Prevalence Of And Risk Factors For Intraoperative Non-euglycemia Events In Premature Neonates >2500 Grams

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PREVALENCE OF AND RISK FACTORS FOR INTRAOPERATIVE NON-EUGLYCEMIA EVENTS IN PREMATURE NEONATES <2500 GRAMS

by

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ABSTRACT

This study examined the rates and risks of premature neonates <2500grams developing intraoperative non-euglycemia events (IONEE).A retrospective chart review of 26 premature neonates <2500 grams who underwent surgical procedures between January 1 and December 31, 2009 was conducted. Statistical analysis was done using Chi square and t-tests.

Ten of the 26 subjects (38%) experienced an IONEE. Hyperglycemia was the primary IONEE that was noted in the neonates. (Mean: 143.19; sd: 56.041) Length of surgery was significantly longer in those premature neonates with IONEE than those with euglycemia (71.7 0± 27.03 vs. 45.62 ± 17.98 minutes). All IONEE subjects received general anesthesia (n=10) while none of those with only intravenous anesthesia had an IONEE (X^2 (1) = 4.875, p=.027). Subjects with IONEE had a higher mean preoperative glucose level (127.11 gm/dL ± 31.66) than those who did not experienced IONEE (86.36 gm/dL ± 29.39; t(21) = 3.151, p=.005). A higher proportion of subjects who developed IONEE had the capillary heel (60%) as opposed to an arterial (40%) site for blood collection (X^2 (1) = 6.518, p =.001). Also, subjects free of preoperative pulmonary complications were more prone to develop IONEE (X^2 (1)= 8.60, p = .003). The presence of IONEE was associated with development of metabolic acidosis (X^2 (1)= 5.426, p=.020) and lower postoperative pH values (7.19 ± 0.20 vs. 7.35 ± 0.11).

Anesthesia providers need to establish intraoperative guidelines for the monitoring and treatment of IONEE to protect these premature neonates from having complications such as developmental delay.

I dedicate this thesis to my husband, Steve, who has supported me day after day during this journey. I also dedicate this thesis to my boys, Angel, Miguel, and Luis who are the sunlight of my dark days.

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CHAPTER 1: INTRODUCTION

Introduction

With the preterm birth rate in the United States reaching 12.6% and the premature neonates with low birth weight (<2500 grams) rate rising to 8.7%, there is an increased need for health care providers to monitor and support the complex physiological needs of this vulnerable group (Hamilton, 2009). For purposes of this study, *a premature neonate is defined as those neonates whose gestational age at birth is < 37 weeks.* One critical physiological need is maintaining euglycemia (American Academy of Pediatrics, 2006; Karlsen, 2006; Kattwinkel, 2006; Zaichkin, 2006). Preterm neonates have both limited glycogen stores and an immature insulin response, which makes maintaining euglycemia in this population difficult (Blanco, Baillargeon, Morrison, & Gong, 2006; Garg, Agthe, Donohue, & Lehmann, 2003; Heimann, et al., 2007; Kao, et al., 2006; Sharma, et al., 2009). Premature neonates experiencing recurrent non-euglycemic events (hyper- and hypoglycemia) are at increased risk for a number of adverse health outcomes including intraventricular hemorrhage, sepsis, and even premature death (Blanco, et al., 2006; Garg, et al., 2003; Heimann, et al., 2007; Kao, et al., 2006; Sharma, et al., 2009). The risk for experiencing non-euglycemic events increases when preterm neonates require surgical intervention. The intraoperative environment includes several risk factors for non-euglycemic events, such as the premature neonate's immature hormonal response, surgical stress response, and metabolic effects of anesthetics and analgesics (Agus & Jaksic, 2002; Heimann, et al., 2007; McEwan, 2009). Despite the combination of a high-risk population and a high-risk environment, anesthesia providers do not consistently monitor or manage blood glucose levels in premature neonates during the intraoperative period (Ayers & Graves, 2001). There is a need to

determine both the prevalence of, and risk factors for, intraoperative non-euglycemic events (IONEE) in preterm neonates to direct the development of clinical practice guidelines.

Maintaining Euglycemia is Essential in Premature Neonates because Non-Euglycemic Events are Associated with Adverse Health Outcomes

Compared to adults, neonates have higher per body weight energy requirements, decreased energy stores, and a decreased tolerance for noneuglycemic events (McHoney, Eaton, & Pierro, 2009; Pierro & Eaton, 2008). In fact, euglycemia is considered an essential clinical goal in neonatal resuscitation curricula such as NRP and STABLE (AHA, 2006; International Liaison Committee on Resuscitation (ILCOR), 2006: Karlsen, 2006; Zaichkin, 2006) Premature neonates experiencing recurrent or persistent noneuglycemic events have significantly more adverse health outcomes than those with euglycemia. Hyperglycemia events in premature neonates are associated with an increased risk for intraventricular hemorrhage, osmotic diuresis, dehydration, retinopathy of prematurity, early death, sepsis and further release of insulin to rebound hypoglycemia events (Blanco, et al., 2006; Garg, et al., 2003; Heimann, et al., 2007; Kao, et al., 2006; Sharma, et al., 2009). Hypoglycemic events in premature neonates increase the risk for events seizures, and short and long-term neurodevelopment and physical growth deficits in preterm neonates (Basu, Som, Choudhuri, & Das, 2009; Boluyt, van Kempen, & Offringa, 2006; Mao, Chen, Fu, Li, & Xue, 2007; Memon & MM, 2006; Narayan, Aggarwal, Deorari, & Paul, 2001; Sankar, Agarwal, Aggarwal, Deorari, & Paul, 2008; Tam, et al., 2008)

Euglycemia is More Difficult to Achieve and Maintain in Premature Neonates

Although maintaining euglycemia in the neonate population is difficult, it is particularly challenging in preterm neonates whose weight is < 2500 grams. Preterm neonates have

significantly higher resting energy expenditures (110-160 kcal/kg/day) than full-term neonates (100-120 kcal/kg/day) (Pierro & Eaton, 2008). Hypoglycemic events are commonly reported in preterm neonates, more commonly among newborns and those classified as low birth weight (McHoney, et al., 2009; Van Kempen, 2005). In addition, premature neonates may have a decreased response to insulin and when dextrose infusions are administered, these neonates may experience hyperglycemia events. Preterm neonates are at higher risk of developing noneuglycemic events due to many factors including decreased glycogen stores, immature insulin response, and increased metabolic demands (Mericq, 2006; Motoyama & Davis, 2009; Simmons, 2007). In fact, a direct correlation between birth weight and glycogen stores has been reported (Mitanchez, 2007; Pierro & Eaton, 2008; Van Kempen, 2005).

Euglycemia is More Difficult to Maintain in Preterm Neonates Undergoing Surgery due to Metabolic Responses to Surgical Stress, Anesthetic Agents, and Analgesic Medications

Although not common place, some preterm neonates require surgical interventions such as those with patent ductus arteriousus repair, omphalocele, and gastroschisis. Tissue damage and pain associated with surgical procedures trigger a stress response involving endocrine, inflammatory, and metabolic components with local and systemic consequences. Of particular note is the rapidness of the metabolic elevation seen in the neonate population. For instance, neonates undergoing abdominal surgery had a peak increase in resting energy requirements within 4 hours (Pierro & Eaton, 2008). The increased demand may even be more pronounced if the neonate has severe underlying illness – which frequently necessitates the surgical procedure. Premature neonates of 26-32 weeks of gestational age or older have an integrated nociceptive system resulting in an effective metabolic and hormonal response to catecholamines (McEwan, 2009; Pierro & Eaton, 2008). Surgical stress responses, including noneuglycemic events, have

been associated with premature neonatal mortality and morbidity (Agus & Jaksic, 2002; Heimann, et al., 2007; McEwan, 2009). Severity of the stress response is directly proportional to the magnitude of the operative intervention (Jones, Pierro, Hammond, & Lloyd, 1993). Furthermore, preoperative fasting further increases the premature neonate operative stress response (McHoney, Eaton, & Pierro, 2009). However, not every intraoperative event has an adverse impact on metabolism. Anesthetic agents (both general and local/regional) as well as analgesic medications have reportedly reduced some metabolic responses (McHoney, et al., 2009). The preterm neonate in the intraoperative environment *combines a high risk population with a high risk situation* with regards to development of noneuglycemic events.

Problem

Intraoperative Neonatal Euglycemia is not Routinely Monitored

Premature neonates receiving preoperative total parenteral infusions receive dextrose infusion during the intraoperative period. Surgical stimuli and drugs administered during the intraoperative can further alter blood glucose levels. Clinical guidelines for monitoring and maintaining euglycemia in premature neonates have been established for the preoperative and postoperative periods. Therefore, the establishment of intraoperative glycemic control guideline for the monitoring and maintenance of euglycemia in premature neonates in order to avoid the occurrence of non-euglycemic events is imperative.

Significance/Importance of Problem to Nursing Practice

The *contribution* of the proposed research is expected to be empirical evidence regarding the magnitude and risk factors for INOEE to support the development of clinical guidelines to maintain intraoperative euglycemia in the preterm neonate population. *This contribution will be*

significant because anesthesia providers currently do not consistently monitor or manage blood glucose levels in premature neonates despite the intraoperative period being a combination of high risk patients and conditions. Results of this study will advance knowledge regarding both the prevalence and risk factors for IONEE. Furthermore, they will provide empirical evidence to support future research toward preventing IONEE in other populations as well.

Goals of the Project

Develop Neonatal Intraoperative Clinical Guidelines for Monitoring and Treating Non-Euglycemic Events

The long-term goal is to improve health outcomes for premature neonates experiencing a surgical procedure by developing intraoperative clinical guidelines for monitoring and treating IONEE.

Determine Neonatal Intraoperative Non-Euglycemic Events Prevalence Rate and Risks Factors

The *overall objective* of this project, which is the first step in achieving this long-term goal, is to determine both the prevalence of and risk factors for IONEE in preterm neonates. The *rationale* underlying the proposed research is that actions maintaining intraoperative euglycemia decrease the risk for adverse health outcomes in this vulnerable group. For purposes of this study, *a premature neonate is defined as those neonates whose gestational age at birth is < 37 weeks.*

Project Question

What is the prevalence and risk factors of intraoperative non-euglycemic events in premature neonates less than 2,500 grams?

Specific Aims

Aim 1: Identify the prevalence of intraoperative non-euglycemic events in premature neonates < 2,500 grams.

Aim 2: Determine the association between intraoperative non-euglycemic events and specific operative characteristics.

Aim 3: Determine the association between intraoperative non-euglycemic events and preterm neonatal physiological characteristics.

Aim 4: Determine association between intraoperative non-euglycemic events and specific anesthesia provider resuscitation measures.

Summary

Neonates who require surgery are at a high risk for non-euglycemic events. Data are needed to support development of clinical practice guidelines for the anesthesia providers.

