 1.59) and mild IVH (6.27 ± 1.56) groups. Between 36 and 72 hours of life (HOL), allantoin concentration in the no IVH and mild IVH groups remained relatively stable at 00.43 ± 0.007 and 0.037 ± 0.01 $u$mol, respectively. A significant elevation in allantoin (0.098 ± 0.013 $u$mol) was observed between 36 and 48 HOL in neonates with severe IVH (p = 0.002) compared to controls and those with mild IVH. Allantoin remained significantly elevated (0.079 ± 0.14 $u$mol; p = 0.021 in this group even at 72

HOL. Elevated urinary allantoin levels were associated with severe IVH, 36 to 72 hours of life, which suggests that oxidative stress played a role of importance in the pathophysiology of IVH (Esiaba et al., 2016). The researchers concluded that these results are consistent with prior observations that neonates with poor outcomes experience increased oxidative stress shortly after birth and that oxidative stress is likely the cause of the elevated allantoin observed in the severe IVH neonates (Esiaba et al., 2016).

Barriers to Kangaroo Mother Care

Anderson, Moore, Hepworth, and Bergman (2003) conducted a randomized clinical trial to describe the percent of time and the type of contact 0–48 hours post birth in the mother–preterm infant dyad. The researchers studied four groups in the postpartum unit and in the NICU. Groups were assigned to either KMC or standard care (wrapped in blanket holding). Both postpartum (PP) and NICU units had an experimental group defined as KC-PP or KC-NICU and a control group, defined as wrapped holding in the postpartum unit (WH-PP) and wrapped holding in the NICU (WH-NICU). The researchers used minimization to obtain balance in the groups and controlled for threats to internal validity such as selection bias. They reported that the amount of skin-to-skin contact was far less than expected in the KMC groups but that KMC groups had more contact with their infants than the control group. Their findings were concerning and highlighted the fact that although researchers helped engage mothers in KMC, KMC was not occurring in practice as frequently as they had expected that it would. They strongly recommended a supportive environment with physicians and nurses coaching mothers to

facilitate early, frequent, and uninterrupted mother–infant contact due to the beneficial effects of KMC (Anderson et al., 2003).

Currently, there are also persistent barriers to adopting KMC by the nation's 20,000 neonatal nurses and 112,000 labor and delivery, or newborn nurses. These include fear of the physiologic instability and infant stress that can be caused by the moving infants to the KMC position and from KMC back to bed, as well as the need for a physician order for KMC. In order to mitigate the impact of these barriers, there is a need to educate neonatal healthcare personnel. This could be carried out utilizing the concept of trans-disciplinary translational research to synthesize the knowledge regarding physiological and behavioral aspects of KMC as informed by intervention research studies such as this (Ludington-Hoe, 2011).

Summary

Review of the benefits of KMC evidenced in the literature supports physiological, behavioral, bonding and attachment, social interaction, and developmental effects. Research studies reviewed have shown evidence of enhanced physiologic stability in the infant and enhanced biologic coregulation and synchrony between infant and mother, better weight gain, better quality of sleep, better temperature control, better brain development and maturation with increased complexity, better motor development, decreased stress in both infant and mother, decreased crying, and decreased mortality and overall morbidity. In spite of these overwhelming positive effects, we find the adoption of KMC is slowly progressing and is impeded by the lack of education regarding the science of KMC. By providing insights into the biochemical effects of KMC in the

mother–infant dyad, we can potentially encourage KMC as an important strategy for energy conservation in clinical practice.

Conclusion

Given the prevalence of prematurity and the associated impairment, disability, and economic burden to both healthcare organizations and families, accurate assessment with more rigorous measures could address the gap between the science and practice and inform the use of KMC in research and the clinical setting. The correlation of ATP degradation, oxidative stress, and cell injury linked to physiological and behavioral benefits is an important step that will strengthen the existing evidence and science of KMC.

Chapter Three

Introduction

Premature infants admitted to the Neonatal Intensive Care Unit (NICU) are at high risk of suffering the consequences early maternal separation. Bonding processes of mother and infant may also be at risk. Consequently, infants become vulnerable to a myriad of internal and external events that increase energy loss (Blass, 2015). Kangaroo mother care (KMC), a parent holding the infant skin-to-skin on the bare chest for extended periods of time, has been shown to be important for reducing mortality and morbidity among premature infants resulting from direct physiological effects of stability and decrease maternal stress levels as evidenced by lower cortisol levels (Johnson, 2013). Maternal stress and anxiety associated with having a premature infant has been shown to interfere by delaying the natural physiological effects and bonding processes that occur in early puerperium. Kangaroo mother care (KMC) has been identified as an intervention that activates mechanisms of energy preservation in this population by stabilization of physiological parameters, minimizing dyad separation, and maximizing a battery of physical, physiological, and behavioral effectors that are energy-conserving and mediated by several central and peripheral mechanisms (Blass, 2015). Processes mediating energy conservation have not been adequately investigated. This is the first study that attempts to link physiological biochemical data to the theorized physiological effects on the infant's growth and development.

Psycho-neuro-biological studies have shown that early interaction and bonding can impact the growth and organization of the developing brain and positively affect the physiological and psychological development (Mäntymaa et al., 2003). However,

biological documentation of energy conservation of KMC is lacking. This study aims to link biochemical data to physiological benefits of KMC to add further evidence to the science of early dyad interaction, in order to educate for the primacy of KMC in clinical practice. For the mother, evidence of bonding was measured with MIBS self- scale instrument. For the infant, reduction in energy utilization was quantified by examining urinary biochemical markers of ATP degradation (hypoxanthine, xanthine, and uric acid) and further measure of oxidative stress (Allantoin)(Angeles et al., 2015; Plank, Calderon, Asmerom, Boskovic, & Angeles, 2011). See figure 1 and 2.

Study Design

A prospective, stratified, single-blind, randomized controlled design was used to test the hypothesis that exposure to KMC will significantly alter biochemical markers of ATP utilization, oxidative stress and cell injury in the infant, and enhance maternal-infant bonding.

Setting

Data were collected at a large, regional children's hospital in the 84-bed NICU, caring for both inborn and out born infants with an average daily census of 84 babies and an admission rate of over 1,200 neonates per year. This facility is the largest interdisciplinary NICU in the western United States. The institutional review boards of the facility and the University of San Diego approved this study.

Population/Sample

Premature infant and mother dyads 24-36 weeks born at the facility who were admitted to the NICU for care were eligible to participate in the study**.**

Sample Size

Power analysis revealed the need for a sample size of 50 potential mother-infant dyads to be randomized to 25 to the control group and 25 to the intervention group based on gestational age and yield an effect size of 0.35. Specifically, we calculated the power to detect differences in purine levels among premature infants 24-36 weeks' gestation in terms of a moderate effect size of 0.35. The calculations assumed an outcome with, a Type I error rate (α) of .05, a Type II error rate (ß) of .20 (power of .80), and a two-tailed statistical test, as is appropriate for research purposes. We believed this effect size to be large enough that the intervention could detect differences between conditions, but not small enough to be clinically and statistically irrelevant.

Inclusion/ Exclusion criteria

Potential infant participants were premature infants 24-36 weeks' gestation, less than 1 day of age postnatal and who were deemed medically stable as determined by a SNAPPE_II score of less than 9 (Score for Neonatal Acute Physiology- Perinatal extension SNAPPE –II). Mothers of potential infant participants who were medically stable were also included. The enrollment of subjects before DOL 1 was attempted.

Exclusion Criteria

Infant exclusion criteria included 1) requirement for surgery; 2) intraventricular hemorrhage (IVH) > or equal to grade 3; 3) on medication such as morphine, fentanyl, versed, muscle relaxants, phenobarbital, or Dilantin; 4) renal injury (plasma creatinine > 1mg/dl; 5) severe cyanotic heart disease or severe respiratory distress; 6) known abdominal wall or intestinal anomaly or injury (NEC); 7) chromosomal anomaly; and 8) facial anomaly. Failure to enroll infant resulted in failure to enroll mother.

Study Procedures

Recruitment

Parents of premature infants meeting the inclusion and exclusion criteria were approached for informed consent soon after birth. Once families provided their consent and their infant was determined to have met study eligibility criteria and deemed medically stable, they were then randomized by permuted block randomization and stratified by birthweight of 1,000g or less (small, SM) or 1,001g or above (large, LG). The KMC study intervention protocol was initiated. Envelopes were numbered from 1 to 35 for the small and large group and sealed after a consulting researcher placed a piece of paper indicating assignment to the intervention or control group. The envelopes were placed in a shoebox in the lab and only after the mothers consented, the baby's hospital identification sticker was placed on the envelope and could then be opened by the researcher. This type of randomization helped to lower the risk of selection bias.

Intervention Protocol

The primary investigator (PI; DF) performed the KMC intervention for all participants. The PI followed existing unit policy guidelines for transfer of infant from incubator to the mother's chest, for positioning the infant, to assess tolerance, and documentation in addition to manual documentation specific to the research project. On the day of the intervention the PI consulted with the infant's bedside nurse. The PI assisted the mother and her assigned nurse to the bedside from postpartum and met at the baby's bedside in the NICU. A NIRS probe and a temperature probe was attached to the infant's abdomen. The NIRS probe was attached particularly to the lower left quadrant of the abdomen each time. The instruments such as NIRS monitor, and Massimo Pulse oximeter for capturing

perfusion index values needed for the study were brought to the bedside by the PI. Bedside nurses were trained before the study started regarding the frequency and timing of the urine collection, which was before, during, and after KMC intervention. The PI and the bedside nurse assisted the mother to remove the baby from the incubator and to sit in the special KMC chair. The physiological dependent variables included heart rate, respiratory rate, oxygen saturation, abdominal NIRS, perfusion index, FIO2, ventilator setting, and abdominal temperature and were monitored by both the bedside monitors and manually collected by the PI for a period of 1 hour from the start of time zero.

Demographics: Mother–infant dyads that were born prematurely and admitted to the NICU with a gestational age of 24-36 weeks.

Data Collection

Infant variables

Information collected for infant variables included birth weight, gender, gestational age at birth, gestational age at time of sampling severity of illness, medications, heart rate, oxygen saturation, perfusion index, abdominal temperature, and near infrared spectroscopy measuring abdominal tissue saturation during the hour of intervention or incubator care. Current illness severity of infants was quantified using the Score for Neonatal Acute Physiology (SNAPPE-II) scoring tool, a risk-adjustment instrument with established reliability and validity (Harsha & Archana, 2015; Richardson, Corcoran, Escobar, & Lee, 2001).

Near infrared spectroscopy (NIRS). The gastrointestinal system becomes the primary source of nutrition that the neonate must be transitioned to after birth. In premature

newborns, the gastrointestinal system is underdeveloped. This is a challenge for neonatologists who must assess intestinal function in order to manage enteral feeds. NIRS is one of the noninvasive technologies that have demonstrated the potential to assess intestinal function. Intestinal perfusion and oxygenation was tested on day 3 and 4 during 1 hour of KMC or during 1 hour of incubator care. Data were collected using the Fore- Sight II NIRS tissue oximeter monitor for splanchnic StO2. The NIRS–infrared probe (Casmed, Fore-Sight II Branford, CT, USA) was placed on the left lower abdominal quadrant immediately before skin-to-skin care with mother or immediately before incubator care.

Abdominal Temperature - Normal 36.5 to 37.3 degrees Centigrade. Knobel-Dail et al., (2016) investigated thermal stability by measuring central and peripheral temperatures in premature infants during two weeks in the incubator. Researchers used abdominal skin temperatures as a proxy for measuring central temperatures. They found that infants less than 29 weeks' gestational age have poor auto regulation along with developmental circulation and abdominal temperatures that remained sub-optimal for up to two weeks in the incubator in the face of optimal core temperatures (Knobel-Dail et al., 2016). Placing infants skin-to-skin with mother may increase abdominal temperatures gradually over time due to the position of the abdomen against the mother. This was an important reason to assess intestinal perfusion during the KMC intervention versus incubator care.

Neonate

Urine was collected in 6-hour aliquots between 0701-1900 (AM) and 1901-0700 (NOC) and time noted before KMC, during KMC, and after KMC over DOL 3 by placing cotton balls over the opening of the subject's urethra. We have found this method to be highly

successful in collecting urine non-invasively. Bedside nurses caring for the baby were instructed by the PI on the procedure at the start of DOL 3 and a special container was labeled and placed at the bedside with an appropriately labeled container for placing urine-soaked cotton balls. A data collection sheet placed at the bedside was used to record each time the diaper was changed and cotton balls were placed in designated container. Urine-soaked cotton balls were removed every time the diapers were changed and placed in an appropriately labeled container, and stored at 0 degrees C. Validation studies performed in our laboratory showed that purine and allantoin concentrations remained stable at body temperature for up to 24 hours and were not altered at 0 degrees centigrade for up to one week. We also found significant differences in purine and allantoin concentration measured from urine-soaked cotton balls or from fresh, free flowing urine. Urine-soaked cotton balls were placed in a syringe and pressure was used to extract the urine from the cotton. After extraction, urine was aliquoted into separate Eppendorf tubes and centrifuged in Beckman Microfuge 22R centrifuge (Fullerton, CA) for 30 minutes at 18,000-x *g, 4* degrees C. The supernatant was transferred to syringes and filtered through a millex syringe driven filter (Low protein Binding Dyrapore PVD filter, 0.45um, 13mm; Millipore Corp) Filtrate was transferred to new Eppendorf tubes and stored at -80 degrees C until analysis.