CHAPTER 2: METABOLIC RESPONSE TO SURGERY AND ANESTHESIA DRUGS IN PREMATURE NEONATES

Premature Neonatal Metabolism and Nutritional Support

Achieving glucose homeostasis in premature neonates during the perioperative period may be difficult due to factors including higher metabolic and energy requirements, preexisting illnesses, preoperative treatments, intensity of surgical stimuli, and ability of anesthesia drugs to blunt these stimuli. Neonates have a higher metabolic rate and energy requirement than adults. The neonatal population energy requirements are 120-140 kcal/kg/day of which 40-70 kcal/kg/day are needed for metabolism, 50-70 kcal/kg/day are needed for growth, and 20 kcal/kg/day are needed for energy losses in excreta (Jaksic & Shew, 2004; Pierro & Eaton, 2006). Energy expenditure may vary according to neonate activity level. When neonates cry or move, their energy expenditure may double. On the other hand, during surgery, infants are at rest 80-90% of the time. The maturity level of neonates determines resting energy expenditure (REE) in surgical situations. Full term neonates require 100-120 kcal/kg/day during surgery, while premature surgical neonates require 110-160 kcal/kg/day (Pierro & Eaton, 2008). The REE differences among these types of neonates may explain differences in their growth rates.

Surgical stress from major abdominal surgery affects the postoperative metabolic response of neonates. Neonates respond to surgical stress after major abdominal surgery with an immediate elevation of oxygen consumption and resting energy expenditure that returns to normal rate between 12-24 hours during the postoperative period (Pierro & Eaton, 2006). Additionally, it has been speculated that neonates utilize energy and protein from growth rate for tissue repair. Early growth deficits may cause long-term adverse effects such as poor

neurodevelopmental outcomes (Yu, 2005). Therefore, neonates may require parenteral and other special nutritional supports to overcome growth restrictions caused by the surgical experience.

Parenteral nutrition (PN) is commonly used for neonates who require surgery to support metabolic needs related to surgical procedures, critical illness, and/or sepsis. When enteral feeding for more than 4-5 days is inadequate, parenteral nutrition is indicated. Parenteral nutrition includes carbohydrates, fat, protein, vitamins, trace elements, and water (Pierro & Eaton, 2008). Carbohydrates and fat are necessary sources of calories to avoid protein oxidation for energy. Glucose supply must be initiated at 6mg/kg/min and may be increased daily up to 12 mg/kg/min in order to maintain glucose levels above 45 mg/dL. Additionally, studies have found that the administration of glucose must not exceed 18g/kg/day in surgical neonates to avoid excessive production of CO_2 and plasma triglycerides (Pierro, 2002). The quantity of glucose administered determines how much fat or carbohydrates are utilized. In neonates with surgical procedures, only 18/g/kg/day may be oxidized to comply with their energy expenditure. When excessive quantities of glucose are administered in this population, the oxidative capacity is reached resulting in a number of metabolic changes, including cessation of fat oxidation, increased fat synthesis, decreased glucose metabolism, increased carbon dioxide production and increased triglyceride levels (Pierro & Eaton, 2008). Therefore, carbohydrate intake must remain below energy requirements to avoid fat accretion (Hulzebos & Sauer, 2007; Pierro, 2002).

The supplementation of intravenous essential fatty acids is essential in premature neonates due to their inability to acquire fatty acids from dietary sources. Additionally, the limited adipose tissue in premature neonates makes them vulnerable for this deficiency. Therefore, to prevent essential fatty acid deficiency in premature neonates, 0.25 to 0.5 g/kg/day of essential fatty acids is recommended for intravenous administration. Simmer and Rao (2009)

reviewed five randomized clinical trials and concluded that there was not a significant difference between administering 'early' versus 'no early' lipids to premature neonates who developed complications such as bronchopulmonary dysplasia and retinopathy of prematurity. The time difference between 'early' and 'no early' is only five days. Theoretically, the early administration of lipid emulsions could decrease the prevalence of complications associated with free radical formation, such as bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) (Simmer & Rao, 2009). This hypothesis was not accepted in the clinical trials reviewed, perhaps because of the preexisting morbidities that contribute to the formation of BPD and ROP in premature neonates.

The supply of intravenous protein to premature neonates should provide enough amino acids to support tissue growth. The more immature or small the neonate, the higher the need for protein and energy to support the rapid growth rate (Valentine & Puthoff, 2007). Term neonates require approximately 110 to 120 kcal/kg/day of energy for an adequate growth rate. On the other hand, low-birth-weight (<1500g) neonates may need up to 150 kcal/kg/day of energy to achieve an adequate growth rate (Chwals, 2003). Neonatal protein requirements are between 2.5 to 3.0 g/kg/day but premature infants may require up to 4g/kg/day to maintain stores and support growth (Parish & Bhatia, 2008; Pierro & Eaton, 2008; Valentine & Puthoff, 2007).

Since surgical premature neonates experience elevation of oxygen consumption and resting energy requirements (REE), the risk of non-euglycemic events may increase. Therefore, it is essential that these surgical neonates receive an adequate nutritional support such as no more than 18 g/kg/day of glucose, essential fatty acids and up to 4g/kg/day of protein to support their tissue repair process and growth rate.

Other factors such as preexisting pathophysiological conditions and treatment modalities may contribute to the nutritional challenges found in neonates undergoing surgical procedures. For example, preexisting critical illness, sepsis, prematurity, respiratory distress, mechanical ventilation, chronic lung disease, and thermal environment have been identified as factors that may increase energy expenditures in surgical neonates (Hulzebos & Sauer, 2007). Possible therapeutic measures to restore the damages of metabolic response to sepsis in neonates are under study. Eaton (2003) discussed how the administration of glutamine in septic neonates could restore their mitochondrial structure and metabolism. When neonates acquire a bacterial infection, pro-inflammatory cytokines (the antimicrobial activity of macrophages and neutrophils), H_2O_2, Nitric Oxide, superoxide, and peroxynitrite are produced (Eaton, 2003). These reactive products are responsible for the impairment of mitochondrial oxidative function causing hypothermia and hypometabolism in neonates.

Metabolic Response to Surgery

Surgical Procedures in the Neonatal Population May Alter Physiological Conditions

All neonates with a viable 26-32 weeks of gestational age have nociceptive systems that are integrated with brainstem cardiovascular control centers (Kinouchi, 2004; McEwan, 2009). These cardiovascular control centers are capable of triggering humoral and circulatory responses to pain and stress. Hormonal stress responses in surgical neonates are three-fold to five-fold greater than adult responses in similar surgical procedures (McEwan, 2009). Increases of circulating catecholamines, glucagon, cortisol, beta endorphins, growth hormone, and insulin have been identified as surgical stress responses that might last for several days (24-72 hours) postoperatively. It has been suggested that these surgical stress metabolic responses may be

associated with mortality and morbidity during the postoperative period. The metabolic responses to surgical stress in neonates include increases in oxygen consumption, glycogenolysis, gluconeogenesis, and lipolysis (Agus & Jaksic, 2002; McEwan, 2009). In addition, these metabolic responses cause substantial intraoperative and postoperative catabolism. The metabolic responses to surgical stress are the result of changes in plasma cortisol, catecholamines, and regulatory hormones such as growth hormone and glucagon. Net results from these metabolic responses are perioperative hypoglycemia and hyperglycemia, lactic acidemia, and postoperative negative nitrogen balance (McEwan, 2009). Factors such as fast growth rate; limited endogenous reserves of carbohydrates, proteins and fats; high glucose requirements for a relative large brain; immature hormonal control of intermediary metabolism; and immature enzymes systems in the metabolic organs, contribute to an impaired tolerance to surgical stress (McEwan, 2009; Owens & Musa, 2009).

Heiman, Peschgens, Kwiecien, Stanzel, Hoernchen and Merz (2007) studied how recurrent hyperglycemia episodes during the first week of life in premature infants ≤ 1500 grams affected the morbidity and mortality of these neonates. In this study, neonates less than 27 weeks of gestational age with repeated episodes of hyperglycemia (more than 4 times) greater than 150 mg/dL, had a significant increase in mortality. The authors also found that the incidence of intraventricular hemorrhage and sepsis in the premature neonates was higher; and therefore, these two factors perhaps contributed to their mortality rate. Glucose aberration could have been secondary to these other large insults.

Chwals, Letton, Jamie and Charles (1995) studied how preexisting illness in neonates and infants up to 47 days old predicted their increased hypermetabolic response after a surgical procedure. C-reactive protein concentration greater than 6.5 mg/dL in plasma was present in

infants with preoperative sepsis or major inflammatory processes, indicating an increase in energy expenditure (hypermetabolism). The measured energy expenditure (MEE) was elevated during the postoperative period in those infants with elevated C-reactive plasma protein. The authors concluded that by measuring the postoperative MEE in sick surgical neonates and infants, clinicians could measure the severity of injury in neonates and support their nutritional needs (Chwals, 1995). This study contributed to the understanding of when to expect hypermetabolism in surgical neonates.

Powis, Smith, Rennie, Halliday and Pierro (1998) studied whether major abdominal surgeries affected the energy and protein metabolism in infants and children (2 days to 3 years old). Surgery durations were between 28 to 285 minutes and the mean operative stress scores was 8. The anesthesia was standardized in the study. Whole body protein flux, protein synthesis, amino acid oxidation, and protein degradation were measured for four hours preoperatively and six hours after surgery. The authors found that infants and children did not increase their whole body protein turnover and metabolic rate after major abdominal surgery. They concluded that infants and children diverted protein synthesis from growth to tissue repair. This study points out the importance of nutritional support for surgical neonates. More research studies are needed particularly on premature neonates since this population has a greater growth rate and may have increased nutritional needs to support growth during perioperative periods.

In 2008, Reynolds, Bass and Thureen studied if neonates undergoing abdominal surgery on their first day of life were able to achieve a positive balance of protein with the administration of parenteral amino acids. The neonates were full term and had appropriate weight for their gestational age. The authors concluded that these neonates tolerated nutritional support with amino acids; however, the study classified them as “ill” without defining their illness. Also, part

of the exclusion criteria was the presence of sepsis and congenital or metabolic abnormalities. Administration of analgesia during the anesthesia management may also have contributed to the final positive protein balance found immediately after surgery. It would be relevant to repeat this study on premature neonates since this population has a higher incidence of illness, surgical procedures, and metabolic needs.

Research evidence shows that premature neonates experience metabolic responses to surgical experience. Increases in their oxygen consumption, gluconeogenesis, glycogenolysis and lipolysis may occur as metabolic responses to surgery. However, preexisting diseases such as sepsis may lead to hypometabolism. The degree of metabolic response to surgical stimuli in premature neonates is unknown. This lack of knowledge affects the ability to support the surgical neonates' nutritional needs leaving them vulnerable for a growth and neurodevelopmental deficit. Finding the relationship between intraoperative non-euglycemic events and type and length of surgery and preexisting diseases, could guide us to support their nutritional needs for tissue repair and normal growth.

Metabolic Response to Anesthesia Drugs

During anesthesia management, opioids are used to blunt pain caused by surgical stimuli. Different anesthesia techniques are implemented to decrease the hormonal and metabolic responses to surgical stimuli. Anand, Phil and Hickey (1992) compared two different anesthetics to hormonal and metabolic response: the use of Halothane (volatile agent) and morphine (opioid) versus the use of high dose of sufentanil. The anesthesia technique that included sufentanil was deeper and significantly reduced hormonal and metabolic responses. The surgical procedures in this study included five different cardiac surgeries which could have variations in the intensity of

surgical stimuli (Anand & Hickey, 1992). Additionally, the neonates that participated in this study were full term therefore their capacity for metabolic response to surgical stimuli could have differed from premature neonates.

Bouwmeester, Anand, van Dijik, Hop, Boomsma and Tibboel (2001) studied the hormonal and metabolic responses of children between the ages of 0-3 years old who were undergoing twenty-two different thoracic and abdominal surgical procedures. Morphine was administered intermittently and continuously during the postoperative period. The authors found that the neonates had higher preoperative levels of norepinephrine and lactate, while their postoperative plasma epinephrine levels were significantly lower than in the older children group. Additionally, the neonates needed less amounts of opioids during their postoperative period than the older children. No significant differences were found between the effectiveness of continuous versus intermittent administration of morphine in the study groups. The authors concluded that the immaturity of organs for drug clearance in neonates decreased the need for opioid administration during the postoperative period. Additionally, the elevated epinephrine levels in children during the postoperative period could be explained as being related to the higher levels of anxiety that the subjects experienced during the study. In this study, the neonates were full term which could have assisted the metabolic adaptation response to stress. Additionally, the neonate group underwent more gastrointestinal surgeries, which may have altered the intensity of surgical stress in comparison with the children group.

Gruber, et al. (2001) studied the stress response of infants younger than six months undergoing cardiac surgery. Three different techniques of Fentanyl administration were used: fentanyl bolus, fentanyl infusion, and the combination of fentanyl-midazolam infusion. Metabolic responses were measured during five different times: after sternotomy, 15 minutes

after initiating cardiopulmonary bypass, at the end of surgery, and 24 hours after surgery in the intensive care unit. The authors concluded that none of the fentanyl dosing strategies, with or without midazolam, would prevent a hormonal or metabolic response in infants undergoing cardiac surgery. Subjects in the study underwent four different cardiac surgeries which could have caused variation in surgical procedure duration and intensity of surgical stimuli. Additionally, the number of subjects per surgical procedure group or fentanyl administration technique was unequal therefore the study conclusions may not be reliable due to analysis inconsistencies. Within each group of infants receiving fentanyl bolus, fentanyl infusion, and the combination of fentanyl-midazolam infusion; epinephrine, norepinephrine, cortisol, glucose and lactate levels were significantly larger at the end of surgery.

Kussman, Gruber, Zurakowski, Hansen, Sullivan, and Laussen (2001) studied the relationship of Bispectral Index (BIS) data to stress response and plasma fentanyl levels in nineteen infants less than six months old who underwent cardiac surgery. Four types of cardiac surgery were chose for this study: complete atrioventricular canal, tetralogy of Fallot, ventricular septal defect, and hemitruncus arteriosus. The BIS has been recommended as a monitor of consciousness level in anesthesia, but use of this monitor has not been validated in pediatric patients. These authors looked for a correlation between hemodynamic (changes in heart rate and blood pressure) and neuroendocrine responses (epinephrine, norepinephrine, cortisol, ACTH, glucose, and lactate) with changes in BIS data. Three opioid administration techniques were used: fentanyl bolus, fentanyl infusion, and fentanyl-midazolam infusion. Metabolic and hormonal responses were measured during four intraoperative times: 15 minutes postinduction, 15 minutes poststernotomy, 15 minutes on cardiopulmonary bypass during cooling, and at the completion of surgery. The authors concluded that there was no correlation between the changes

in hormonal or metabolic responses and the changes in the BIS. They did find a correlation between hypothermic events, hypoperfusion, and changes in the BIS. Given that the use of BIS in neonates has not been validated, the efficacy of this device to monitor deepness of anesthesia in preterm infants is even more questionable. Changes in hormonal and metabolic responses in the preterm population may be more reliable in identifying increases in metabolic and hormonal responses caused by changes in the intensity of surgical stimuli.

Other opioid anesthetic techniques have been studied in relationship to pain control and surgical stress. Bell, Dickson, Arana, Robinson, Marshall, and Morton (2004) compared the effects of remifentanil and fentanyl on surgical stress in pediatric patients (4-108 months old) undergoing cardiac surgery. Glucose and cortisol levels were measured periodically from the period before induction into the postoperative intensive care period. The seven cardiac surgeries performed in this study were similar; however, the anesthesia induction drugs used for subjects were different. For example, three of the 17 pediatric patients received ketamine as an inductive drug. Ketamine causes catecholamine release and analgesia; therefore, the use of this drug with opioids may have altered metabolic and hormonal responses to the cardiac procedures. The authors concluded that there was no clinically significant difference between the two opioid techniques in decreasing hormonal and metabolic responses to cardiac surgery stimuli. Additionally, the subjects in the study were four or more months old which make generalization of results to premature infants problematic.

Remifentanyl has been the opioid of choice to blunt pain in pediatric patients due to its unique rapid titratable effect. Weale, Rogers, Cooper, Nolan, and Wolf (2004) studied the metabolic responses to surgical stimuli in infants and children undergoing cardiac surgery after the administration of four different Remifentanil infusion rates (0.25, 1.0. 2.5, or 5.0 ug/kg/min).

Cortisol, neuropeptide Y, and glucose were measured at induction, pre-surgery, 5 minutes after opening the heart, and immediately before going on cardiopulmonary bypass. The authors reached two conclusions: remifentanil infusion rates greater than 1.0 ug/kg/min can suppress increases in blood glucose and tachycardia during the pre-bypass phase, and neonates with complex cardiac conditions (transpositions of the great arteries) may develop severe bradycardia. In this study, the specific ages of subjects were not given therefore it is unknown if preterm neonates participated. Additionally, seven different cardiac surgeries were performed on study subjects and could have affected the degree of surgical stimuli experienced.

Mechanical ventilation may also increase energy demands in the neonatal population during their intraoperative period. Neonatal intensive care unit providers have studied the effects of morphine on plasma adrenaline and norepinephrine concentration levels. Simons, et al. (2005) evaluated the effects of morphine on neonates with mechanical ventilation. Study neonates were between 27.5 to 32.1 weeks of gestational age. The authors concluded that morphine infusion may suppress metabolic stress caused by mechanical ventilation. However, one third of the group receiving morphine infusion also received dopamine infusion, which may also have had some effect on the metabolic responses during mechanical ventilation. Therefore, the effects of morphine infusion on these neonates could have been greater that what the authors actually found. This study contributes to anesthesia provider knowledge since mechanical ventilation is needed for respiratory support during neonatal surgical procedures requiring general anesthesia.

Another anesthesia technique used to blunt metabolic responses in surgical patients is the administration of epidural anesthesia. Schricker, Meterissian, Wykes, Eberhart, Lattermann, and Carli (2004) measured metabolic responses to major abdominal surgeries in adult patients. Postoperative amino acids were measured with a leucine stable isotope tracer technique

(Schricker, et al., 2004). Additionally, the researchers administered a hypocaloric Dextrose10% infusion for 24 hours from the day before surgery until the second day after surgery. The authors concluded that the administration of epidural anesthesia (bupivacaine and fentanyl) with a hypocaloric dextrose infusion blunted amino acid oxidation saving more than 100 grams of lean body mass. More research studies are needed to evaluate regional anesthesia and hypocaloric combined treatment in the neonatal population. Neonates who are premature may benefit from saving amino acids not only for wound healing but also for growth rate needs. Perhaps the epidural anesthesia approach should be substituted with a caudal block (McEwan, 2009).

Another anesthesia technique that preserves total body protein after a major upper gastrointestinal surgical procedure is the administration of an epidural (opioid and local anesthetic) combined with an intravenous anti-inflammatory drug for 48 hours and intravenous lipid-based nutrition (Barratt, Smith, Kee, Mather, & Cousins, 2002). This study examined the administration of patient-controlled opioid analgesia (PCA) along with intravenous lipid-based nutrition. The subjects in this study were adults (49 to 68 years of age). They found that the combination of multimodal analgesia (epidural anesthesia and intravenous anti-inflammatory drugs) and the administration of lipid-based intravenous nutrition significantly reduced pain and preserved total body protein and fat. More research on how to blunt metabolic responses to surgical stimuli with the use of regional anesthesia (caudal block) combined with administration of parenteral nutrition to avoid catabolism is needed on the neonatal population.

Crozier, et al. (1993) conducted a study to measure the immediate postpartum condition of neonates delivered by the anesthetic induction drug used for cesarean section where an anesthesia induction agent was used. They compared the metabolic effects on full term neonates whose mothers received either etomidate or methohexitone for general anesthesia induction for

cesarean section. Plasma cortisol and blood glucose levels were measured before induction, after umbilical clamping, 2 hours postpartum, and 6 hours postpartum. Neonates delivered via emergency caesarean section who suffered intrauterine distress and whose mothers received etomidate for general anesthesia induction had a temporary decrease in plasma cortisol and glucose levels. More studies are needed to evaluate the effects of etomidate on premature neonate metabolic responses to this drug.

Minor surgeries such as tympanoplasty and skin graft are usually managed without opioids and only use Sevoflurane and nitrous oxide to blunt metabolic responses to surgical stimuli. Terajima and Ogawa (2000) studied the effect of glucose infusion administration on usage of energy sources during these two minor surgeries. The adult patients in their study received three different glucose 20% infusion rates, 0.1, 0.2, 0.3 g/kg/h. The authors concluded that low glucose infusion rate (0.1 g/kg/h) was needed to prevent hyperglycemia and lipolysis events in adults undergoing tympanoplasty and skin graft without opioid administration and only use of Sevoflurane for general anesthesia. More research is needed on general anesthesia administration without opioids in neonates undergoing minor surgery. Since adults and neonates differ in metabolic needs, perhaps the requirements for glucose infusion to maintain adequate usage of energy resources during minor surgeries would be higher in neonates.

In summary, anesthesia care providers are responsible for preparing and supporting preterm neonates during their perioperative period. Today, this mission is harder to accomplish since the viability of premature neonates at 23-26 weeks of gestational age has increased. The neonate immaturity, decreased energy storage, and higher metabolic demands for growth make it challenging for care providers to respond to their unique needs during surgical procedures. More research studies are needed to determine the effects of surgical procedures and anesthesia drugs

on premature neonatal metabolic responses. The identification of metabolic responses to specific surgical procedures in premature neonates may facilitate the planning of nutritional support during their perioperative period. Additionally, the identification of anesthesia drugs, neonatal physiological characteristics, and anesthesia provider resuscitation measures effects on neonatal metabolic responses also would facilitate the designing of an adequate clinical guideline that would support euglycemic events during their perioperative period.

Definition of Hypoglycemia for Premature Neonates

Limited evidence and no consensus were found for the definition of hypoglycemia in premature neonates. Some authors have studied the effects of moderate to severe hypoglycemia events on immature brains of premature neonates that experienced brain injury.. Some of the effects of hypoglycemia on immature brains identified are cortical atrophy, white matter T2 prolongation in the occipital area of the brain, periventricular leucomalasia in the occipital area of the brain, and diffuse white matter volume loss in the parietal area of the brain (Montassir, et al., 2009; Tam, et al., 2008). Hypoglycemia in these neonates who experienced brain injury was defined as premature and full term neonates (>37 weeks of gestation) who had whole blood glucose concentration below 35 mg/dl 0-3 hours after birth, 40 mg/dl 3-24 hours after birth, and 45 mg/dl after 24 hours of birth time. Other authors guide themselves to treat hypoglycemia in premature neonates according to the existence of symptoms of seizures and irritability and expect their blood glucose levels to be < 36 mg/dl during the first 24 hours of life (Hernandez, 2006; Milcic, 2008). In addition, Milcic in 2008 explained that the hypoglycemia definition in premature neonates cannot be defined with a single value because of the different causes that might be present. Some of these causes could be a diminished hepatic glucose production or

excessive insulin productions which are possible pathologies of premature neonates or simply the result of these neonates immaturity level (Milcic, 2008). Some neonatal intensive care units have defined hypoglycemia in premature neonates whose blood glucose level is < 40 mg/dl if they are small for gestational age and may be experiencing illness such as necrotizing enterocolitis and sepsis (Adamkin, 2009).