Neonatal purine

Purine quantification measurements. Urinary hypoxanthine and creatinine concentrations were determined using an adaptation of the high-performance liquid chromatography (HPLC) method described by Holden et al. (2014). Urine samples were thawed and sonicated before 200 μL was transferred to an Eppendorf tube containing 1×10^{-7} mol of 2-aminopurine (internal standard). The samples were then analyzed on

an HPLC (Waters 996 PDA, Waters 600 controller, and 717plus autosampler; Millipore Corp) by injecting 35 μL onto a Supelcosil LC-18-S 15 cm × 4.6 mm, 5 μm column (SGE; Austin, TX), with the following isocratic conditions: 10 mM potassium dihydrogen phosphate buffer, pH 4.7, flow rate 1.0 mL/min. Creatinine and hypoxanthine and 2-aminopurine will be quantitated by obtaining peak areas at the appropriate retention times (~3.5, 8, and 13.5 minutes, respectively) and wavelengths (230, 248, and 305 nm, respectively). The area ratios of each compound to 2-aminopurine were determined and converted into concentration using standard curves. Samples were analyzed in triplicate and values with a coefficient of variation less than 10% included in the final analysis. The limits of detection were 1.58 μM for hypoxanthine and 3.2 μM for creatinine.

Neonatal allantoin

Measurement of Allantoin. Allantoin was measured in the urine by the adaptation of the method outlined by Esiaba et al. (2016). Twenty-five μL of urine was spiked with 400 μL of 10 μM internal standard (DL-allantoin-5-13C;1-15 N). The spiked samples were simultaneously deproteinized and extracted with 100 μL acetonitrile, vortexed and centrifuged at 20,000 g, 4 °C, for 5 min. The supernatant was dried using the speed vacuum drier and derivatized with 50 μL of MTBSTFA (i.e., N-methyl-N-tert-butyl-dimethyl-silyltrifluoroacetamide) in pyridine (1:1 v/v). The derivatization process was facilitated by incubation at 50 degrees C for 2 h. Analysis was performed on Agilent 6890 N Network GC System connected to an Agilent 5973 Inert Mass Selective Detector (both Agilent Technologies, Inc, Santa Clara, CA). Separation was performed using an Agilent 122-5532G

capillary column (25.7 m length, 0.25 mm internal diameter). Allantoin was quantified using selected ion monitoring mode with the 398.00 m/z ion being monitored for Allantoin and the 400.00 m/z for DL-allantoin-5-13C;1-15 N. The ion abundance ratios (398.00/400.00) were converted to micro molar concentrations by use of a standard curve.

Maternal variables

Maternal demographic data and delivery records were collected. Maternal demographic variables included: name, medical record number, maternal age, date of birth, parity, race, body mass index, weight, mode of delivery, complications of pregnancy marriage status, medication history alcohol intake and whether mother smokes or not. Bonding was measured using The Mother-to-Infant Bonding Scale (MIBS). It is a self-report instrument by the mother that has reliability and validity in the general and NICU populations. It was first devised to screen the general population for postnatal difficulties relating to the maternal emotional behavior towards her baby in the first days (48-72h) postpartum. A principal components and reliability analysis demonstrated a Cronbach's alpha of 0.71 (Bienfait et al., 2011). The instrument has 8 words (adjectives) describing feelings mothers have toward their babies in the first days after birth and is a simple questionnaire to administer. In a study in the NICU population, MIBS satisfactorily detected difficulties in mother child bonding; the area under the ROC curve was 0.93 with a sensitivity of 0.9 and a specificity of 0.8 for a threshold score ≥2. The positive predictive value for this threshold was 40.9% (IC95% (20.36-61.45) and the negative predictive value was 98.1% (IC 95% (89.93-99.95). This is a reliable instrument that generates valid data in the NICU population (Bienfait et al., 2011).

Mothers of both the intervention and control groups were given the MIBS self-rating instrument 24 hours postpartum and 72 hours postpartum at 3-6 hours after incubator care or 3-6 hours post KMC intervention and a final time at 3-6 hours post KMC on Day 4 (Table 2).

Table 2.

Timeline for data Collection

	DOL 1 & 2	DOL 3	DOL 4
Control 25 Infants	MIBS at 24 h	Urine samples: 3-6 h pre-incubator care; 3 & 6 h post-incubator care No KMC MIBS a second time at 72 h postpartum &3 hours post-routine NICU care Abdominal NIRS	KMC initiated Urine samples 3-6 h pre-KMC, 3 & 6 h post- KMC MIBS at 3 h post-KMC
Intervention 25 Infants	MIBS at 24 h	KMC – initiated and sustained for 1 hour Urine samples 3-6 hours pre-KMC, 3 and 6 hours post-KMC MIBS a second time at 72 h postpartum & 3 h post-KMC. Abdominal NIRS	KMC continued Urine samples as on Day 3 MIBS at 3 h post-KMC

Table 3.

Mother-to-Infant Bonding Scale (MIBS).

MIBS Example:

	Very much	A lot	A little	Not at all
Loving	0	1	2	3
Resentful	3	2	1	0
Neutral or felt nothing	3	2	1	0
Joyful	0	1	2	3
Dislike	3	2	1	0
Protective	0	1	2	3
Disappointed	3	2	1	0
Aggressive	3	2	1	0

Note. From "A new Mother-to-Infant Bonding Scale: links with early maternal mood," by A. Taylor, R. Atkins, R. Kumar, D. Adams, and V. Glover, 2005, *Archives of Women's Mental Health, 8*, p. 50. Copyright 2005 by Springer. Adapted with permission.

MIBS Questionnaire

This questionnaire is about your feelings for your child. The adjectives listed below describe some of the feelings mothers have for their babies in the first weeks after birth. For each word in the left column, please make a tick in the box that best describes how you feel.

The numbers in the rows corresponds to the weights of scores and reverse scores given to the potential responses. These numbers did not appear on the self-report questionnaires that the mothers fill out. For each mother, the numerical values corresponding to each of the ticked boxes were added to obtain the MIBS score. If scores detected difficulties in mother-child bonding, the researcher would have advised the patient of the score and then a consultation with the attending neonatologist for hospital follow-up care.

Timeline: Subject enrollment occurred from August 2017-January 2018. Samples were analyzed within one week of collection. Preliminary analysis of data was performed monthly to determine trends or significant results.

Data Analysis

Statistical analysis was performed using SPSS Statistics software (version 25.0, IBM Corp.). Descriptive statistics for quantitative variables were presented using the mean with standard deviation if the values were normally distributed; median and range values were used when there were extreme outliers. Categorical variables were presented with number and percentage. The comparison of quantitative variables between the two groups was performed using Independent Samples *t*-tests when assumptions of parametric tests were met, while the Mann-Whitney U test was used when extreme

outliers were present. The researcher also used a Chi-square test to assess the association of the categorical variables between the two groups. When assumptions of Chi-square were not met, Fisher's exact test was used.

In order to analyze specific aim 1 which examined the association of KMC and biochemical markers of ATP degradation and oxidative stress in urine of premature infants 24-36 weeks on DOL 3, by measuring urinary concentrations of hypoxanthine (Hx), xanthine (Xa), uric acid (UA), and allantoin in human premature neonates who receive KMC on day of life 3 compared to not receiving KMC until day of life 4, or receiving standard incubator care on DOL 3, we used mixed models analysis of variance with the use of unstructured covariance matrix, adjusted for multiplicity using the Bonferroni method to assess the changes in the outcome measures to account for missing data in the outcome variables. We also used mixed models ANOVA to examine specific aim 3 which examined the association of KMC and physiological measures of stress to include abdominal temperature, heart rate, respiratory rate, oxygen saturation, perfusion, index, fraction of inspired oxygen and abdominal oxygenation and perfusion using abdominal, near-infrared spectroscopy (NIRS) during KMC intervention or incubator care. MIBS for specific Aim 2 was calculated using relative risk. The number and percentage of subjects who changed their MIBS scores from baseline to time 3 were measured, and the comparison of these changes between the KMC on DOL 3 and DOL 4 as measured by the Mother-Infant-Bonding- Scale (MIBS) in intervention and control groups were calculated. Significance was set at an alpha of 0.05.

Summary

Premature infants have increased morbidity/mortality from early maternal separation and their physiological/metabolic immaturity. The physical separation from the mother negatively influences maternal sensitivity. This stratified, randomized controlled study of KMC among infants 24-36 weeks' gestation examines the potential biologic mechanism for KMC efficacy through measuring infant energy utilization biomarkers in urine (hypoxanthine, xanthine, and uric acid, and allantoin) and maternal bonding. Knowledge linking biochemical evidence with physiologic benefits of KMC will further support spread of its practice.

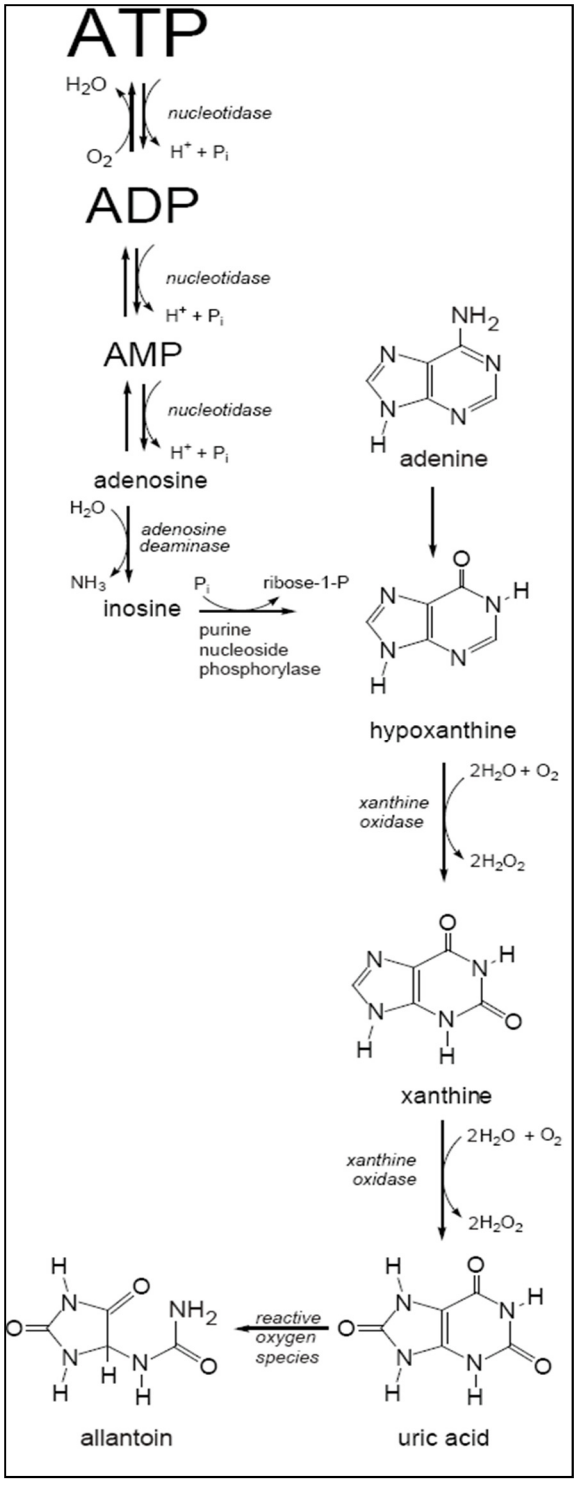


Figure 4. ATP degradation pathway: Calderon et al. (2008)

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Chapter Four

Results

The main purpose of this study was to test the hypothesis that exposure to Kangaroo Mother Care (KMC) would significantly alter biochemical markers of adenosine triphosphate (ATP) utilization and oxidative stress and enhance maternal-infant bonding when compared to the control. The specific aims of this study were to measure allantoin, a metric of oxidative stress, and the urinary purines of hypoxanthine, xanthine, and uric acid, in preterm neonates after exposure to 1 hour of KMC or 1 hour of incubator care to determine whether data would reveal an increase in energy conservation from the KMC intervention. Additional aims for this study included an evaluation of mother–infant bonding on Day 2, Day 3, and Day 4 of life using the Mother–Infant Bonding Scale (MIBS) and evaluation of StO2 (abdominal NIRS) during KMC.

This chapter begins with a consort diagram of the study and a description of the diagram. Next there is a detailed description of the study's participant sample, with descriptive statistics shown in Table 2. The chapter continues with a presentation of the physiological and biological data gathered, including a comparison between the characteristics in the intervention and the control groups. Finally, a description of the data analysis process is presented**.**

Consort Diagram

As shown in Figure 5, 61 subjects met the criteria but 5 subjects refused to give consent without providing a specific reason. Fifty-six parental consents were obtained from subjects who met study criteria between the months of August 2017 and January 2018. From the consented group, 5 subjects withdrew, either because the mother became too ill, and could

not participate or they simply changed their minds about being included in the study. From the remaining consented group, 51 subjects were randomized to the intervention (KMC) group, or standard care group, stratified by weight of < 1,000grams or > 1,001grams. In the intervention group, (n = 3) <1,000 g + (n = 23) >1,001 g for a total (n = 26), and in the standard care group (n = 5) <1,000 g + (n = 20) in the >1,001 g for a total (n = 25). A total of (n =51) were analyzed.

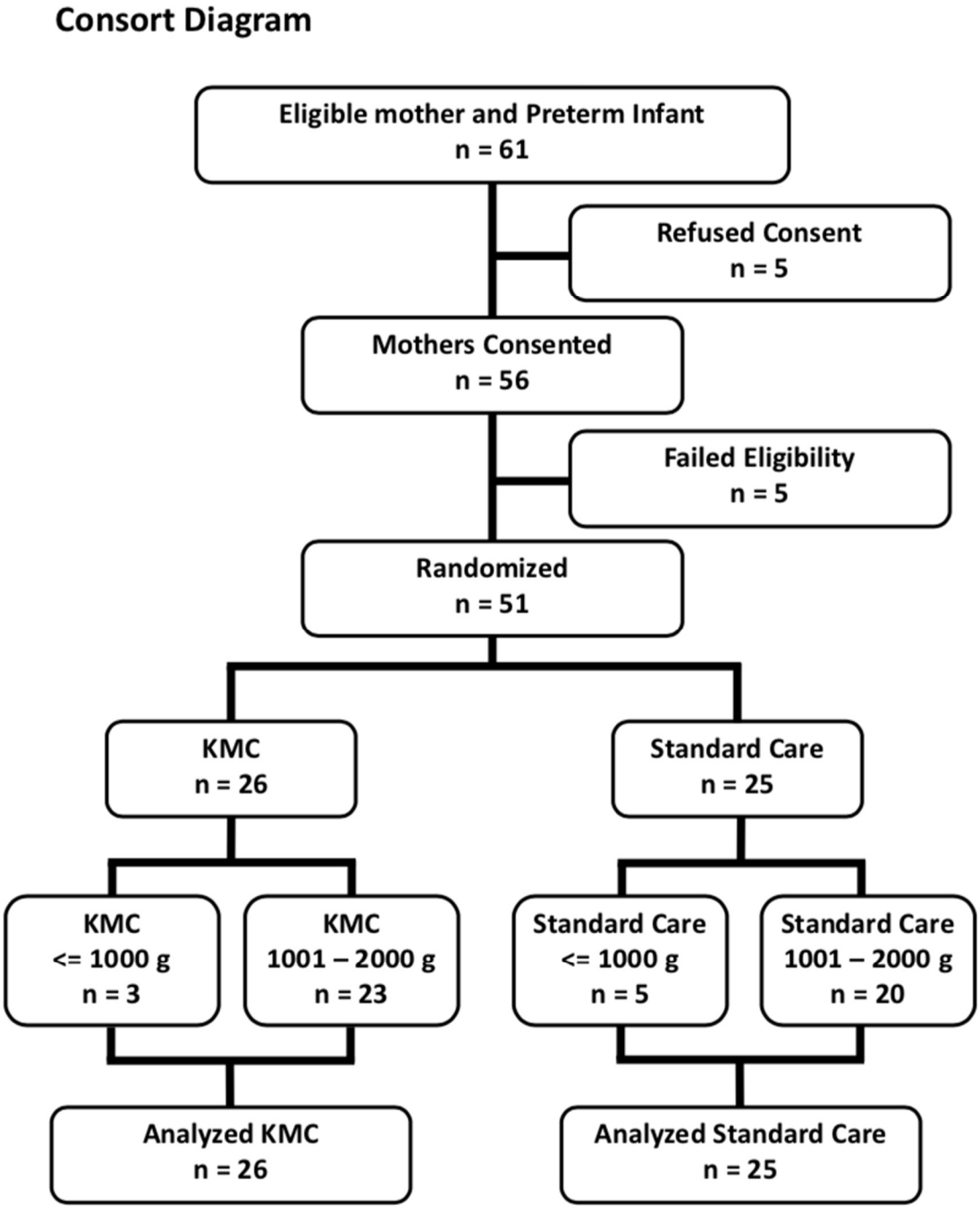

Figure 5. Consort Diagram

Sample Demographics

A total of 51 premature infant dyads 24-36 weeks' gestation participated in this study, 25 in the control group and 26 in the intervention group. Maternal age, gravidity, and parity of both intervention and control groups were similar. There were no statistically significant differences noted. The neonates were also similar in gestation age at birth, corrected gestational age, and gestational age at intervention. Again, there were no statistically significant differences. The birth weight and procedure weight between groups were homogenous as well. The SNAPPE 2 scores that are usually gathered as a measure of illness severity in the first 12 hours were performed at 12–24 hours, and again on Day 3 of life at the commencement of study protocol, which yielded parallel results in both groups. APGAR scores at 1 minute and 5 minutes in both intervention and control groups yielded the similar data.

The control group had 16 males and 9 females, while the intervention group had 10 males and 16 females. There was a statistically significant difference in ethnicity between the two groups. In the intervention group, 15 neonates were White, 6 were Black/African American, and 5 were Hispanic. In the control group, 5 neonates were White, 9 were Black/African American, 8 were Hispanic, and 3 were other races (p = 0.027). The mode of birth was similar between the two groups with cesarean delivery ranking highest for each. The mode of oxygen delivery was almost identical for both intervention and control groups with most infants being maintained on room air or very minimal respiratory support. Randomization was successful in creating two groups with similar characteristics on major important variables. Table 4 shows the descriptive statistics for the study sample.

Table 4

Descriptive Statistics for Study Sample

Subjects' Characteristics		Kangaroo Care		Control		p-value
Maternal age (years)[2]		30.1 ± 4.9		28.1 ± 6.9		0.245
Gravida[2]		3.7 ± 2.4		3.2 ± 2.7		0.454
Parity[2]		2.4 ± 1.8		1.7 ± 1.4		0.125
Gestation at birth[2]		32.0 ± 2.6		31.4 ± 2.1		0.405
Gestation corrected[2]		31.8 ± 2.5		31.3 ± 2.1		0.430
Gestation at sampling[2]		31.8 ± 2.5		31.4 ± 2.1		0.559
Birth weight[2] (g)		1827 ± 492		1642 ± 545		0.210
Procedure weight[2] (g)		1707 ± 484		1552 ± 537		0.286
Snappe 2 scores first 24 hours[3]		0.0 (0-35)		0.0 (0-18)		0.264
Snappe 2 scores day of sampling[3]		0.0 (0-49)		0.0 (0-49)		0.675
1-minute Apgar[2]		6.5 ± 2.2		6.6 ± 2.5		0.647
5-minute Apgar[2]		8.2 ± 1.0		7.8 ± 1.4		0.260
Gender[1]	Male	10	(38.5)	16	(64.0)	0.068
	Female	16	(61.5)	9	(36.0)	
Ethnicity[1]	White	15	(57.7)	5	(20.0)	0.027*
	Black	6	(23.1)	9	(36.0)	
	Hispanic/Mexican	5	(19.2)	8	(32.0)	
	Others	0	(0.00)	3	(12.0)	
Mode of	Vaginal	11	(44.0)	7	(30.4)	0.681
birth[1]	Planned CS	13	(52.0)	15	(65.2)	
	Emergency CS	1	(4.0)	1	(4.3)	
Mode of	Spontaneous RA	17	(65.4)	11	(45.8)	0.341
oxygen	Nasal Cannula/ HFNC	5	(19.2)	4	(16.7)	
delivery[1]	NCPAP	4	(15.4)	6	(25.0)	
	NIPPV	0	(0.0)	1	(4.2)	
	SIMV	0	(0.0)	2	(8.3)	

All values are n (%)[1], Mean ± SD[2], and Median (Min - Max)[3]

* Significant at an alpha of 0.05

CS = cesarean; RA = room air; HFNC = high flow nasal cannula; NCPAP = nasal continuous positive airway pressure; NIPPV = nasal intermittent positive pressure ventilation; SIMV = synchronized intermittent mechanical ventilation

Association of KMC with Biochemical ATP Degradation and Oxidative Stress

KMC and Physiological Measures of Stress

Heart Rate

The normal heart rate range for premature neonates is 120–160 beats per minute (bpm). The mean heart rate scores for the intervention group appeared to trend as more stable than those in the control group on the graph. Heart rate after KMC on Day 3 of life remained lower than the control group; the heart rate then increased higher than the control group as they received their first hour of KMC on Day 4 of life. There was no statistically significant difference, however, because the mean scores were comparable for the two groups and also comparable over time. (Figure 6).

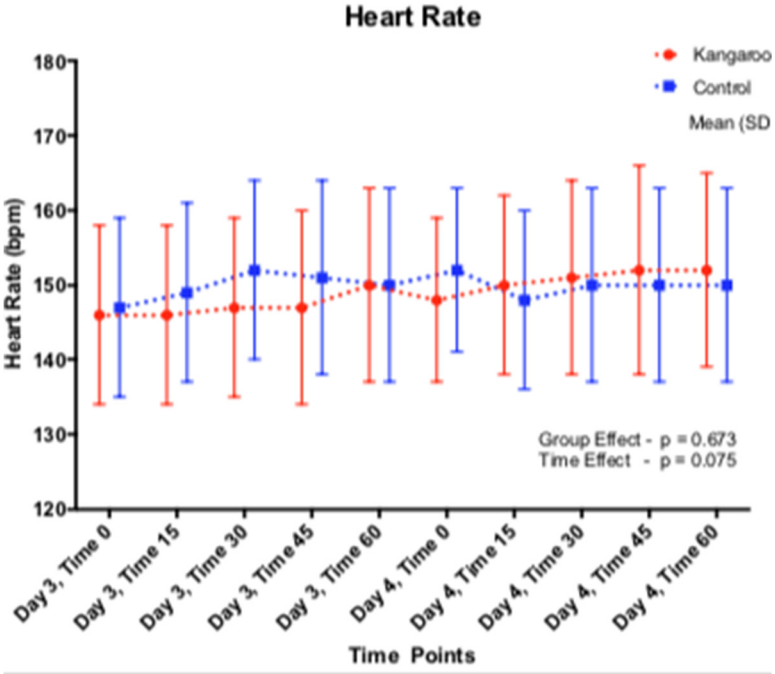

Figure 6. Heart rate mean scores for intervention and control groups.

Respiratory Rate

The respiratory rate mean scores also appeared to trend stable in the intervention group and the control group. While the respiratory rate for both groups appeared to have the same starting point, after incubator care, the rate for the control group appeared to be slightly elevated and started decreasing with KMC on Day 4. There was no statistically significant difference between the two groups and no difference over time (Figure 7).

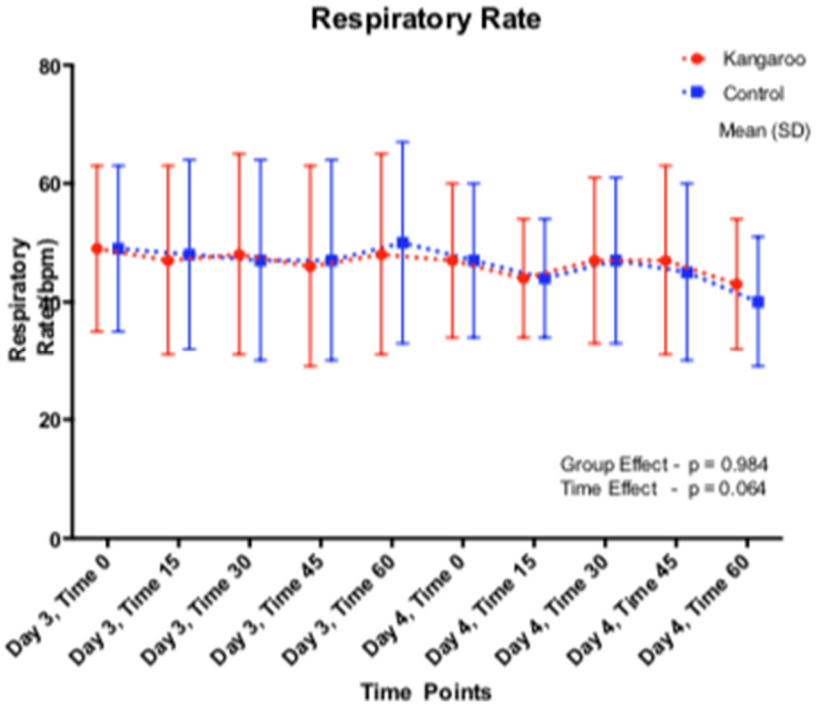

Figure 7. Respiratory rate mean scores for intervention and control groups.

Abdominal Temperature

The normal abdominal temperature range for premature infants is 36.5–37.3°C. The mean abdominal temperature scores reflected a similarity between both intervention and control groups. It appeared that both group scores increased with KMC intervention, while the control group experienced no variability on Day 3 during incubator care. Both groups had higher mean scores after KMC intervention, but there was no statistically significant difference between the two groups but there is a statistically significant correlation over time ($p = 0.004$) (see Figure 8).