Considering that neonatal surgical procedures in premature neonates are for the most part due to illness and those premature neonates less than 2,500 grams include different levels of maturity, in this retrospective study hypoglycemia is defined as a blood glucose level <40 mg/dL.

Definition of Hyperglycemia

Hyperglycemia in premature neonates has also not been clearly defined. Hyperglycemia in premature neonates has been defined as whole blood glucose level > 150 mg/dl. The range value for hyperglycemia in premature neonates (> 150 mg/dL) compared to full term neonates (> 125 mg/dL) is higher due to the higher nutritional demands that premature neonates have (Hey, 2005; Kairamkonda & Khashu, 2008; Sinclair, Bottino, & Cowett, 2009). However, blood glucose levels >216 mg/dl have been used as operational definition of hyperglycemia in premature neonates as a cut off to assess for the presence of osmotic diuresis. On the other hand, there is evidence that suggests that a blood glucose level > 360 mg/dL is required to cause significant osmotic diuresis in this neonatal population (Kairamkonda & Khashu, 2008). Since premature neonates are unable to inhibit gluconeogenesis when intravenous glucose infusions are administered (Hume, Burchell, Williams, & Koh, 2005), and evidence has suggested that sick premature neonates have showed a delayed or decreased secretion of insulin as a response to

excessive glucose concentrations in blood (Mena, Llanos, & Uauy, 2001), hyperglycemia in this retrospective study is defined as a blood glucose level > 150 mg/dL.

Definition of Euglycemia in Premature Neonates

For the purpose of this research study, euglycemia in surgical premature neonates is defined as a blood glucose level within the range of 40 to 150 mg/dL.

Accuracy of Glycemic Measurements with Point of Care Testing Devices

One of challenges that health care providers who care for neonates encounter when monitoring blood glucose levels is that blood volume in premature neonates must be preserved because of their small body size. Obtaining just 1 mL of blood from premature neonates younger than 28 weeks of gestational age with a weight ≤500 grams can account for almost 2.5% of their total blood volume. When blood glucose levels and arterial gases are tested several times a day these premature neonates risk blood volume depletion. For this reason, point-of-care testing (POTC) devices such as the glucometer are used to decrease the amount of blood needed for blood glucose testing.

Several research studies have addressed factors that must be considered when POCT devices are used. Some of these factors are: human error, differences in blood glucose values among sites of blood collection (arterial versus capillary blood samples), hematocrit levels, presence of maltose in blood sample, accuracy of POCT glucometers, and the relationship between the level of patient acuity and the accuracy of blood sample site. Kavsak, Zielinski, Li, Namara, and Adeli (2004) examined the factors that contributed to analytical bias in POCT glucose values obtained in a Neonatal Intensive Care Unit versus the central laboratory. They concluded that differences in the amount of blood volume applied to glucometer strips affected

the POCT glucose values by increasing values up to 15% above the central laboratory results. Boyd, Leigh, and Stuart (2005) examined differences between capillary and venous blood glucose values taken at the bedside in emergency department patients in comparison with central laboratory glucose values (Dade-Behring Multichannel Analyzer). They concluded that venous samples could be accurately tested in capillary glucometers (Medisense Precision Plus). However, when extreme values were obtained using this POCT, the authors recommended that blood glucose must be re-tested at the central laboratory (Boyd et al., 2005). Karon, et al. (2007) compared blood glucose values using POCT for capillary, arterial and venous whole blood, and central laboratory blood glucose testing. The POCT device was the Accucheck Inform. The authors found no significance difference between the POCT capillary blood glucose values and the central laboratory blood glucose values (Double P Modular Sytem: hexokinase method). However, the arterial and venous whole blood glucose values were significantly higher than the central laboratory blood glucose values.

Abnormal hematocrit levels have been identified as an important factor when obtaining POCT glucose values. Ghys, Goedhuys, Spincemaille, Gorus and Gerlo (2007) tested the accuracy of the Precision PCX and Accucheck Inform POCT devices in diabetic patients between 17 to 95 years of age. The blood glucose values for venous and capillary samples were measured with both POCT devices in individuals who had normal, abnormal high, and abnormal low hematocrit values. In addition, individuals who received maltose solutions for peritoneal dialysis were also tested with these devices. Glucose levels were overestimated in patients receiving maltose solutions when tested with the Accucheck Inform. In addition, when hematocrit levels were elevated, blood glucose measurements were underestimated with both

POCT devices. When hematocrit levels were abnormally low, the Precision PCX showed an overestimated blood glucose value (Ghys et al., 2007).

Critically ill patients may have inadequate peripheral perfusion which could alter the quality of, or access to, capillary blood samples. Salter-Maclean et al. (2008) compared differences in blood glucose values of whole blood capillary and arterial samples measured with three different glucometers (SuperStepFlexx, Accu-check Inform, and FreeStyle) and one blood gas analyzer (Chiron 865). All samples were compared with central laboratory values (Yellow Springs Instrument). The authors found that capillary blood glucose values were higher than arterial values measured at the same time. Therefore, the authors recommended that arterial blood samples should be used in critically ill patients using the FreeStyle or Chiron 865 POCT devices to obtain more accurate blood glucose values. Kanji et al. (2005) also examined the accuracy of three POCT devices for blood glucose measurement using a sample of critically ill patients on insulin infusion. The sites for blood collection for this study were capillary and arterial. Blood glucose levels were measured with the Accucheck Inform (glucometer), Rapid lab 860 (blood gas analyzer), and LX20 analyzer (central laboratory oxidase/catalase method). The authors concluded that all POCT devices were inadequate measurement tools during hypoglycemic events. Arterial blood gas testing demonstrated the most reliable blood glucose level results and was recommended by the authors as the safer method to use during hypoglycemic events

Meynaar, et al. (2009) suggested that blood glucose levels in whole blood are 15% lower than in plasma. The International Federation of Clinical Chemistry and Laboratory Medicine Scientific Division established a conversion factor between plasma and whole blood glucose values of 1.11 (D'Orazio et al., 2006). This factor was established under normal values of

hematocrit since a decreased hematocrit increases whole blood glucose values. In order to ensure that whole blood glucose measurements and plasma glucose measurements are compatible, POCT devices are calibrated to correct for differences in blood glucose values (Karon et al., 2007).

In summary, when whole blood glucose values are measured with POCT devices, several factors such as hematocrit levels, present morbidities, site of blood collection, accuracy of the POCT device, presence of maltose in blood, and human error may alter the blood glucose values obtained. Until more research studies identify how these factors can be controlled when blood glucose levels are measured in premature neonates, extreme low or high blood glucose values must be confirmed with central laboratory testing before treatment is implemented.

The AccuCheck Inform POTC has been used at the study facility to measure capillary and arterial blood glucose levels. The AccuCheck Inform has been calibrated with a reagent strip and a specific chip inserted in the glucometer. A conversion factor of 1.08 has been assigned to this POCT to convert a whole blood glucose value to a plasma blood glucose value (Meex, Poncin, Chapelle, and Cavalier, 2006).

Summary

The association between the effects of surgical stimulus and anesthesia drugs on premature neonates' metabolic response needs to be explored. The length of exposure and type are two variables examined in this study.

CHAPTER 3: RESEARCH DESIGN AND METHODS

Problem

Intraoperative neonatal euglycemia is not routinely monitored. Premature neonates receiving preoperative total parenteral infusions receive dextrose infusion during their intraoperative period. Surgical stimuli and drugs administered during the intraoperative procedures can further alter their blood glucose levels. Clinical guidelines for monitoring and maintaining euglycemia in neonates have been established for the preoperative and postoperative periods. Therefore, the establishment of intraoperative glycemic control guidelines for the monitoring and maintenance of euglycemia in premature neonates in order to avoid the occurrence of non-euglycemic events is imperative.

Research Question

What is the prevalence of, and risk factors for, intraoperative non-euglycemic events in premature neonates less than 2,500 grams?

Aims

Aim 1: Identify the prevalence of intraoperative non-euglycemic events in premature neonates under 2,500 grams.

Aim 2: Determine the association between intraoperative and specific operative characteristics.

Aim 3: Determine the association between intraoperative non-euglycemic events and neonatal physiological characteristics.

Aim 4: Determine the association between intraoperative non-euglycemic events and specific anesthesia provider resuscitation measures.

Research Design

A retrospective chart review of all eligible surgical cases from January 1 to December 31, 2009 was used to achieve all specific aims. *Inclusion criteria* included preterm neonates (< 37 weeks) that had any type of surgical intervention with general or total intravenous anesthesia whose weight was <2500 grams on the day of surgery, and had complete data for all study variables. *Exclusion criteria* included premature neonates that underwent surgical procedures within 24 hours after birth and whose mothers were treated with beta-sympathomimetics, beta-blockers, chlopropamide, benzothiazide diuretics, or tricyclic antidepressants in the third trimester (as documented in the maternal history of the neonatal medical record). Furthermore, preterm neonates with the following metabolic disorders were excluded: type I glycogenesis storage disease with glucose-6-phosphate deficiency, Beckwith-Wiedemann Syndrome, nesidioblastosis, islet cell adenomas, adenomatosis, or adrenal insufficiency.

Sample

This retrospective, descriptive study used a convenience sample of all premature neonates meeting inclusion criteria over a 12 month time period. All eligible cases from January 1 to December 31, 2009 were screened for possible inclusion. In preparation for research, the PI reviewed the surgical scheduling log for January 1 to December 31, 2009 to identify potential study subjects. The electronic and paper charts for each potential subject were evaluated for inclusion and exclusion criteria. If excluded, the information obtained from the surgical scheduling log for that patient was immediately destroyed. The information obtained from the

surgical scheduling log for included subjects were destroyed upon completion of the study (see confidentiality plan below). The records of 200 preterm neonates were reviewed.

Setting

This study was conducted at The Children's Hospital of Southwest Florida. It is designated as Level III neonatal facilities and a regional referral center for critically ill neonates.

Subject Risks

The project was a retrospective chart review. Consequently, there were no direct or indirect benefits to any subjects. Furthermore, there were no risks to subjects aside to a minimal risk for loss of confidentiality. The study was approved by the Institutional Review Board via expedited review by the University of Central Florida and the study facility (Appendices L and M).

Confidentiality

In order to maintain confidentiality data collected for this study were deidentified. Each subject was assigned an identification number that was used to code all subject data retrieved from the medical record. A confidential list of subjects and their study identification numbers was placed in a secured file to which only the researcher has access. No unique identifying information was placed onto computer files. The listing of subjects and their study identification numbers was destroyed on completion of the study.

Data Collection

A formal data collection tool was used to obtain data (see Appendix A). This data collection tool was piloted on the first 5 charts. Also, a random double-check of 5 data points for each chart was conducted to ensure accuracy of the data collection tool. Data collection issues were not found and the tool did not require modification.

Data Collection Procedures

Medical records (electronic and paper) for all surgical premature neonates meeting the above mentioned inclusion criteria were reviewed. All data extracted from the medical records were entered directly onto the Prevalence of and Risk Factors for Intraoperative Non-Euglycemia Events in Premature Neonates <2500 grams l Data Collection Tool (Appendix N).

Data Analysis

All data were entered into SPSS 16 to facilitate data analysis. Demographic data were examined using descriptive statistics. Study variables were examined to achieve their specific aims.