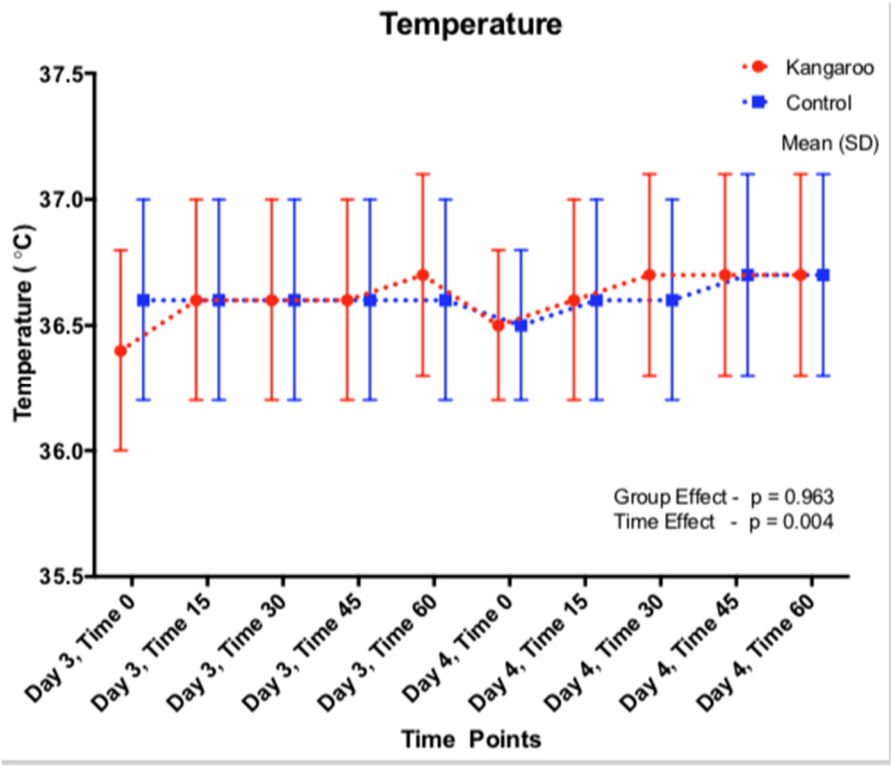

Figure 8. Abdominal temperature mean scores for intervention and control groups.

Oxygen Saturation

Oxygen saturation (SaO2) describes a measure of the amount of oxygen bound to hemoglobin in arterial blood. The normal values for premature infants are 88–96. The mean scores reflected parallelism in both the intervention and control group. While the intervention group appeared to start out with slightly higher mean scores than the control group, after the control group was exposed to KMC on Day 4, the mean scores appeared to equal the scores of the intervention group. There was no statistically significant difference between the two groups for SaO2 or over time (Figure 9).

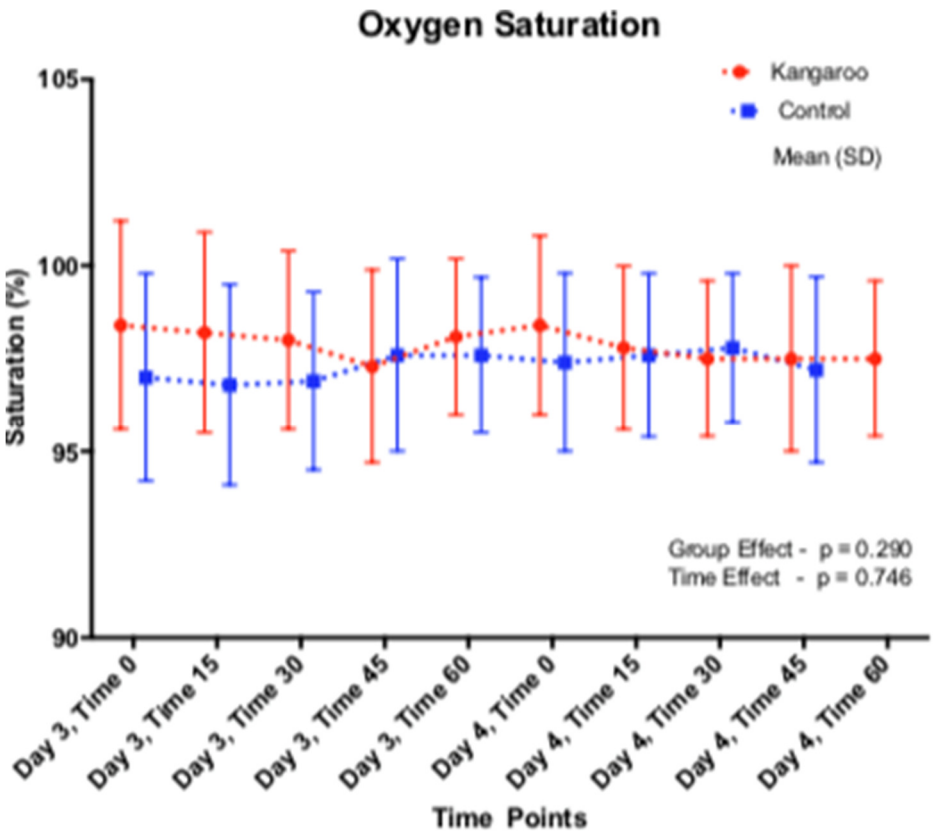

Figure 9. Oxygen saturation mean scores for intervention and control groups.

Perfusion Index

Perfusion index (PI) as measured from a pulse oximeter is used as a clinical indicator of peripheral perfusion. The PI mean scores between the intervention and control groups showed variation for both groups, with the intervention group starting and maintaining slightly lower mean scores throughout the study time points although this was not statistically significant. However, the trend in PI over time for the intervention group was statistically significant ($p = 0.031$) (Figure 10).

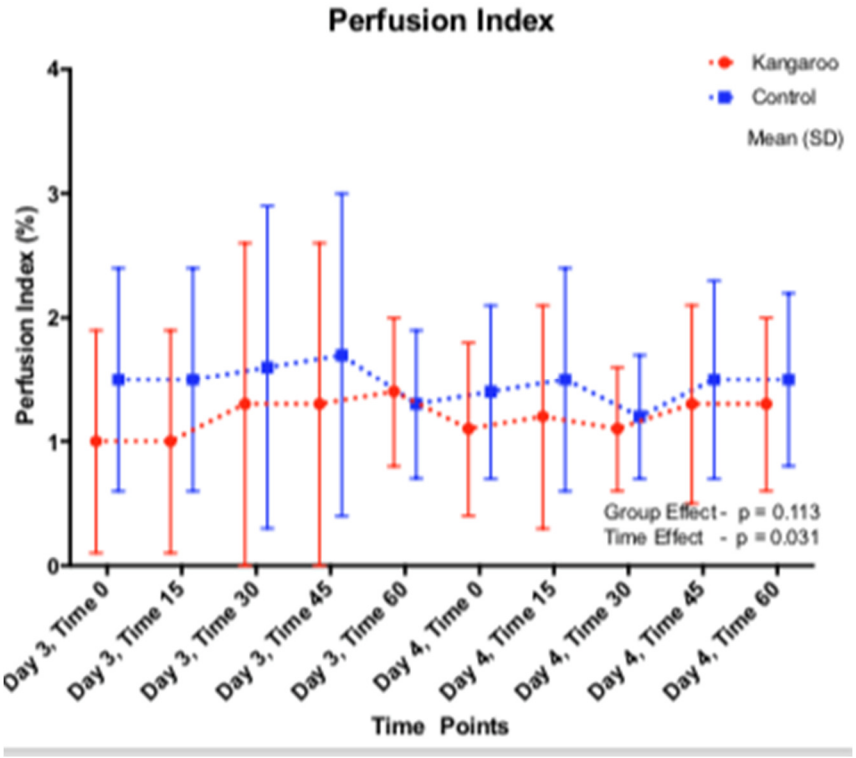

Figure 10. Perfusion index mean scores for intervention and control groups.

The Fraction of Inspired Oxygen

The fraction of inspired oxygen (FIO2) median scores for both intervention and control groups showed a range of 21–40%. Most of the subjects were maintained at room air or 21% FIO2, except for 2 or 3 subjects that needed 40% in both groups. It appeared that after Day 3 of KMC in the intervention group, the 40% FIO2 for those subjects was decreased to 30%. However, there was no statistically significant difference in the FIO2 between the two groups or over time. Looking at the graph the KMC group trending lower on Day 4 of life (Figure 11). In summary, we can see a trend of better stability in the KMC infants and control infants during KMC intervention and we can conclude that there is a relationship between KMC and physiological processes**.** In perfusion index and abdominal temperatures, we found a statistical significant change in both groups over time.

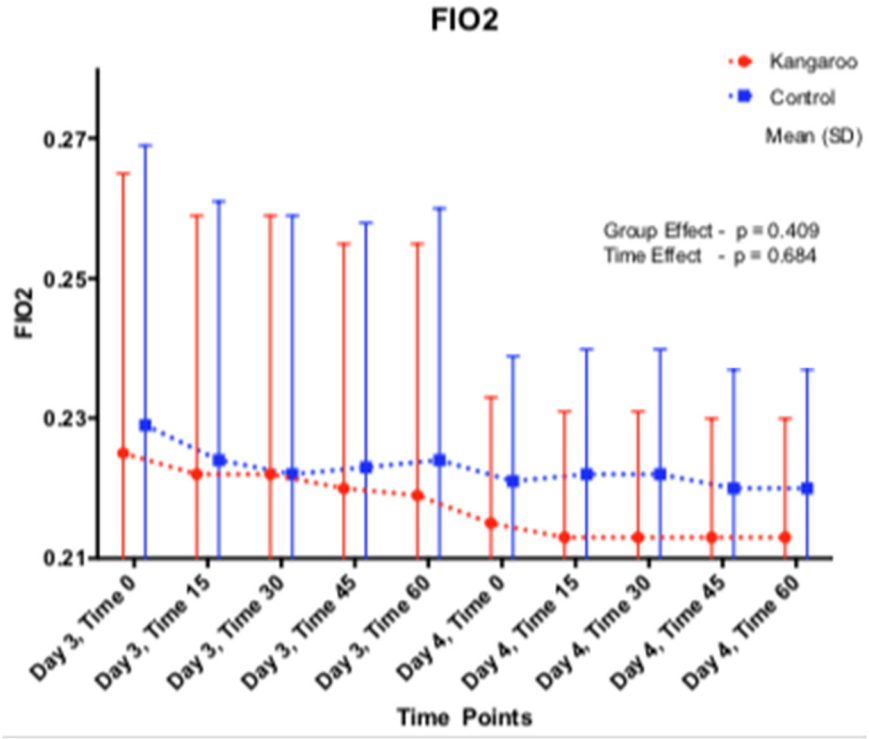

Figure 11. FIO2 for intervention and control groups.

Association of KMC with Biochemical Markers

Urinary Purines

In this section, the biochemical markers for study subjects in both groups are presented, including urinary purines and other measures. These include uric acid, hypoxanthine, xanthine, allantoin.

Uric Acid

Uric acid is a purine metabolite and a marker for increased adenosine triphosphate (ATP) degradation and hypoxia. Both intervention and control groups showed similar mean scores, with decreasing mean scores recorded for both groups after KMC. There was no statistically significant difference between the two groups but there was a statistical significant correlation over time ($p = 0.025$). (Figure 12).

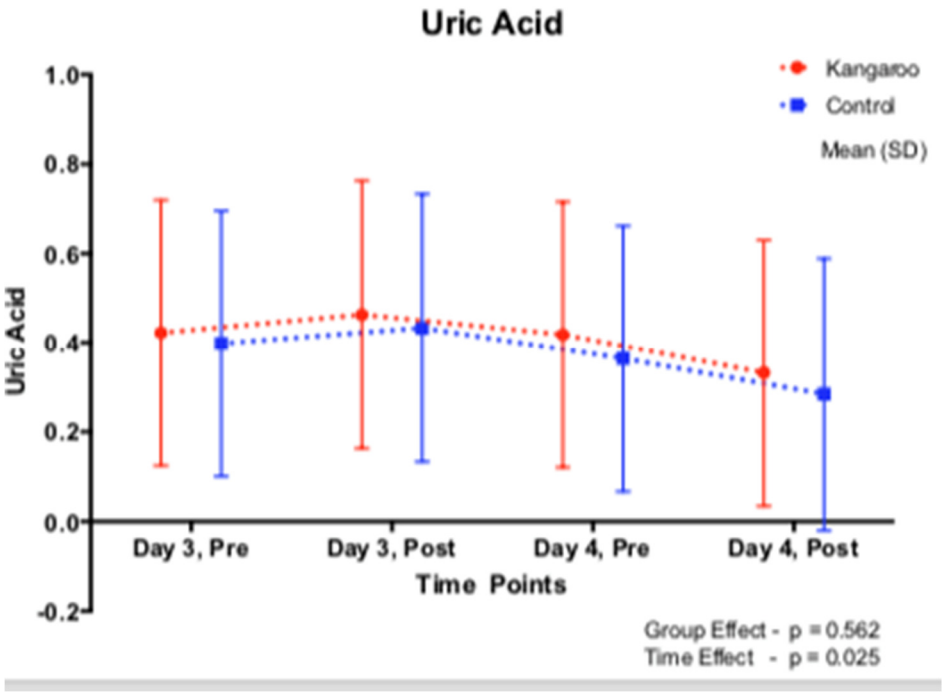

Figure 12. Uric acid levels for intervention and control groups.