Specific Aim 1: Identify the Prevalence of IONEE in Premature Neonates <2500 Grams

The prevalence of IONEE in premature neonates is currently not known. Knowing the prevalence of IONEE is an essential for two reasons. First, it provides empirical evidence regarding the magnitude of IONEE to support the development of a clinical guideline. It addresses the question, “Is IONEE a common enough problem to warrant a clinical guideline?” Second, it establishes a baseline IONEE measure that can be used to evaluate the effectiveness of future interventions.

The variable measured for this outcome was the initial blood glucose level immediately after surgery. It was measured as a continuous level variable and classified into nominal (normal or abnormal) and ordinal (hypoglycemia, euglycemia, or hyperglycemia) as well. This variable was reported as ACCU-CHECK results. All values were converted by ACCU-CHECK Inform to an approximate plasma value.

Traditional epidemiological analysis was used to compute a prevalence rate for IONEE per 1000 surgical cases.

Specific Aims 2-4

Development of a clinical guideline includes the notion of risk stratification. Specifically, which preterm neonate characteristics or intraoperative conditions are associated with an increased IONEE risk? Knowing these risk factors affords the opportunity to match the combination of individual and circumstantial risks with monitoring efforts to effectively maintain intraoperative euglycemia. Furthermore, these results will help identify potentially modifiable clinical actions for future research activities.

Specific Aim 2: Determine the Association between IONEE and Specific Operative Characteristics

Independent variables included length of surgery (minutes), length of anesthesia (minutes), type of surgery by body system (e.g., cardiac, gastrointestinal, etc) and type of anesthesia (e.g., general, total intravenous anesthesia, etc.). The dependent variable was presence or absence of IONEE.

Chi-square and odds ratio were used to evaluate the association between the presence of IONEE and all categorical/nominal level variables. Student's t-test was used to evaluate the

association between the presence of IONEE and all continuous variables.

Specific Aim 3: Determine the Association between IONEE and Neonatal Physiological Characteristics

Independent variables included the following: Intraoperative and postoperative hypothermia; intraoperative desaturation; pre-, intra- or postoperative acidosis; pre-, intra or postoperative hypobicarbonatemia; pre-, intra- or postoperative hypercarbia; and preoperative blood glucose level. The dependent variable was presence or absence of IONEE.

Chi-square and odds ratio were used to evaluate the association between the presence of IONEE and all categorical/nominal level variables. Student's t-test was used to evaluate the association between the presence of IONEE and all continuous variables.

Specific Aim 4: Determine Association between IONEE and Specific Anesthesia Provider Resuscitation Measures

Independent variables included intraoperative endotracheal tube placement, intraoperative administration of dextrose-containing crystalloids, nondextrose-containing crystalloids (e.g., saline), colloids (e.g., albumin), blood products (PRBC, platelets, FFP), vasopressors (e.g., Dopamine, Epinephrine, etc.) or anticholinergic drugs (e.g., Atropine, Glycopyrrolate). The dependent variable was presence or absence of IONEE.

Chi-square and odds ratio were used to evaluate the association between the presence of IONEE and all categorical/nominal level variables. Student's t-test was used to evaluate the association between the presence of IONEE and all continuous variables.

Table 1. Variables Used in IONEE Study

Variable	Specific Aim	Level of Measurement	Measurement Issues
Dependent Variable			
Proxy measure of intraoperative blood glucose level	1, 2, 3, and 4	Continuous and categorical	May be reported as either ACCU-CHEK or serum value. **Resolution:** Convert all values to ACCU-CHEK.
Independent Variables			
Premature neonate weight	3	Continuous	Weight on day of surgery
Length of surgery	2	Continuous	Arrival in the OR to leaving OR
Type of surgery	2	Categorical	Multiple surgeries will be reflected with multiple categories
Length of anesthesia	2	Continuous	Anesthesia administration begins to end
Type of anesthesia	2	Categorical	Multiple types of anesthesia will be reflected with multiple categories
Site for blood collection	3	Categorical	Multiple types of blood collection site will be reflected with multiple categories
Intraoperative hypothermia	3	Nominal	< 37˚ C = Yes
Postoperative hypothermia	3	Nominal	< 37˚ C = Yes
Intraoperative desaturation	3	Nominal	SaO_2 < 90% = Yes
Underlying medical history for neonates	3	Categorical	Multiple medical history will be reflected with multiple categories
Preoperative acidosis	3	Nominal	pH < 7.30 = Yes
Intraoperative acidosis	3	Nominal	pH < 7.30 = Yes
Postoperative acidosis	3	Nominal	pH < 7.30 = Yes
Intraoperative blood glucose level	3	Continuous	May be reported as either ACCU-CHEK or serum value. **Resolution:** Convert all values to ACCU-CHEK.
Postoperative complications for premature neonates	3	Categorical	Development of postoperative complications during the first 24 h of postoperative period will be reflected with multiple categories
Preoperative hypobicarbonatemia	3	Nominal	< 19 mEq/L = Yes
Intraoperative hypobicarbonatemia	3	Nominal	< 19 mEq/L = Yes
Postoperative hypobicarbonatemia	3	Nominal	< 19 mEq/L = Yes

Variable	Specific Aim	Level of Measurement	Measurement Issues
Preoperative hypercarbia	3	Nominal	> 45 mm Hg = Yes
Intraoperative hypercarbia	3	Nominal	> 45 mm Hg = Yes
Postoperative hypercarbia	3	Nominal	> 45 mm Hg = Yes
Preoperative blood glucose level	3	Continuous and categorical	May be reported as either ACCU-CHEK or serum value. **Resolution:** Convert all values to ACCU-CHEK.
Endotracheal tube placement	4	Nominal	
Intraoperative intravenous fluid administration (Dextrose-containing)	4	Nominal	
Intraoperative intravenous fluid administration (Non-dextrose-containing)	4	Nominal	
Intraoperative colloids administration (albumin)	4	Nominal	
Intraoperative blood product administration (PRBC, platelets, FFP)	4	Nominal	
Intraoperative vasopressor administration	4	Nominal	
Intraoperative anticholinergic administration	4	Nominal	

The AccuCheck Inform POTC was used in this study to measure capillary and arterial blood glucose levels. The AccuCheck Inform has been calibrated with a reagent strip and a specific chip inserted in the glucometer. A conversion factor of 1.08 has been assigned to this POCT to convert a whole blood glucose value to a plasma blood glucose value (Meex, Poncin, Chapelle, and Cavalier, 2006).

Not every variable initially identified for this study was able to be analyzed due to missing data. However, the variables that were analyzed shed light on possible causes for the development of IONEE.

Summary

This chapter summarized the methods for conducting the study. Findings will be described in the next chapter.

CHAPTER 4: RESULTS

Description of Subjects

During the 12-months included in this review, 72 premature neonates <2500 grams underwent surgical procedures. Of that group, 26 met inclusion criteria for this study. Subjects were excluded because they were not premature on the day of surgery (n=9), they weighed more than 2500 grams on the day of surgery (n=35), or they did not have an anesthesia provider (n=2). Additionally, five subjects required more than one surgical procedure. Each procedure was included in this study as a separate event. Table 3 summarizes characteristics for the study sample. Table 4 summarizes the average weight and gestational for the study sample.

Table 2. Characteristics of Premature Neonates <2500 Grams Undergoing Surgical Procedures

Characteristic	**n (%)**
Gender	
Male	15 (57.7%)
Female	11 (42.3%)
Ethnicity	
Caucasian	11 (42.3%)
Black	8 (30.8%)
Other	7 (26.9%)
Weight category[1] day of surgery	
ELBW	3 (11.5%)
VLBW	13 (50.0%)
LBW	10 (38.5%)

[1]ELBW-extremely low birth weight, VLBW-very low birth weight, LBW-low birth weight

Table 3. Average Weight and Gestational Age on Day of Surgery of Premature Neonates

Characteristic	Mean	SD
Weight on day of surgery (grams)	1380.92	618.17
Gestational age on day of surgery (weeks)	30.46	3.75

Prevalence of IONEE

Of the 26 premature neonates who underwent surgical procedures, 10 (38%) experienced an IONEE. All abnormal values were hyperglycemia events (see Table 4). The average of blood glucose in these 10 subjects was 199 mg/dL.

Table 4. Prevalence of IONEE in Premature Neonates <2500 Grams

	Frequency	Percent
Hypoglycemia	0	0
Hyperglycemia	10	38.5
Euglycemia	16	61.5
Total	26	100.0

Specific Aim 1: Association between IONEE and Specific Operative Characteristics

Mean surgical times for IONEE subjects (71.70 $\pm$ 27.03 minutes) was significantly longer than those with euglycemia (45.62 $\pm$ 17.98 minutes; $t_{(24)} = 2.96$, p=0.007). IONEE subjects were in surgery about 50% longer than those with euglycemia (Mean Difference = 26.08 minutes, 95% CI: 7.92, 44.23). There was no difference in anesthesia time (see Table 5). Type of anesthesia was significantly associated with IONEE as well. All IONEE subjects received

general anesthesia (n=10) while none of those with regional anesthesia had an IONEE ($X^2_{(1)}$ = 4.875, p=0.027). No association was noted between surgical procedure and IONEE (see Table 6).

Table 5. Association between Length of Anesthesia, Length of Surgery, and IONEE

Operative Characteristic	**Mean (Minutes)**	**Std. Deviation**	**IONEE**	**t (df)**	**p**	**Mean Difference (95% CI)**
Length of anesthesia (mins)	105.15	53.15	Yes	1.889 (10.192)	.088	32.788 (-5.778, 71.353)
	72.21	17.21	No			
Length of surgery (mins)	71.70	27.03	Yes	2.965 (24)	.007	26.08 (7.92,44.22)
	45.62	17.98	No			

Table 6. Relationship between Surgical Procedures and IONEE

Characteristic	**Chi-Square**	**df**	**p**
Type of surgical procedures	4.875	2	.087
Type of anesthesia	4.875	1	.027

Specific Aim 2: Association between IONEE and Neonatal Physiological Characteristics

There were no differences in presence of IONEE based on gender, ethnicity, or weight class. The development of IONEE was not associated with specific preoperative medical conditions or intraoperative temperature. Furthermore, IONEE was not associated with an

increased risk for postoperative complications. Tables 7 and 8 present a summary of the association between IONEE and neonatal physiological characteristics.

Patients with IONEE had higher mean preoperative glucose levels (127.11 g/dL $\pm$ 31.66) than those who did not experience IONEE (86.36 g/dL $\pm$ 29.39; Mean Difference = 40.75 g/dL, 95% CI: 13.86, 67.65; $t_{(21)} = 3.151$, p=0.005). Two subjects had preoperative hyperglycemia, and only one of those experienced IONEE.

Table 7. Association between Neonatal Physiological Characteristics and IONEE

Variable	Chi-Square	df	P
Preoperative glucose levels	.109	1	.742
Site of blood collection	6.518	1	.011
Preoperative pulmonary complication	8.603	1	.003
Preoperative respiratory acidosis	.266	1	.606
Preoperative medical condition of anemia	.005	1	.946
Preexisting medical condition of sepsis	.005	1	.946
Preoperative Intraventricular Hemorrhage	.396	1	.529
Preoperative cardiac complication	3.718	1	.054
Preoperative necrotized enterocolitis	.006	1	.937
Intraoperative temperature of premature neonates	.000	1	1.000
Postoperative metabolic acidosis	5.426	1	.020
Postoperative complication of sepsis	1.354	1	.245
Postoperative complication of respiratory acidosis	1.140	1	.286
Postoperative pulmonary complications	.006	1	.937
Postoperative bleeding complication	.650	1	.420
Postoperative complication of anemia	.885	1	.347
Postoperative cardiac complications	3.291	1	.070

A higher proportion of premature neonates who developed IONEE had the capillary heel (60%) as opposed to an arterial (40%) site for blood collection (X2(1) = 6.518, p = 0.001) . Sixty percent of the premature neonates that developed intraoperative hyperglycemia had their blood sample collected from their capillary heel, while 40% had blood sample collected from arterial site. In fact, premature neonates who had capillary heel as a blood collection site were more than 10 times as likely to have hyperglycemia (OR=10.50, 95% CI: 1.5, 73.7).

Also, premature neonates free of preoperative pulmonary complications were more prone to develop IONEE ($X^2_{(1)} = 8.60$, p = .003). In fact, none of the neonates with preoperative pulmonary complications developed IONEE.

The presence of IONEE was associated with development of metabolic acidosis ($X^2(1) = 5.426$, p=0.020). Every identified case of metabolic acidosis was in a neonate with IONEE. In fact, patients with IONEE had significantly lower postoperative pH values (7.19 $\pm$ 0.20) than those not experiencing IONEE (7.35 $\pm$ 0.11; Mean Difference = -.16028, 95% CI: -.32001, -.00055; $t_{(23)} = -2.22$, p=0.049).

A number of complications were not found in this sample and were excluded from analysis (see Table 8).Several following neonatal physiological variables were not present or minimal (less than five) in our data, therefore, statistical analysis were not performed in these variables (Table 9).

Table 8. Association of IONEE with Neonatal Physiological Characteristics Measured with Independent Sample T-test

Neonatal Characteristics	t	df	p	Mean Difference (95% CI)
Preoperative glucose	3.151	21	.005	40.75 (13.85, 67.65)
Preoperative pH	-1.945	19	.067	-.050 (-.103, .004)
Preoperative PCO2	-.186	19	.854	-1.286 (-15.729, 13.156)
Preoperative Bicarbonate	-1.289	19	.213	-4.230 (-11.096, 2.636)
Intraoperative Temperature	-1.145	23	.264	-.340 (-.954, .274)
Weight (grams) on the day of surgery	.571	24	.573	144.262 (-377.120, 664.64)
Gestational age on the day of surgery	1.008	24	.324	1.525 (-1.598, 4.648)
Postoperative temperature	-1.520	23	.142	-.790 (-1.866, .285)
Postoperative pH	-2.220	10.57	.049	-.160 (-.320, -.000)
Postoperative PCO2	1.339	10.01	.210	17.616 (-11.697, 46.929)
Postoperative Bicarbonate	-1.136	23	.268	-3.330 (-9.395, 2.734)

Table 9. Neonatal Physiological Variables not Statistically Analyzed

Preoperative metabolic acidosis
Intraoperative blood glucose level
Postoperative necrotized enterocolitis
Postoperative intraventricular hemorrhage

Specific Aim 3: Association between IONEE and Specific Anesthesia Provider Resuscitation Measures

Evaluation of resuscitation medication, intravenous fluids, and endotracheal tube placement found no association between these variables and the presence of IONEE (see Table

10). A number of intraoperative interventions were not required in this sample and were excluded from analysis (see Table 11).

Table 10. Association between IONEE and Specific Anesthesia Provider Resuscitation Measures during Intraoperative Period

Intraoperative Intervention	Chi-Square	df	p
Administration of saline	1.66	1	.197
Administration of colloids	.038	1	.846
Administration of atropine	2.82	1	.093
Administration of dextrose	.038	1	.846
Administration of dopamine	.439	1	.508

Table 11. Intraoperative Anesthesia Provider Interventions not Statistically Analyzed

Intraoperative administration of packed red blood cells
Intraoperative platelets administration
Intraoperative neosynephrine administration
Intraoperative glycopyrrolate
Intraoperative administration of ephedrine
Intraoperative administration of epinephrine
Intraoperative endotracheal tube placement
Intraoperative administration of fresh frozen plasma

Summary

Almost 40% of the study sample developed hyperglycemia events as IONEE. Detailed discussions of variables associated with these are discussed in chapter 5.

CHAPTER 5: DISCUSSION

Anesthesia providers must understand the importance of monitoring and treating intraoperative non-euglycemic events in surgical premature neonates. It is believed that premature neonates are at higher risk of developing non-euglycemic events during their perioperative period because their glycogen storage is lower and their insulin hormone is immature (Mericq, 2006; Motoyama & Davis, 2009; Simmons, 2007). However, few studies have investigated the metabolic responses of neonates to surgical procedures. This study aimed to identify the prevalence of non-euglycemic events in a study population of 26 premature neonates. The study also sought to identify operative characteristics, premature neonate physiological characteristics, and anesthesia provider resuscitation measures associated with occurrence of non-euglycemic events during surgery.

Study Aim 1: Prevalence of Intraoperative Non-Euglycemic Events (IONEE) in Premature Neonates < 2500 Grams

The main objective of this study was to determine the prevalence of IONEE in premature neonates less than 2500 grams undergoing surgery. It is acknowledged that both the small sample size (n=26) and the low representation of subjects in the ELBW group (n= 3) are study limitations. Because the study sample size was small, it is unclear whether the 38% (n = 10) occurrence of IONEE hyperglycemia is truly representative of the occurrence of IONEE in the larger population of premature surgical neonates.

One possible pertinent factor requiring attention when examining IONEE occurrence rate is the site for blood sample collection (capillary heel or arterial). Sixty percent of IONEE events

had blood samples collected from their capillary heel, while 40% had blood samples collected from an arterial site. This difference is significant and is worthy of more detailed discussion.

Karon et al. (2007) compared blood glucose values of capillary, arterial, and venous whole blood samples to the accuracy of point-of-care testing (POCT) results. Subjects were adults (40-87 years), and all received insulin. Laboratory plasma and capillary whole blood glucose levels measured during the first 5 postoperative hours did not differ (p=.88). However, arterial (p=.02) and venous (p=.001) blood glucose values were significantly higher than capillary blood glucose values. Compared with the present study, the samples differed in age, type of surgery, and treatment with insulin. Results suggest that the capillary heel blood glucose values obtained in this study were reliable.

Slater-Maclean et al. (2008) examined the difference in blood glucose values obtained from capillary and arterial blood samples in 50 critically ill adult patients. They concluded arterial blood glucose values were more accurate than those obtained from capillary blood samples. Quality of blood samples collected from capillary sites in critically ill patients was questioned due to inadequate perfusion and possible edema at capillary sites. The presence of edema or hypoperfusion in capillary sites used for blood sample collection from premature neonates in this study is unknown. If present, this may have affected the quality of blood samples used for blood glucose measurements. More research is needed to determine the accuracy of capillary blood samples using the AccuCheck Inform instrument in critically ill surgical premature neonates.

The near 40% IONEE rate in the study sample is clinically significant for anesthesia providers. Many anesthesia providers do not routinely monitor glucose levels in premature neonates during surgery (Ayers & Graves, 2001). Since the outcomes of IONEE in premature

neonates can be so adverse even resulting in early death, anesthesia providers cannot afford to be lax in not monitoring glucose levels during surgery. All subjects in this study who developed IONEE, developed hyperglycemia. Hyperglycemia events in premature neonates are associated with increased risk for intraventricular hemorrhage, osmotic diuresis, dehydration, retinopathy of prematurity, early death, sepsis and further release of insulin to rebound hypoglycemia events (Blanco et al., 2006; Garg et al., 2003; Heimann et al., 2007; Kao et al., 2006; Sharma et al., 2009). There is a need for blood glucose monitoring to be a standard of anesthesia practice during the intraoperative period for surgical neonates.

In addition, it is unknown if any subjects who developed IONEE received pre- or postoperative insulin. It is been suggested that premature neonates with immature insulin response (proinsulin) are at higher risk to develop hyperglycemia events (Mericq, 2006). Therefore, insulin infusion is needed for them to utilize the available glucose.

Hypoglycemia events were absent in the surgical premature neonates in this study. It is possible that the surgical stress was not large enough to decrease blood glucose levels below 40 mg/dL. Also, 88.5% of the study population received intravenous fluid containing dextrose during surgery. Since concentration of dextrose in these intravenous fluids was not measured in this study, further research is needed to identify any association between such fluids and IONEE.

Study Aim: 2 Association between IONEE and Specific Operative Characteristics

Two operative characteristics were significantly related to the occurrence of IONEE - type of anesthesia and the length of surgery.

Type of Anesthesia

Premature neonates under general endotracheal anesthesia were more likely to develop IONEE. This may be because general anesthesia agents decrease insulin response, thereby increasing blood glucose concentrations. Anand, Phil, and Hickey (1992) examined stress responses of neonates undergoing cardiac operations and concluded that the general anesthesia group significantly decreased insulin responses after sternotomy (p=.0032). The blood glucose concentrations in the general anesthesia group were twice those of the total intravenous anesthesia group (p=.017). Although the neonates in Anand, Phil, and Hickey study were full term (more than 37 weeks of gestational age) and weighed more than 2500 grams, their findings on the influences of general anesthesia on blood glucose are consistent with the findings in this study.

It is unknown what factors are responsible for this metabolic response, the surgical stress or the drugs administered during general anesthesia. Also, during the administration of general anesthesia, less amount of opioids may have been administered to control the release of catecholamines as a metabolic response to surgical stress since inhaled agents may potentiate the effects the opioids in depressing the cardiovascular system. Opioids are used during anesthesia administration to blunt the nociceptive effects on metabolic response.

Duration of Surgery

Subjects who developed IONEE in this study had significantly longer mean surgical time. Tsubo, Kudo, Matsuki, and Oyam in 1990 examined the decreased glucose utilization during long surgical procedures (mean duration = 13 hours) in adults and concluded that blood glucose

was higher in patients with longer surgical procedures (p=.05). Although ages and types of surgery differed, the association between longer surgical time and hyperglycemia is consistent.

It is possible that since subjects with IONEE were undergoing longer surgical procedures, their metabolic response was higher due to increased intensity of surgical stress. Longer surgical procedures such as exploratory laparatomy stresses visceral organs causing a higher release of catecholamines responsible for gluconeogenesis. Therefore, gluconeogenesis could have increased blood glucose levels in these neonates.

Duration of Anesthesia

No association between duration of anesthesia and IONEE was found in this study. One potential explanation is that anesthesia is administered during surgical procedures to minimize the effects of surgical stress on metabolic responses. General anesthesia agents are gamma-amino butyric acid type a (GABAa) receptor agonists and minimize brain activity. Furthermore, opioids and general anesthesia blunt the nociceptive effect of surgery - catecholamine release, hepatic glucose release, decreased glucose utilization, and decreased insulin secretion. Another possible explanation is that subjects were not intubated in the operating room. Endotracheal tube placement can trigger a release of catecholamines. However, these neonates may have been intubated in the Neonatal Intensive Care Unit prior to surgery. Location of endotracheal tube placement was not collected.

Type of Surgery

There was no association between type of surgery and IONEE. It is possible that the type of surgeries that these neonates underwent did not cause enough surgical stress to cause a significant metabolic response such as IONEE. However, 80% of the IONEE population (n=8)

underwent abdominal surgeries and 20% (n=2) underwent vascular surgery. No IONEE events were noted with cardiovascular surgeries. The small sample size certainly played a role in this result. A larger sample may help identify whether type of surgery, length of surgery, or intensity of surgical stimuli are associated with IONEE.