Xanthine

Xanthine is a purine metabolite used as a measure of catabolic metabolism and adenosine triphosphate (ATP) degradation in preterm infants. The mean scores of the intervention and control groups were similar, although it appeared that the intervention group maintained higher mean scores. Nevertheless, there was no statistically significant difference between the two groups but there was statistical significance over time (p = 0.042) (Figure 13).

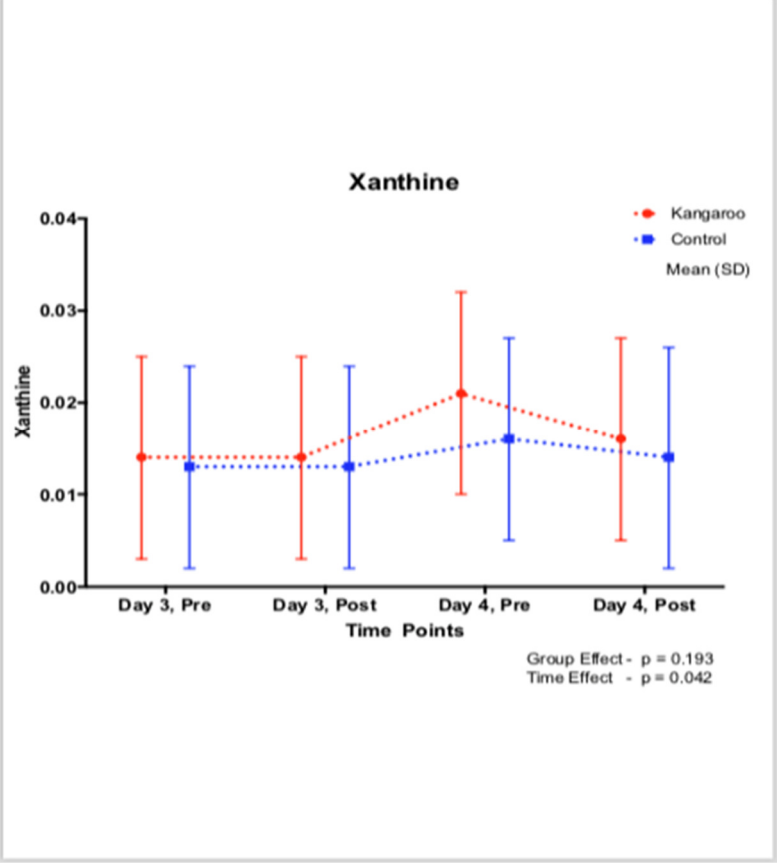

Figure 13. Xanthine values for intervention and control groups.

Hypoxanthine

Hypoxanthine is a purine metabolite signaling catabolic metabolism and hypoxia in preterm infants. While the intervention group appeared to register somewhat lower median scores at the end of Day 4, the median scores recorded for both the intervention and control groups showed no statistically significant difference between the two groups and over time (Figure 14).

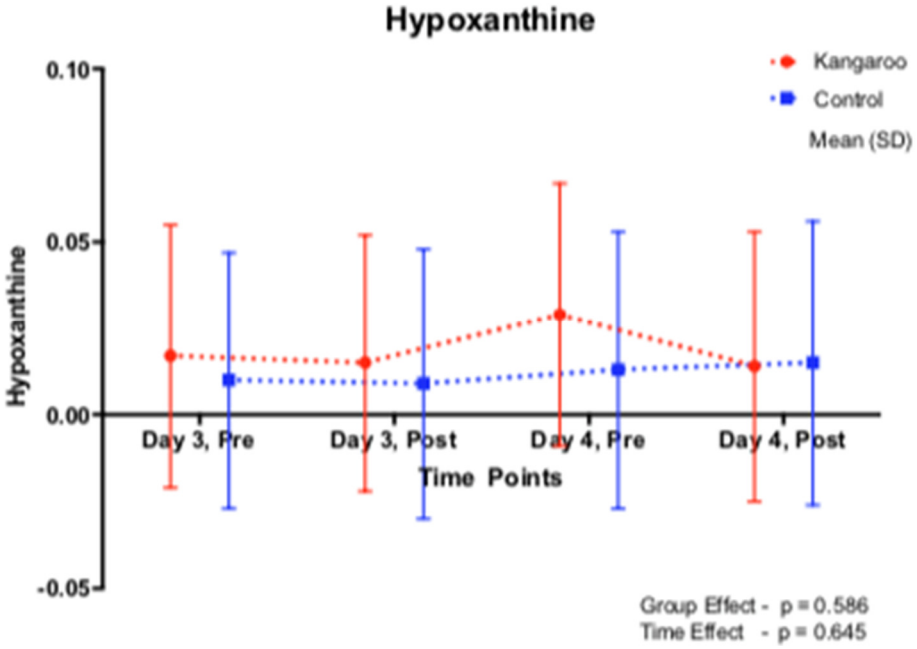

Figure 14. Hypoxanthine levels for intervention and control groups.

Allantoin

Allantoin is a purine metabolite that is used particularly as a marker of oxidative stress in preterm infants. The allantoin mean scores were statistically significantly lower in the intervention group than in the control group ($p = 0.026$). However, there was no statistically significant difference over time (Figure 15). In this marker of oxidative stress, we see that infants in the KMC group had decreased levels of stress when compared to the control group. This biochemical biomarker of stress signals a reduction in inflammatory processes in the presence of KMC. Based on this finding we can reject the null hypothesis in favor of the alternate hypothesis.

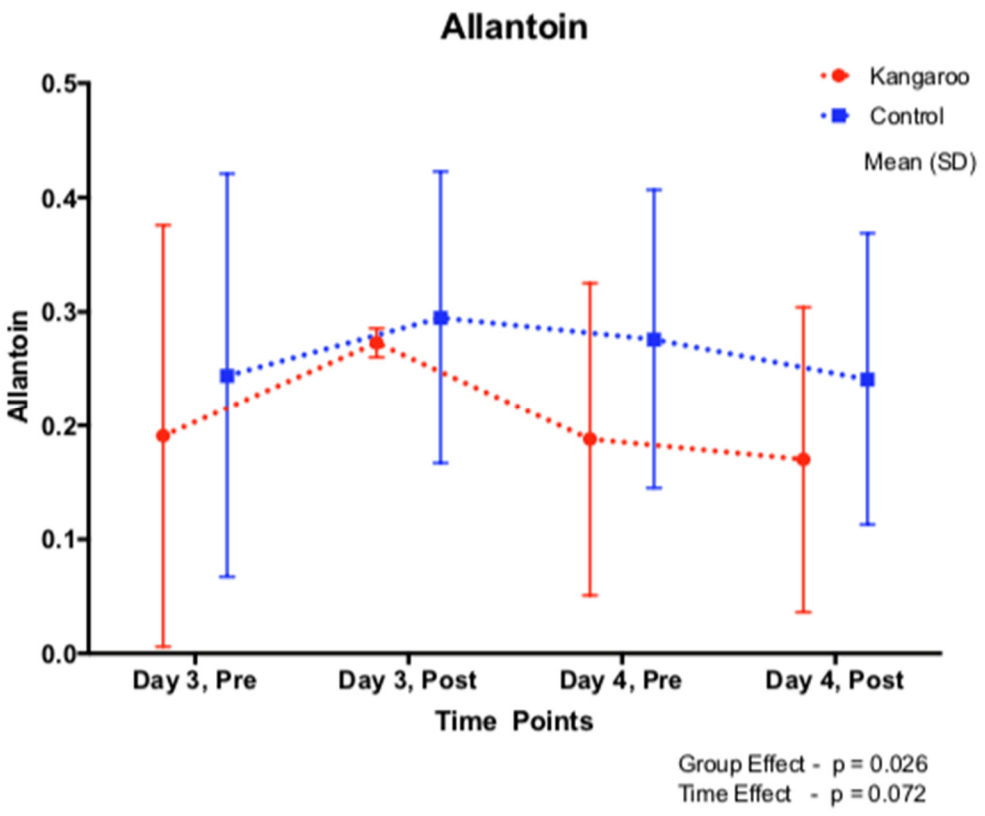

Figure 15. Allantoin values for intervention and control groups.

Association of KMC with Mother to Infant Bonding Score

Bonding between mother and infant was measured using the Mother–Infant Bonding Scale (MIBS). Baseline MIBS scores ranged between 0 and 3 with 86% recorded as 0. By time 3, MIBS scores had the range of 0-6. Among those in kangaroo care group, 93% had no change in MIBS score between baseline and Time 3 and among the control mothers 73% had no change between baseline and T3. However, 19% more mothers in kangaroo care demonstrated an increase in MIBS score or a 26% increase relative risk for an increase of score (RR=1.26; 95% CI 0.97, 1.63).

Association of KMC and Near Infrared Spectroscopy

The normal values for near infrared spectroscopy (NIRS) for preterm infants values are 45–85. Abdominal NIRS mean scores showed a slight increase in the intervention group over the control group on Day 4. However, both group scores were homogenous and there was no statistically significant difference between the two groups (Figure 16). Therefore, we cannot reject the null hypothesis of no difference in NIRS due to KMC. Our specific aim was to find out if gut perfusion and oxygenation was better in the KMC group, but these values describe that KMC group is equal to the control group.

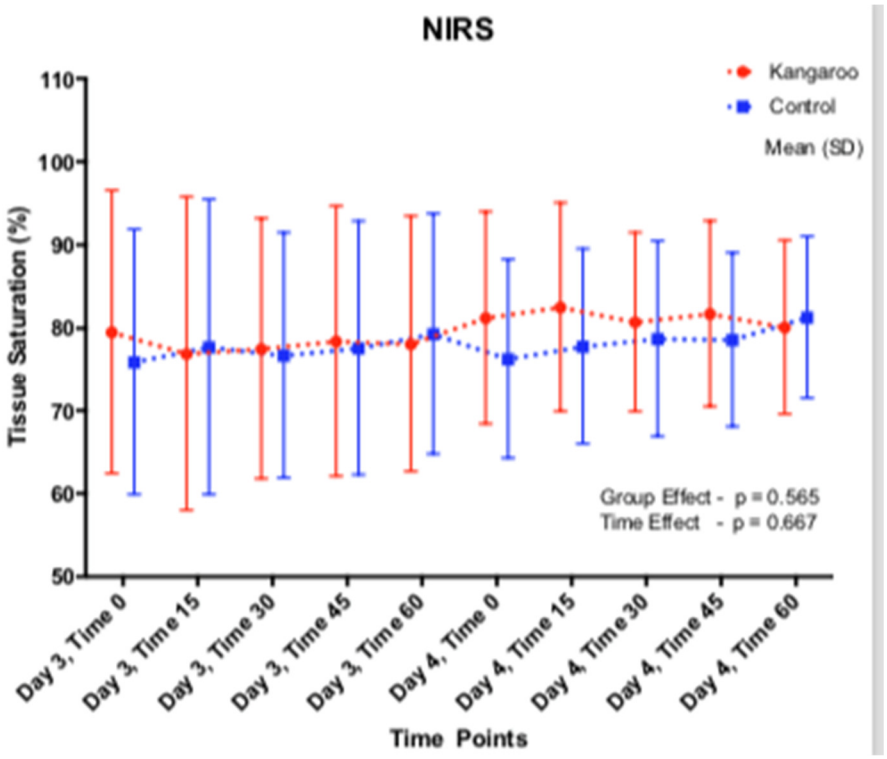

Figure 16. NIRS mean scores for intervention and control groups.

Table 5.

Heart Rate, Respiratory Rate, Abdominal Temperature

Variables	Time	Kangaroo Care	Control	Group Effect P-value	Time Effect P-value
Heart Rate	1 (Ref.)	146 ± 12	147 ± 12	0.673	0.075
	2	146 ± 12	149 ± 12		
	3	147 ± 12	152 ± 12		
	4	147 ± 13	151 ± 13		
	5	150 ± 13	150 ± 13		
	6	148 ± 11	152 ± 11		
	7	150 ± 12	148 ± 12		
	8	151 ± 13	150 ± 13		
	9	152 ± 14	150 ± 13		
	10	152 ± 13	150 ± 13		
Respiratory Rate	1 (Ref.)	49 ± 14	49 ± 14	0.984	0.064
	2	47 ± 16	48 ± 16		
	3	48 ± 17	47 ± 17		
	4	46 ± 17	47 ± 17		
	5	48 ± 17	50 ± 17		
	6	47 ± 13	47 ± 13		
	7	44 ± 10	47 ± 10		
	8	47 ± 14	47 ± 14		
	9	47 ± 16	45 ± 15		
	10	43 ± 1	40 ±1 1		
Temperature	1 (Ref.)	36.4 ± 0.4	36.6 ± 0.4	0.963	0.004*
	2	36.6 ± 0.4	36.6 ± 0.4		
	3	36.6 ± 0.4	36.6 ± 0.4		
	4	36.6 ± 0.4	36.6 ± 0.4		
	5	36.7 ± 0.4	36.6 ± 0.4		
	6	36.5 ± 0.3	36.5 ± 0.3		
	7	36.6 ± 0.4	36.6 ± 0.4		
	8	36.7 ± 0.4	36.6 ± 0.4		
	9	36.7 ± 0.4	36.7 ± 0.4		
	10	36.7 ± 0.4	36.7 ± 0.4		

All values represent mean±standard deviations

* Significant at an alpha of 0.05

Table 6.

Oxygen Saturation, Near-infrared Spectroscopy, Perfusion Index, Fraction of Inspired Oxygen.

Variables	Time	Kangaroo Care	Control	Group Effect P-value	Time Effect P-value
Oxygen Saturation	1 (Ref.)	98.4 ± 2.8	97.0 ± 2.8	0.290	0.746
	2	98.2 ± 2.7	96.8 ± 2.7		
	3	98.0 ± 2.4	96.9 ± 2.4		
	4	97.3 ± 2.6	97.6 ± 2.6		
	5	98.1 ± 2.1	97.6 ± 2.1		
	6	98.4 ± 2.4	97.4 ± 2.4		
	7	97.8 ± 2.2	97.6 ± 2.2		
	8	97.5 ± 2.1	97.8 ± 2.0		
	9	97.4 ± 2.5	97.2 ± 2.5		
	10	97.5 ± 2.1	97.4 ± 2.1		
Near-infrared Spectroscopy	1 (Ref.)	79.5 ± 17.1	75.9 ± 16.0	0.565	0.667
	2	76.9 ± 18.9	77.7 ±1 7.8		
	3	77.5 ± 15.7	76.7 ± 14.8		
	4	78.4 ± 16.3	77.6 ± 15.3		
	5	78.1 ± 15.4	79.3 ± 14.5		
	6	81.2 ± 12.8	76.3 ± 12.0		
	7	82.5 ± 12.6	77.8 ± 11.8		
	8	80.7 ± 10.8	78.7 ± 10.1		
	9	81.7 ± 11.2	78.6 ± 10.5		
	10	80.1 ± 10.5	81.3 ± 9.8		
Perfusion Index	1 (Ref.)	1.0 ± 0.9	1.5 ± 0.9	0.113	0.031*
	2	1.0 ± 0.9	1.5 ± 0.9		
	3	1.3 ± 1.3	1.6 ± 1.3		
	4	1.3 ± 1.3	1.7 ± 1.3		
	5	1.4 ± 0.6	1.3 ± 0.6		
	6	1.1 ± 0.7	1.4 ± 0.7		
	7	1.2 ± 0.9	1.5 ± 0.9		
	8	1.1 ± 0.5	1.2 ± 0.5		
	9	1.3 ± 0.8	1.5 ± 0.8		
	10	1.3 ± 0.7	1.5 ± 0.7		
Fraction of Inspired Oxygen	1 (Ref.)	22.5 ± 4.0	22.9 ± 4.0	0.409	0.684
	2	22.2 ± 3.7	22.4 ±3.7		
	3	22.2 ± 3.7	22.3 ± 3.7		
	4	22.0 ± 3.5	22.3 ± 3.5		
	5	21.9 ± 3.6	22.4 ± 3.6		
	6	21.5 ± 1.8	22.1 ± 1.8		
	7	21.3 ± 1.8	22.2 ± 1.8		
	8	21.3 ± 1.8	22.2 ± 1.8		
	9	21.3 ± 1.7	22.0 ± 1.7		
	10	21.3 ± 1.7	22.0 ± 1.7		

All values represent mean±standard deviations

* Significant at an alpha of 0.05

Table 7.

Uric Acid, Xanthine, Hypoxanthine, Allantoin.

	Time	Kangaroo Care	Control	Group Effect P-value	Time Effect P-value
Uric Acid	1 (Ref.)	0.422 ± 0.298	0.398 ± 0.298	0.562	0.025*
	2	0.463 ± 0.300	0.433 ± 0.300		
	3	0.418 ± 0.298	0.364 ± 0.298		
	4	0.332 ± 0.298	0.284 ± 0.305		
Xanthine	1 (Ref.)	0.014 ± 0.011	0.013 ± 0.011	0.193	0.042*
	2	0.014 ± 0.011	0.013 ± 0.011		
	3	0.021 ± 0.011	0.016 ± 0.011		
	4	0.016 ± 0.011	0.014 ± 0.012		
Hypoxanthine	1 (Ref.)	0.017 ± 0.038	0.010 ± 0.037	0.586	0.645
	2	0.015 ± 0.037	0.009 ± 0.039		
	3	0.029 ± 0.038	0.013 ± 0.040		
	4	0.014 ± 0.039	0.015 ± 0.041		
Allantoin	1 (Ref.)	0.191 ± 0.185	0.244 ± 0.177	0.026*	0.072
	2	0.273 ± 0.128	0.295 ± 0.128		
	3	0.188 ± 0.137	0.276 ± 0.131		
	4	0.170 ± 0.134	0.241 ± 0.128		

Conclusion

This study examined the association between KMC and both physiological and biochemical markers of stress as well as attempted to examine differences in mother–infant bonding, specifically, near infrared perfusion measurements of the abdomen during KMC. There was no statistical difference between the two groups or over time, in heart rate, respiratory rate, oxygen saturation, near-infrared spectroscopy (NIRS), and fraction of inspired oxygen. However, there was a statistically significant difference over time in abdominal temperature, perfusion index.

It is noteworthy that in examining the two groups, there were trends of cardiorespiratory and physiological stability in preterm infants that were exposed to KMC compared to the control and the biochemical markers of energy depletion appeared to be lower in the intervention group.

In biomarkers of adenosine triphosphate (ATP) degradation in the evaluation of energy conservation in preterm infants 24–36 weeks' gestation, we found a statistically significant difference between the intervention and control groups in the biomarker allantoin, a marker of oxidative stress ($p = 0.026$), but no statistical significance over time, and two biochemical markers namely uric acid, and xanthine, showed statistical significance over time, but no statistically significant difference between the two groups on these variables.

In the Mother-infant-bonding-scale, we found that scores showed that KMC mothers showed a higher risk of bonding problems than those in the control group. Nineteen percent more mothers in KMC group demonstrated an increase in MIBS score or a 26% increase relative risk for an increase of score (RR=1.26; 95% CI 0.97,

1.63). However, the results were not statistically significant as the null value was included in the 95% confidence interval. The next chapter will discuss the study findings and provide recommendations for future research.

CHAPTER FIVE

Study Implications

This study examined the relationship between Kangaroo Mother Care (KMC) and physiological and biochemical markers of energy conservation in neonates, specifically hypoxanthine, xanthine, uric acid, and allantoin, a marker of oxidative stress. We also investigated the potential impact of KMC on maternal–infant bonding. This chapter assesses the implications of these results, factors that may have influenced the results, the strengths and limitations of the study, and recommendations for future research and practice in neonatal care based on our findings. Our results provide increased evidence for the positive benefits of KMC intervention on preterm neonates given that all subjects moved toward more stable physiological outcomes after just one hour of KMC intervention. To our knowledge, this was the first study to link biochemical factors and physiological factors in premature neonates who received KMC intervention for the purpose of improving infant and maternal well-being.

Study Results and Implications

Markers of Energy Expenditure and Oxidative Stress

During this study, urinary markers of adenosine triphosphate (ATP) degradation (hypoxanthine, xanthine, and uric acid) and oxidative stress (allantoin) were measured before KMC intervention/incubator care and after KMC intervention/incubator care. Physiological variables were measured at time zero, every 15-minutes during the intervention, and at the end of the intervention to assess the potential correlation between energy conservation and KMC intervention. Our study results were consistent with findings by Ludington (1990) that suggested skin-to-skin contact as a simple cost-

effective intervention to reduce state-related energy expenditure assessed through heart rate, behavioral state, and activity level as proxy indicators for energy expenditure. We built upon Ludington's study by examining similar physiological variables as well as the added the measurements of biochemical energy markers and estimations of maternal-infant bonding to better understand the association between biological and psychological factors, in infant energy conservation.

Our study measured several physiological variables and biochemical markers of energy expenditure and oxidative stress in neonates. Physiological variables of perfusion index and abdominal temperature showed statistically significant changes over time (p = 0.031, and p = 0.004 respectively), but the difference between the control and treatment groups did not reach statistical significance, (p = 0.13, and p = 0.963 respectively). There was clearly a positive relationship between physiological measures of stress as measured through the perfusion index and abdominal temperature and time in this study. Previous studies have found that abdominal temperatures can remain below normal in neonates kept solely in incubators, even when these infants have optimal core body temperatures. Research has also shown that KMC can help regulate infant body temperature via thermal regulators in the mother's breast that heat or cool the baby depending on the infant's need (Bergman et al. 2004), and can also improve perfusion (Chi Luong et al., 2016). Our findings further supported the positive impact of KMC on neonatal abdominal temperatures because we found an overall trend towards thermoneutral abdominal temperatures with KMC intervention.

Among the biological variables of urinary biomarkers (hypoxanthine, xanthine and uric acid) and oxidative stress (allantoin), we found statistical significance over time

for uric acid ($p = 0.025$) and xanthine ($p = 0.042$) and a statistically significant difference between the control and treatment groups for allantoin ($p = 0.026$). These findings demonstrated that preterm infants who were exposed to KMC intervention in this study had significantly decreased markers of ATP utilization, specifically allantoin, which is an important marker of oxidative stress. Previous studies have shown that although placement in the NICU is often necessary for preterm infant survival, infants are stressed in that environment. They can suffer dissociative stress through separation from their mother, hypercortisolemia, and irregular and active sleep (Bergman & Bergman, 2013; Chi Luong et al., 2016; Ludington, 1990). Our findings further supported the hypothesis that KMC intervention conserved energy and lowered stress in preterm infants.

Gut Circulation

It is widely recognized that babies experiencing KMC do better with food digestion, metabolism, and thrive more in general, gaining weight more quickly than infants in an incubator. However, the biological mechanisms for this are not entirely clear. There are likely two reasons: (a) human contact reduces the newborn's stress which improves their GI function and digestion, and/or (b) the warmth and upward position of the baby during KMC improves perfusion to the gut which enhances food utilization. This study expanded on the findings of previous seminal studies about KMC and infant gut health by using novel methods to capture important physiological data about infant gut perfusion during KMC treatment. Specifically, this was the first study to examine this phenomenon using abdominal near-infrared spectroscopy (NIRS) to measure gut oxygenation and perfusion during one hour of KMC compared to one hour of incubator care. We did not find significant differences in gut perfusion between groups over time,

but the mean scores of all subjects moved towards better gut perfusion over time. Through continuous NIRS monitoring during KMC, it may be possible to demonstrate enhanced abdominal circulation as the reason for KMC's beneficial effects on digestion. Although we did not find significant differences over time in the NIRS mean scores between treatment and control groups in this study, peripheral perfusion was significantly different over time. This demonstrated that peripheral perfusion did improve with KMC intervention and could indicate that a study design with a longer NIRS monitoring time might identify a positive trend in abdominal circulation after KMC treatment. Adding NIRS monitoring to neonatal care methods would enable a clearer understanding of infant tissue perfusion pathology and alert clinicians to changes before any clinical manifestations become apparent. Moreover, NIRS monitoring during the skin-to-skin position of KMC would provide real-time information about neonatal intestinal perfusion and tissue oxygenation. Akotia et al. (2016) found that this may have significant implications for premature infants at risk of feeding intolerance. Generally, NIRS is used over long periods, but due to the ease of use and sensitivity of this method, it could be helpful during short-term bedside monitoring to aid in more timely care changes in the NICU.

Abdominal Temperatures and Thermal Stability

Normothermia is a goal that demands constant nursing and medical surveillance using different strategic and mechanical measures to keep infant body temperature optimal. The Knobel-Dail et al. (2016) study investigated thermal stability in premature infants by measuring their central and peripheral temperatures and found that infants with less than 29 weeks' gestational age had poor auto-regulation. Developmental circulation

changes in preterm infants caused their abdominal temperatures to remain suboptimal during the first two weeks of life in an incubator, despite having optimal core and peripheral foot temperatures (Knobel-Dail et al., 2016). In our study, we found statistically significant differences in abdominal temperatures over time. It seems reasonable to expect that placing an infant skin-to-skin with their mother would increase neonatal abdominal temperature over time due to the frog-like position of the infant's abdomen against the mother or caregiver. We found statistical significance over time for both the perfusion index and abdominal temperature, suggesting that KMC generated warmth directly to an infant's abdomen and increased their peripheral circulation. Additionally, the upright position of the baby during KMC appeared to increase their peripheral circulation. These factors may influence better infant digestion and are important reasons to further assess infant intestinal perfusion and oxygenation during KMC intervention.

It is particularly noteworthy that we found significant changes over time to the perfusion index and abdominal temperature, along with a significant difference in the oxidative stress biochemical marker between treatment and control groups. This indicated that the KMC intervention produced a statistically significant change in oxidative stress, shown through the reduction in urinary purines over time. These findings further support the use of biomarkers to study energy and stress reduction in neonates.