Study Aim 3: Association between IONEE and Neonatal Physiological Characteristics

There was an association between IONEE and three neonatal medical conditions – absence of preoperative pulmonary complications, preoperative glucose levels, and postoperative metabolic acidosis. While this study found that premature neonates *without* pulmonary complications were more likely to develop intraoperative hyperglycemia events, there is no evidence suggesting that premature neonates with pulmonary complications have a higher risk of developing hyperglycemia. Further research is needed to clarify the association between pre-existing respiratory disease and the development of IONEE. The small size of this study may have contributed to these results. It is possible that premature neonates free of preoperative pulmonary complications were medicated with beta adrenergic agonist medications. These medications may have been used to support hypotensive events in cardiovascular complications such as patent ductus arteriousus. The use of these medications may cause hyperglycemia. It is unknown if the subjects free of pulmonary complications were receiving these drugs.

One of the two subjects in the study with preoperative hyperglycemia developed IONEE. The relationship between preoperative IONEE and the occurrence of intraoperative IONEE is unknown. It is possible that differences in the rate of dextrose administered during the intraoperative period or the intensity of surgical procedures may have contributed to the

development of IONEE in this subject. More research is needed to identify what factors contributed to the development of IONEE when preoperative hyperglycemia is present.

In addition, a significantly higher proportion of surgical premature neonates with IONEE developed postoperative metabolic acidosis (70%) compared to surgical neonates with euglycemia. These findings differ from those of Anand and Hockey (1992) where the neonates receiving total intravenous anesthesia during cardiac surgery who developed IONEE had a significant alkalosis during the postoperative period (pH=7.55±.02; p=.01). In this study, mean postoperative pH was significantly lower for those with IONEE (7.19 $\pm$ 0.20) than those who were euglycemic (7.35$\pm$0.106). The presence of acidosis is consistent with what is known about the metabolic response to hyperglycemia where there is an overproduction of ketoacids and a corresponding decrease in both plasma pH, and bicarbonate (HCO_3^{-}).

In this study, underlying medical conditions in premature neonates were examined to determine their relationship with IONEE in this sample. Respiratory acidosis, sepsis and necrotized enterocolitis were not significantly related to IONEE in this study. It is difficult to determine if these medical conditions contributed to IONEE since only hyperglycemia and not hypoglycemia occurred during the intraoperative period, which could reflect the administration of intravenous containing dextrose infusion. In addition, preoperative intraventricular hemorrhage history may represent previous episodes of hyperglycemia events in this sample reflecting the neonate's inability to respond to insulin infusions or their own insulin, which could be a factor for the development of IONEE. However, no significant relationship was found between preoperative IVH and IONEE. Preoperative cardiac complications could have affected IONEE. Hemodynamic support with vasopressors (e.g., dopamine) may have improved

perfusion during the intraoperative period. No relationship between IONEE and preoperative cardiac complications was found.

Intraoperative hypothermia may also contribute to hypoglycemia events in premature neonates. However, no association between intraoperative temperature and IONEE was noted in this study. Intraoperative dextrose administration may have prevented hypoglycemia and exacerbated hyperglycemia. Postoperative complications such as respiratory acidosis, and sepsis were not associated with IONEE. The postoperative bleeding, anemia and cardiac complications were complications that were not significant in this study. This study was limited to complications arising within 24 hours of surgery. It is possible that subjects' hyperglycemia was not severe or prolonged enough to contribute to these postoperative complications. The small sample size of this study may have contributed to these results.

Study Aim 4: Association between IONEE and Specific Anesthesia Provider Resuscitation Measures

Specific anesthesia provider resuscitation measures that may impact IONEE include IV fluids, vasopressors, and resuscitation medications. In this study, no associations between resuscitation measures and IONEE were found. One possible reason is that during the intraoperative period these specific measures were not needed. In addition, the small size of this study may have contributed to these results.

The administration of saline and colloids could have reflected the need for the intraoperative volume replacement in these premature neonates. Hypovolemia may cause hypotensive events, which decrease perfusion and may alter the quality of a capillary blood sample. In addition, Atropine administration may indicate symptomatic bradycardia due to hypovolemia or hypoventilation. However, no significant relationship was found between

atropine administration and IONEE. It is possible that the duration of the bradycardia events were not significantly long to stimulate the metabolic responses in these neonates. Furthermore, intravenous solutions containing dextrose could have altered blood glucose levels, but no significant association between IONEE and intravenous solutions were found.

Study Limitations

There were a number of limitations to this study. The eligible sample size was small and there was a small amount of missing data. The study findings are limited to only one region of the state of Florida. For this reason, this study results cannot be extrapolated to all premature neonates < 2500 grams. A prospective study with controls for sample size, achievement of equal weight category representation of premature neonates <2500 grams, measurement of blood glucose (controlling blood sample site, glucometer, human error during testing), evaluation of specific drugs used during anesthesia for general anesthesia and total intravenous anesthesia, and measurements of blood glucose levels at specific times (i.e., right after anesthesia starts, right after surgery begins, and at the end of anesthesia or surgery) is warranted.

Conclusion

The study results suggest that there is a higher incidence of IONEE, specifically hyperglycemia, in premature neonates < 2500 grams who are exposed to prolonged surgical procedures under general anesthesia. Also, those premature without preoperative pulmonary complications were more prone to develop IONEE. In addition, premature neonates < 2500 grams with IONEE developed postoperative metabolic acidosis with a decreased in pH.

The significant findings found in relation to the site of blood sample collection and the proportion of IONEE events reveals the capillary heel site is 10 times more likely to be

associated with the identification of IONEE (hyperglycemia) in premature neonates < 2500 grams. The question arises as to whether the point-of-care testing used (Accu-Check Inform) is accurate. If the neonates were hypoperfused, this factor could have affected the quality of the capillary heel blood sample. Human error during POCT is another possibility.

Implications for Nursing Practice

The increase in number of premature neonates < 2500 grams that undergo surgical procedures presents challenges for anesthesia providers who support the life of these neonates during surgery. In addition, the occurrences of non-euglycemia events have been related to neurodevelopmental delay in these neonates, limiting their learning capacities. Anesthesia providers need to establish intraoperative guidelines for the monitoring and treatment of IONEE to protect these premature neonates from having these complications. As advanced nurse practitioners, nurse anesthetists are leaders who should be proactive in the endeavor of identifying actions that would improve our patient care and anesthesia practice. In addition, nurse anesthetists must collaborate with other neonatal health care providers to communicate to each other concerns and possible research questions that need to be answered to improve neonatal patient care.

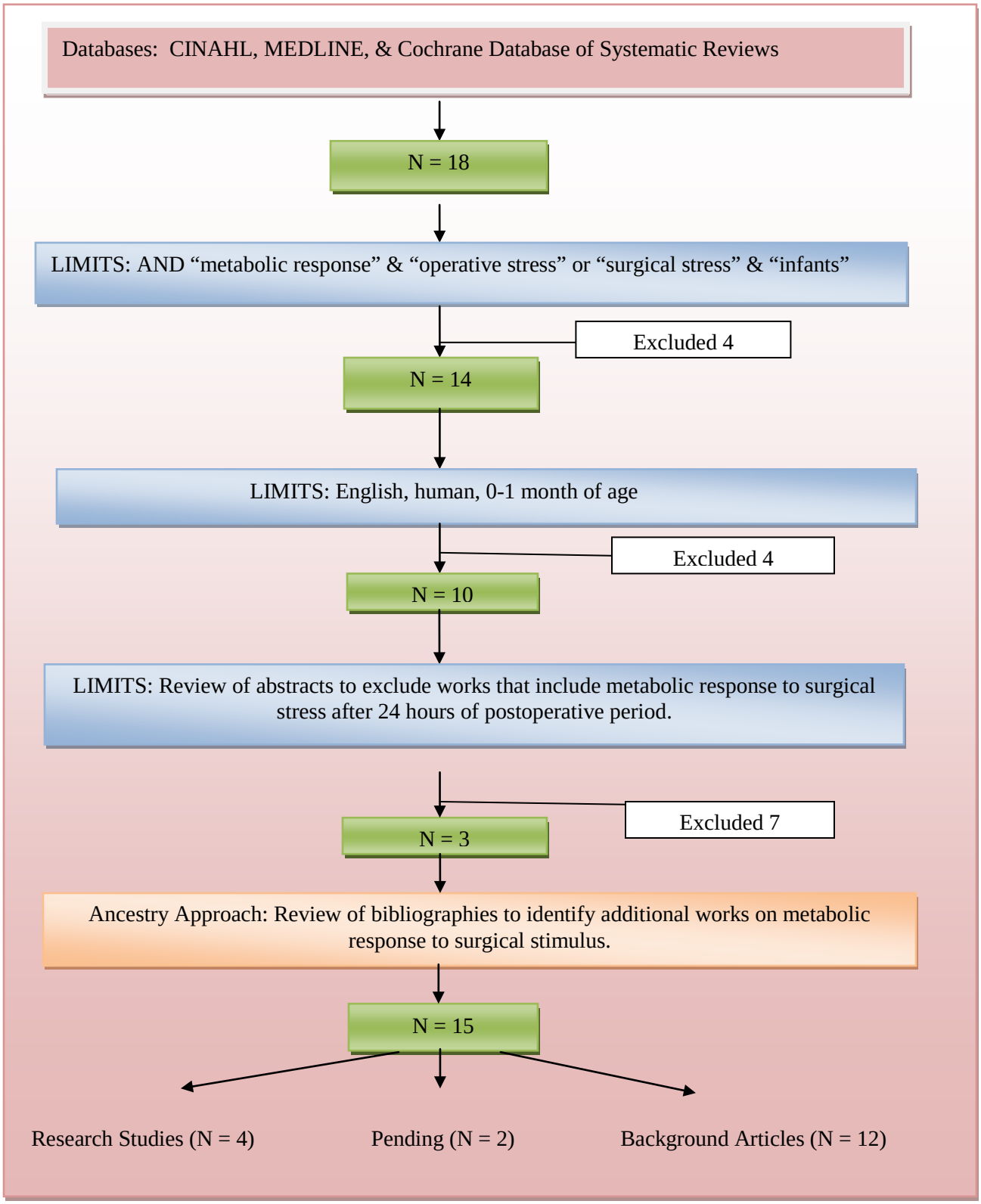
Recommendations for Future Research

Further research must be done to ensure that premature neonates <2500 grams are being identified and adequately treated for IONEE. Additional research studies are needed to better understand the incidence of IONEE. Future research should include larger, prospective, descriptive studies with a goal of identifying risk factors for developing IONEE in a larger population. In addition, a prospective study needs to be conducted to evaluate the factors that