Although there were no significant differences found in heart rate, respiratory rate, oxygen saturation, NIRS, and FIO2, there was a clinically-relevant trend towards stabilization in subjects after KMC intervention compared to incubator care alone. This may mean that implementing KMC intervention over a longer period of time could

significantly decrease adenosine triphosphate (ATP) utilization. Investigating urinary purines in preterm infants is a novel, noninvasive pathway for examining biochemical changes at the cellular level to monitor ATP as an indicator of energy use in premature babies.

Mother–Infant Bonding Scores (MIBS)

Research has shown that the impact of a preterm birth can elicit problems with emotional bonding between family members, defined as family cohesion. Postpartum depression rates in mothers of preterm infants are almost double in the United States (up to 40%), particularly in the early postpartum period, and may adversely affect maternal and infant relationships (Hawes, McGowan, O'Donnell, Tucker, & Vohr, 2016). Preterm infants are already a vulnerable population at increased risk for adverse medical, developmental, and behavioral outcomes. If their mothers are depressed, preterm infants are at an even higher risk of developmental problems due to the combination of their prematurity and mother's mental health. It is not well understood how fulfillment of infant care in the NICU interacts with maternal bonding and competence, so our secondary hypothesis was to examine the impact of KMC on maternal-infant bonding.

The results of responses on the Mother–Infant Bonding Scale (MIBS) were surprising. Scores were recorded at Time 1, (T1), Time 2, (T2), and Time 3 (T3). At the baseline (T1), scores ranged from 0–3, with 86% recorded as zero. By T3, scores ranged from 0–6 and were indicative of barriers to bonding. Among those in the KMC group, 73% had no change in MIBS score between baseline and T3. Among control mothers, however, 93% had no change between baseline and T3. These results are not statistically significant, but they do run counter to our hypothesis that earlier KMC intervention

would result in fewer bonding issues. Demographic factors may have influenced the outcomes, as well as the complication of dealing with multiples. Specifically, the control group had many more African Americans and Hispanics, and infants in these demographics tend to improve more over time during their stay in the NICU. Multiples tend to interfere with the assumption of independence in analysis of variance results. The observation between the two groups should be independent, which basically means the groups are made up of different people. One mother of twins or triplets may have the same response for her two or three babies. We also assumed that each baby is different, but twins and triplets may respond in the same way. The response of multiples may seem like the same response appearing twice in two different groups that can skew the results. Because identical twins develop from a single fertilized egg, they have the same genome, so any differences between twins are due to their environments, not genetics (Lewis, 2014).

In examining the results of demographic factors, there is some research that suggests that African American mothers may experience more barriers to bonding with their infants due to the additional psychological stress they face as a result of social determinants of health (Giurgescu, McFarlin, Lomax, Craddock, & Albrecht, 2011). Many more African American mothers are single and many must deal with stress from medical complications such as hypertension/preeclampsia and/or diabetes. It must also be considered that some subjects in this study may not have been very trusting of research, resulting in a Hawthorne effect where some participants reported what they thought was expected of them rather than their true feelings. Caucasian mothers may have felt more at ease expressing their feelings to a researcher, even if they were negative (Giurgescu et

al., 2011). Finally, depending on how poorly their infants were doing, some mothers may have experienced more stress and less ability to bond with their infants than other mothers, which was not accounted for in this study design.

African American mothers may have more difficulty bonding because of psychological stress from social contexts. These mothers are usually single parents and already have stress and medical complications like hypertension/preeclampsia or diabetes. Studies show that African American mothers may not be trusting of research investigations and possibly showed the Hawthorne effect, which occurred when they said what they thought was expected of them. Caucasian mothers may have felt more at ease in expressing what was evident in their feelings even though a researcher was present and although their babies may not be doing as well (Giurgescu et al., 2011).

Discussion of Findings and Existing Literature

Our findings supported the hypothesis that KMC intervention conserved energy and lowered stress in preterm infants. Allantoin, the first biomarker of stress, signaled a reduction in inflammatory processes during KMC intervention. We also established a relationship between KMC and xanthine and uric acid levels. Finally, we found a relationship between KMC and abdominal temperature and perfusion index. Both treatment and control groups showed improved scores over time in all these biochemical and physiological variables.

This study spanned only two days, but found results that were consistent with two seminal, randomized studies in skin-to-skin neonatal care. The Chi Luong (2016) study confirmed the hypothesis that the environment provided by mother–infant skin-to-skin contact improves neonatal thermoregulation and cardiorespiratory physiology during

extrauterine transition to life compared to incubator care. Bergman et al. (2004) reported that skin-to-skin contact accomplished stability in all experimental subjects, which was reached for only half of the incubator-only subjects. According to Ludington (1990), KMC is a simple, cost-effective intervention that has been shown to reduce state-related energy expenditure, a fact that our findings further supported through lowered stress and ATP degradation levels in infants treated with KMC.

Strengths and Limitations of the Study

This study examined the influence of KMC on biochemical markers of ATP degradation and physiological variables obtained in the bustling, clinical setting of the NICU. To our knowledge, this is the first longitudinal study to link biochemical markers to physiological variables during the application of KMC intervention versus incubator care of neonatal infants. Thus, the findings from this randomized controlled trial must be understood in light of both its strengths and limitations.

This was a prospective, randomized controlled trial with stratified randomization. Our sample size was adequate and powered at 80%. The study period extended for over six months, but implementation of the KMC intervention and data collection occurred for just two to three days for each subject. The inclusion of both biochemical markers and common physiological measures strengthens this study, but the short data collection period may have negatively influenced our ability to determine statistical significance over time for some variables. This may also explain why there was no significant difference found between the treatment and control groups for any of the physiological variables measured, as was expected based on previously published research on this topic. Similarly, studies that use urinary purine measurements typically record values

over five to seven days to increase the chances of seeing effective change over time and between groups (Esiaba et al., 2016). Thus, data collection for one to two weeks instead of just two to three days may have yielded different results in this study and demonstrated a greater percentage of change between the treatment and control groups (Conde-Agudelo, Diaz-Rossello, & Belizan, 2003). As a consequence, the length of data collection was an important limitation of this study design.

Randomization was fairly successful at distributing baseline characteristics equally between treatment groups with the exception of race. There were more African American infants assigned to the control group. This imbalance may have biased results in favor of the control group, because African American infants admitted to the NICU have been shown to have more initial instability and potentially more oxidative stress (Giurgescu, et al., 2011). Moreover, stratified randomization by infant weight only (dividing the treatment and control groups into 1,000 grams and below or 1,001 grams or above) was insufficient to account for potential differences in infant health status related to sex and gestational age. There is evidence that sex has an influence on neonate health outcomes, with male preterm babies having worse outcomes than female preterm babies. The gestational age range of 24–36 weeks may have been too broad to account for the unique needs of the very preterm or very small neonate. In contrast, larger babies may have had different responses, muddying our data and interpretations. With these factors in mind, we believe it is possible that having more African American babies that were slightly older in gestational age may have contributed to better outcomes in the control group in this study. In future research, it may be important to employ stratified

randomization by race, weight/gestational age, and sex to decrease the probability of this imbalance.

A major strength of this study was the ability to monitor cellular metabolism in a noninvasive manner. A single researcher consented subjects, implemented the intervention, and recorded the data at the bedside, which assured study fidelity and consistency for all subjects. We looked at bio-behavioral characteristics and correlated them with a very important nurturing behavior for preterm infants. Furthermore, we followed existing unit policy guidelines for transfer of infant from incubator to the mother's chest for positioning of the infant, and for assessing tolerance, in addition to documentation specific to the research project. However, like all RCTs, the external validity of these findings to a general NICU setting is limited, since nurses may not be able to strictly adhere to these specific unit guidelines for KMC implementation.

We were unable to examine how the NICU interacts with mother–infant bonding, either due to the short study period itself, which was only three days postpartum, or because the simple survey we used was not sensitive enough (Perrelli, Zambaldi, Cantilino, & Sougey, 2014). This research question could not be answered adequately with this data, making it a limitation of the study design.

Implications for Current Neonatal Care Theory

Our findings support the implementation of early KMC intervention in the NICU. The results demonstrated that KMC intervention both conserved energy and assisted infant thermoregulation, as evidenced by the decreased urinary biochemical markers and increased abdominal temperatures and peripheral perfusion over time in preterm

neonates. Thus, KMC is a therapy that should be initiated at birth, or at least within the first 24 hours of birth, in order to maximize its positive effects.

In a Cochrane review of KMC in infants weighing less than 2,500g at birth, Conde-Agudelo et al. (2003) found that KMC was associated with reductions in several clinically important adverse outcomes, including severe illness, nosocomial infections, maternal dissatisfaction with method of care, improved maternal–infant attachment, and failure to exclusively breastfeed after hospital discharge (Anderson et al., 2003). Our findings were similar to those of the seminal Ludington (1990) study, in which she observed that KMC intervention conserved infant energy. Furthermore, the World Health Organization specifically identifies KMC as a necessary intervention in its recommendations to improve preterm birth outcomes (World Health Organization, 2015).

Although our findings failed to support the hypothesis of improved maternal–infant bonding in the KMC group, Feldman (2014) showed that close and sustained contact between mother and infant established and reinforced healthy bonding behaviors that enhanced a secure attachment between mother and infant. That study followed more infants for a longer period (14 consecutive days) than our study was able to, including a follow-up after 10 years, which demonstrated a statistically significant improvement in outcome measures between the KMC treatment and control groups (Feldman et al., 2014). With this in mind, it is reasonable to conclude that limitations of our study design, not limitations of the KMC intervention itself, may explain why we did not find a significant improvement in mother–infant bonding with KMC treatment.

Study Implications for Professional Practice

This study provides important insights for healthcare professionals caring for preterm infants in the NICU. Increased stress to mother or infant is a viable risk factor for poor infant outcomes, so providers must employ effective strategies to implement KMC to reduce stress. This may require attention and change to NICU environmental designs or practices that hinder this important neonatal therapy. For instance, healthcare workers may worry about the transfer of the infant from the incubator to the mother. However, preterm infants need a change in position from being in the incubator at least once per day, even if the transfer from the incubator to the mother is stressful to the infant. Our study indicates that KMC can be safely implemented at the bedside in the NICU for premature infants under 2,000g within a tertiary care setting. The vital signs of infants in this study stabilized quickly after the initial transfer from the incubator to the mother's chest and remained stable throughout the KMC intervention. Considering the potential benefits of this simple treatment, frontline nursing staff should be encouraged to explain KMC practices to parents and support their need to be close to their baby.

Postpartum depression is also a major concern that warrants changes in clinical care procedures. Postpartum units and NICUs are not adequately equipped to address perinatal onset depression early in the postnatal period. In addition, when postpartum depression is identified, healthcare personnel often do not have a comprehensive program to address this problem. There is a great need for novel comprehensive and collaborative mental health screening and follow-up programs that address dysfunctional bonding and maternal depression early in the postpartum period and after discharge.

Recommendations for Future Research

Additional research that assesses energy conservation in preterm infants is needed to explore the meaning of some findings in this study. A better understanding of energy conservation among KMC-treated preterm infants is crucial because infant energy costs are not currently well understood or described. Ludington (1990) suggested that more precise and longitudinal measurements of energy expenditure and conservation are needed to reach more general conclusions. Replicating this study using urinary biomarkers and allowing more time for data collection, such as five to seven days of monitoring, may find clear differences between KMC-treated infants and those who do not receive such an intervention. Additionally, a study with a larger sample size and neonates of similar gestational age should be considered for more clarity in the interpretation of results.

Conclusion

We found a statistically significant difference in biochemical markers of oxidative stress between infants treated with KMC intervention and the control group, with KMC-treated infants exhibiting decreased stress. There was an overall decrease in uric acid and xanthine for both groups over time. The physiological parameters were not significantly different between the treatment groups, but both groups demonstrated improved abdominal temperatures and perfusion index overall with time. This was the first study to reveal a decrease in infant stress biomarkers with KMC intervention, and allantoin may be the first biochemical marker to signal a decrease in inflammatory processes in the presence of KMC. Our study results indicated that early KMC intervention in the NICU is critical; neonatal nurses should thus provide guidance,

education, and support to mothers regarding KMC with the ultimate goal of reducing stress and promoting wellbeing in preterm infants.

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Appendix A

University of San Diego Eileen Fry-Bowers <efrybowers@sandiego.edu>

IRB-2017-189 - Initial: Initial - Expedited

irb@sandiego.edu <irb@sandiego.edu> Tue, Jun 27, 2017 at 2:30 PM
To: dorothyeforde@sandiego.edu, efrybowers@sandiego.edu

University of San Diego®

Jun 27, 2017 2:30 PM PDT

Dorothy Forde
Hahn School of Nursing & Health Science

Re: Expedited - Initial - IRB-2017-189, The Association of Kangaroo Mother Care, Energy Conservation, and Bonding in Preterm Neonates

Dear Dorothy Forde:

The Institutional Review Board has rendered the decision below for IRB-2017-189, The Association of Kangaroo Mother Care, Energy Conservation, and Bonding in Preterm Neonates.

Decision: Approved

Selected Category:

Findings: None: previously approved by external IRB.

Research Notes:

Internal Notes:

Note: We send IRB correspondence regarding student research to the faculty advisor, who bears the ultimate responsibility for the conduct of the research. We request that the faculty advisor share this correspondence with the student researcher.

The next deadline for submitting project proposals to the Provost's Office for full review is N/A. You may submit a project proposal for expedited or exempt review at any time.

Sincerely,

Dr. Thomas R. Herrinton
Administrator, Institutional Review Board

Office of the Vice President and Provost
Hughes Administration Center, Room 214
5998 Alcalá Park, San Diego, CA 92110-2492
Phone (619) 260-4553 • Fax (619) 260-2210 • www.sandiego.edu

Appendix B: MIBS 1 (no score)

Mother-Infant Bonding Scale

These questions are about your thoughts and feelings about your new baby.
Please tick one box only indicating how you feel.

	VERY MUCH	A LOT	A LITTLE	NOT AT ALL
Loving				
Resentful				
Neutral or felt nothing				
Joyful				
Dislike				
Protective				
Disappointed				
Aggressive				

Date of birth of baby: Date form filled in:

Consent for use provided by Dr Alyx Taylor on April 05, 2017 via email

Appendix C: MIBS 1 (scores)

Mother-Infant Bonding Scale
(Scores included)

	VERY MUCH	A LOT	A LITTLE	NOT AT ALL
Loving	**0**	**1**	**2**	**3**
Resentful	**3**	**2**	**1**	**0**
Neutral or felt nothing	**3**	**2**	**1**	**0**
Joyful	**0**	**1**	**2**	**3**
Dislike	**3**	**2**	**1**	**0**
Protective	**0**	**1**	**2**	**3**
Disappointed	**3**	**2**	**1**	**0**
Aggressive	**3**	**2**	**1**	**0**

Date of birth of baby: Date form filled in:
.

Consent for use provided by Dr Alyx Taylor on April 05, 2017 via email

Appendix D: SNAPPE II Score Sheet

SNAPPE II Score

Components/variables	DOL 1	DOS
Lowest Mean Blood Pressure (mm Hg)		
≥ 30	0	0
20 - 29	9	9
< 20	19	19
Lowest Temperature (◦ F)		
> 96	0	0
95 - 96	8	8
< 95	15	15
Po2 (mm Hg) / Fio2 (%) ratio		
>2.5	0	0
1 - 2.49	5	5
0.3 - 0.99	16	16
<0.3	28	28
Lowest Serum pH		
>7.2	0	0
7.1 - 7.19	7	7
< 7.1	16	16
Multiple seizures		
No	0	0
Yes	19	19
Urine output (ml/kg/hr)		
≥ 1	0	0
0.1 - 0.99	5	5
< 0.1	18	18
APGAR score		
≥ 7	0	
<7	18	
Birth weight (gm)		
≥ 1000	0	
750 - 999	10	
<750	17	
Small for gestational age		
≥ 3 rd percentile	0	
< 3 rd percentile	12	

Notes: 1. Score was awarded zero for a particular componen/variable when the investigation was not ordered based on clinical assessment.

2. Ref: D K. Richardon, S K Lee et al. SNAP -II and SNAPPE-II: Simplified newborn illness severity and mortality risk score. J Pediatr (2001); 138: 92-100

3. SNAPPE-II score is the total component score.

Consent for use provided by Dr. Shoo K. Lee on April 18, 2017 via email

Appendix F: Consent Form

LOMA LINDA UNIVERSITY
School of Medicine

Subject Information and Informed Consent

Title of Study: The Association of Kangaroo Mother Care, Energy Conservation, and Bonding in Preterm Neonates

PRINCIPAL INVESTIGATOR
Douglas Deming, MD
Professor of Pediatrics, Department of Pediatrics/Neonatology
Loma Linda University School of Medicine
11175 Campus Street
Loma Linda, CA 92354
Phone: 909.558.8748
FAX: 909.558.0298
Email: ddeming@llu.edu

1. Purpose and Procedures

a. You are invited to allow your baby to participate in a research study because he or she was born premature and is a patient in our neonatal intensive care unit (NICU). While in the NICU, babies experience a variety of procedures some of which can be painful and have an energy cost to the baby.

b. This research is being done to understand the benefits of Kangaroo Mother Care (KMC) and how it can decrease energy costs from medically required procedures and relieve pain, and promote healing and growth and enhance the parent-infant bonding experience. This research study is being conducted by Dorothy Forde as part of her doctoral (PhD) education in collaboration with Dr. Deming who is an attending physician in the NICU.

c. Our long term goal is to improve clinical care and outcome for premature babies.

d. About 50 babies will take part in this study at Loma Linda University Children's Hospital.

e. If your baby becomes part of this study, your child will be randomly (like the flip of the coin) assigned to one of 2 groups: (1) control group, (babies randomized to the control group will receive the regular standard care given to babies at Loma Linda University Children's Hospital NICU, and have KMC on Day of Life 4, or (2) intervention group. Babies randomized to the intervention group will begin KMC on day 3.

f. Mothers with babies in both groups will be asked to fill out the Mother-to-infant Bonding 8-item self-assessment questionnaire 3 times. The questionnaire asks you to describe your feelings towards your baby. This will be given to you on your first day after birth, and on the 3rd and 4th days of your baby's life. This questionnaire will take about 5 minutes and will help us understand how we can help mothers bond with their babies while they are in the NICU.

g. In addition, we will measure your baby's vital signs, energy, and oxygen use through urine specimens. Urine specimens will be collected by placing a cotton ball into the baby's diaper each time the diaper is changed. This procedure will not cause any pain to your baby. Urine samples will be collected 3 hours before Kangaroo Mother Care, 3 hours after KMC, and 6 hours after KMC on the 3rd and 4th day of your baby's life. On the 3rd day of life, babies in the control group will also have urine samples collected 3 hours before standard NICU care in the isolette, 3 hours after standard NICU care, and 6 hours after standard NICU care. Urine specimens will be collected by placing a cotton ball into the baby's diaper each time the diaper is changed. Recording your baby's vital signs and behavioral responses and collecting urine should not interfere with your baby's care and **will not** cause any discomfort to your baby.

2. Risks

a. Participating in this study exposes your baby to a minimal risk of a breach of confidentiality**.**

b. **Privacy**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. PI and research personnel will use a key code and a unique identification number on all study documents so that no personal information will be used in any publication.
Organizations that may inspect and/or copy your research records to assure quality and/or gather data include groups such as Loma Linda University Institutional Review Board. Data will be shared only with authorized research personnel of the LLU department of Neonatology, and Department of Basic Sciences Physiology and Biochemistry.

c. **Confidentiality**

Any published document resulting from this study will not disclose your baby's identity. A key code and a unique identification number will be used instead of the name and medical record number. No personal information (name, date of birth) will be used in any publications. Your rights regarding use of medical records in research is described in the attached document*, Authorization for Use of Protected Health Information.*

3. **Benefits**

This study may directly benefit your baby. KMC has been shown to improve physiological stability, gastric function, decreasing stress, and increased quiet sleep. For the mother KMC is reported to have better milk production, decrease maternal stress, improve bonding and attachment, and increase maternal satisfaction. Due to the negative, long-term consequences of postnatal separation for both the preterm infant and mother, it is imperative to identify the biological and biochemical mechanisms of KMC and its influence on infant growth and development (Johnson, 2013).

Despite the evidence of the benefits of KMC in the literature, it is important to gain further insight into the specific biochemical effects of KMC on the physiological mechanisms of bonding between the neonate and mother. These mechanisms include the natural biochemical mediation affecting maternal–infant attachment and how it relates to the empowerment of the mother in her new maternal role. This study will be the first to link biochemical data to the physiological benefits evidenced in the literature.

Accurate measurement that can detect disruption in bonding processes are needed to provide meaningful assessment for clinical evaluation and research. Thus, the ability to measure and critically evaluate nursing interventions designed to promote mother–infant togetherness is vital to the consistent operationalization of the KMC concept (Waltz, Strickland, & Lenz, 2017).

Alternative Treatment

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

4. **Costs**

There will be no costs to you or your insurance company for participating in this study.

5. **Reimbursement**

You will not be reimbursed for participating in this study.

6. **Participants' Rights**

Participation in this study is voluntary and your decision whether or not to allow your baby to participate will not affect his or her present or future medical care. You are free to withdraw your baby from this study at any time. If you want to withdraw from the study please notify your nurse/physician at any time or Dorothy Forde PHDc, RN, during routine office hours at (909) 558-1000 extension 47936.

7. **Impartial Third Party Contact**

If you wish to have an impartial third party not associated with the study regarding any question or complaint you may have about the study, you may contact the Office of Patient Relations, Loma Linda University Medical Center, Loma Linda, Ca 92354, phone (909) 558-4647 for information and assistance**.**

8. Where Can I get more information?

You may call Dorothy Forde PHDc RNC-NIC, CNS during routine office hours at (909) 558-1000 Extension 47936 or during non-office hours please email: dforde@llu.edu

You will get a copy of the California Experimental Subject's Bill of Rights and this consent document. You may also request a copy of the study protocol.

9. Informed Consent Statement

I have read the consents 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 child to participate in this study. Signing this consent does not waive my rights nor does it release the investigators, institution or sponsors from their responsibilities. I may call Dorothy Forde PHDc, RN during routine office hours at (909) 558-1000 extension 47936 or during non-office hours please email: dforde@llu.edu if I have additional questions or concerns.

This protocol has been explained to me and I give consent for my child to participate in the study.

I have been given a copy of this form and the California Experimental Subjects' Bill of Rights.

_____	_____	_____
Signature of parent	Name of Child	Date/ Time

Printed Name of Parent

I have reviewed the contents of the consent form with the person signing above and I have explained potential risks and benefits of the study.

_____	_____	_____
Signature of Investigator	Printed name of Investigator	Date/Time

Appendix G: Data Collection Variables and Instruments

DATA COLLECTION VARIABLES AND INSTRUMENTS FOR KMC STUDY

Heart rate	Phillips Monitor		
Oxygen Saturation	Phillips Monitor		
Blood Pressure	Phillips Monitor		
Perfusion Index	Massimo		
StO2- Abdominal (NIRS)	CASMED FORESIGHT		
Abdominal temperature	Incubator temp probe		
Bonding	MIBS		
Hypoxanthine	HPLC		
Xanthine	HPLC		
Uric Acid	HPLC		
Allantoin	GCMS		
Maternal age	EMR		
Gravida	EMR		
Parity	EMR		
BMI- maternal	EMR		
Ethnicity/race	EMR		
Mode of delivery	EMR		
Medications pre delivery to mother	EMR		
Apgar - infant	EMR		
gender	EMR		
Birth date	EMR		
Birth weight	EMR		
Socioeconomic status	EMR		
Time of Birth	EMR		
FIO2 requirement	EMR		
Mechanical Ventilation	EMR		
Delayed cord clamping	EMR		

Appendix H: Infant and Maternal Demographic Data Sheet

DEMOGRAPHIC SHEET FOR KMC STUDY

Infant Demographics

MRN: _____ NAME: _____
DOB_____
Time of Birth_____ Gestational Age:____ Corrected Gestational Age:_____
KMC Subject #:_____ Randomization#_____ Current weight_____
Birth Weight: _____ Birth Length_____ Birth HC_____
Gender_____ Ethnicity_____ Race_____
Date of Consent_____ Do they qualify_____
Enrollment date_____
Apgar 1 min____ Apgar 5 min_____
Study date: _____ Withdrawn _____
Reason_____

Maternal Demographics

Name_____ MRN_____ Maternal age_____
DOB_____-
Gravidity_____ Parity_____ Race_____ BMI_____
Weight_____
Mode of Delivery_____ Complications of pregnancy_____
Married_Yes/No_____
Single __Yes/No___ Divorced __yes/No_____ Lives with Father of Baby_____
Diabetes_yes/no_____ Hypertension___yes/no_____
Socioeconomic status_____ Education level_____
Medication History_____ Drug History_____ Smoke_____
Alcohol intake_____
Date _____ Time_____ MIBS_#1, DOL 1 -
Date _____Time_____ MIBS_ #2, DOL 3
Date_____ Time_____ MIBS_ #3, DOL 4

DATA COLLECTION SHEET FOR KMC STUDY

Date_____ **Time**_____**Group Assignment**_____

Name:_____ MRN_____ Gender: M or F_____ Procedure weight: _____

KMC Subject #____ Randomization#____ Informed Consent_____ Date of consent_____

Mode of Ventilation_____ Settings_____ FIO2___ Intubated_____

Feedings _____ Last feeding: Time_____ Type_____ Volume_____

Urine Collection start date_____ Urine collection end date:_____

Date of KMC _____ KMC duration time_____

!!!Double check NIRS Time, Masimo Time, and Philips Monitor Time!!!

Date	**Heart rate**	**Resp rate**	**BP**	**O2 saturation**	**NIRS**	**Perfusion Index**	**FIO2 change**	**Ventilator setting change**	**Temperature**
Time									

KMC Specimen Collection worksheet

Patient ID: Name_____ MRN_____
Date_____ Time_____ Date of Enrollment_____
Subject #_____ Randomization#_____
Date of Birth_____ Time of Birth_____ GA_____
Urine Collection Started Date: _____ Time: _____

Urine specimens

#	Date	Time	Volume
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

URINE COLLECTION ENDED Time: _____ Date _____