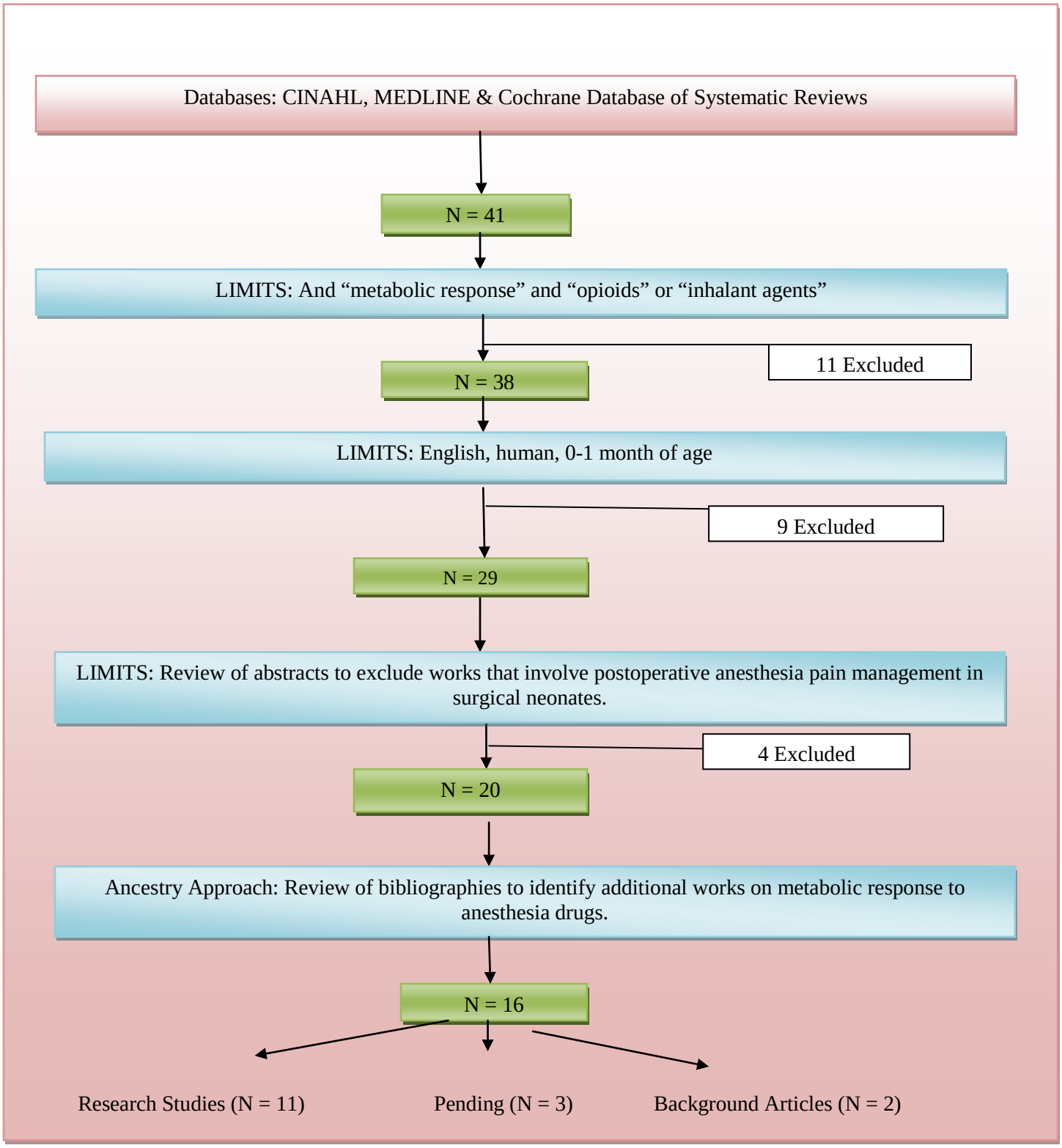
could have contributed that premature neonates with IONEE blood sample site was capillary blood. Outcomes associated with IONEE, including mortality, morbidity, and length of stay needs to be identified.

The findings of this study suggest that anesthesia providers must closely examine the metabolic responses of surgical premature neonates. Because premature neonates are more prone to developing IONEE, guidelines for monitoring and treating IONEE are a clinical practice necessity. Factors such as site for blood glucose collection and hypoperfusion must be considered when monitoring blood glucose levels in premature neonates. In addition, complications such as postoperative metabolic acidosis may be preventable if intraoperative hyperglycemia is treated. More research is needed to clarify the association between length of surgery, type of anesthesia, and IONEE. Also, examination of the intensity of stress in longer surgeries and specific drugs administered during general anesthesia is warranted. Further studies can contribute to evidence-based practice for the prevention of IONEE, resulting in positive outcomes on quality of life for premature neonates.

APPENDIX A: FLOW CHART EBSCO HOST SEARCH AND PUBMED 6/2/09


Databases: CINAHL, MEDLINE, & Cochrane Database of Systematic Reviews
N = 18
LIMITS: AND "metabolic response" & "operative stress" or "surgical stress" & "infants"
Excluded 4
N = 14
LIMITS: English, human, 0-1 month of age
Excluded 4
N = 10
LIMITS: Review of abstracts to exclude works that include metabolic response to surgical stress after 24 hours of postoperative period.
Excluded 7
N = 3
Ancestry Approach: Review of bibliographies to identify additional works on metabolic response to surgical stimulus.
N = 15
Research Studies (N = 4)
Pending (N = 2)
Background Articles (N = 12)

APPENDIX B: FLOW CHART EBSCO HOST SEARCH AND PUBMED 6/2/09


Databases: CINAHL, MEDLINE & Cochrane Database of Systematic Reviews
N = 41
LIMITS: And “metabolic response” and “opioids” or “inhalant agents”
11 Excluded
N = 38
LIMITS: English, human, 0-1 month of age
9 Excluded
N = 29
LIMITS: Review of abstracts to exclude works that involve postoperative anesthesia pain management in surgical neonates.
4 Excluded
N = 20
Ancestry Approach: Review of bibliographies to identify additional works on metabolic response to anesthesia drugs.
N = 16
Research Studies (N = 11)
Pending (N = 3)
Background Articles (N = 2)

APPENDIX C: EVALUATION MATRIX FOR RECORDING STRENGTHS AND WEAKNESSES OF STUDIES FOR A LITERATURE REVIEW ON METABOLIC RESPONSE TO SURGICAL STRESS

Authors	Yr of Pub	Major Strengths	Major Weaknesses	Conclusions	Level of Evidence
Chawls et.al.	1995	Measures preoperative sepsis, bacterial or severe inflammatory injury effect on the postoperative metabolic response in infants after surgery. All surgical procedure were abdominal (gastroschisis, tracheoesophageal fistula, colostomy, and correction of malrotation bowel.	Infants were older than 33 days and did not specify if they were premature. Small sample (12 subjects).	The acute underlying illness (sepsis, bacteremia or severe inflammatory process) determines postoperative measured energy expenditure.	8
Heimann et al.	2007	Large sample (252 premature neonates) It correlates morbidity (IVH, ROP and sepsis) with repetitive events of hyperglycemia.	Retrospective study could have missed data. Necrotizing colitis is not correlated to hyperglycemia in this study.	A positive correlation was found between low gestational age (<27 weeks), high blood glucose levels (>150mg/dL) and more episodes of hyperglycemia. Also IVH was higher in low gestational age (<27 weeks).	10
Powis et al.	1998	Intraoperative and postoperative analgesia varied slightly. Metabolic rate was measured during preoperative and postoperative periods.	Small population of neonates (total of infants and children was 10). Subjects were receiving dextrose or TPN intraoperatively which could have	Infants and children do not increase their whole body protein turnover or metabolic rate after major abdominal sx. Perhaps is due to diversion of protein synthesis from	10

Authors	Yr of Pub	Major Strengths	Major Weaknesses	Conclusions	Level of Evidence
			affected measurement of protein flux. The variation among surgical time was too wide (28-285 minutes); therefore metabolism could have been affected differently among subjects.	growth to tissue repair.	
Reynolds et al.	2008	Subjects were assigned randomly. Analgesia was administered equally to control surgical stress and measure postoperative ability to obtain positive protein balance.	Only 13 neonates participated in study. Surgical repairs of gastroschisis were not equal in every case; therefore, surgical stimulus was not equal.	Neonates were able to achieve positive protein balance after amino acids were administered parentally.	12

APPENDIX D: EVALUATION MATRIX FOR RECORDING STRENGTHS AND WEAKNESSES OF STUDIES FOR A LITERATURE REVIEW ON METABOLIC RESPONSE TO ANESTHESIA DRUGS

Authors	Yr of Pub	Major Strengths	Major Weaknesses	Conclusions	Level of Evidence
Anand et al.	1992	Randomized sample. Dextrose infusion was standardized among subjects. Hormonal and metabolic response was measured during different stages of surgery.	Sample underwent five different cardiac surgeries; therefore, surgical stress could have varied among them. Sample too small for solid conclusions.	Physiologic responses to stress are attenuated with deep anesthesia and postoperative analgesia.	13
Barratt et al.	2002	Excluded patients with cardiac, respiratory, muscular, neurological, renal, hematological, drug dependency or psychiatric disease. Most of surgeries were major abdominal surgeries. Cortisol, insulin and glucagon were measured pre and postoperatively. Epidural anesthesia was used intraoperatively and postoperatively.	Validity and reliability are not specified for all instruments. All subjects were adults.	Multimodal analgesia and IV Nutrition preserves total body protein and fat.	12
Bell, et al.	2004	All 17 subjects received dextrose 5% with normal saline 45%	Infants' history of prematurity is not specified. Instruments and	Remifentanyl vs. fentanyl/morphine techniques for stress control during sx	8

Authors	Yr of Pub	Major Strengths	Major Weaknesses	Conclusions	Level of Evidence
		before rewarming. Blood samples were obtained Prebypass, during bypass and postbypass. Randomized sample.	their validity are not specified. Variation on preexisting conditions and on induction drugs (ketamine vs. thiopenthotal).	did not show differences on stress response.	
Bouwmeester et al.	2001	Randomized and double-blind study. Compares neonates stress response control with older children stress responses. Anesthesia management was standardized. Hormones and metabolic response were measured during different surgical and postoperative stages.	Twenty-two different surgical procedures were performed. Only one instrument is identified as validated.	Continuous infusion of morphine does not provide any major advantages over intermittent morphine boluses for postoperative analgesia in neonates and infants. Neonates receiving postoperative continuous morphine showed higher blood glucose levels.	13
Crozier et al.	1993	Feeding protocol was standardized for every subject. Gestational age was the same in both groups. Elective vs emergency c/s stress was compared.	Emergency c/s subjects had lower weight and APGAR SCORES which could have affected blood glucose homeostasis during extrauterine transition.	Cortisol and blood glucose levels were lower during a transient period on c/s with induced with Etomidate.	12
Gruber et al.	2001	Hormones and metabolic	Anesthesia induction and	Fentanyl with or without midazolam	10

Authors	Yr of Pub	Major Strengths	Major Weaknesses	Conclusions	Level of Evidence
		response were measured during different stages of cardiac surgery. No dextrose intravenous infusion was administered intraoperatively.	management were not standardized. Four types of cardiac surgery were specified; therefore some variability may exist among stress responses during surgery. Duration of deep hypothermic cardiopulmonary arrest varied among groups.	do not prevent hormonal or metabolic response in infants undergoing cardiac surgery.	
Kaussman et al.	2001	Used changes in glucose, lactate and mixed venous oxygen saturation to indirectly assess depth of anesthesia. Subjects were randomized.	BIS has not been validated in pediatric population. Cerebral perfusion pressure was not measured or compared to BIS in the study.	There is not a relationship between the BIS and hemodynamic, metabolic or hormonal indices of anesthetic depth.	11
Schricker et al.	2004	Subjects were assigned randomly. Blood samples were during perioperative period to compare baselines with after treatment levels.	Validity and reliability of instruments are not identified.	Perioperative hypocaloric dextrose infusion and epidural analgesia saves more than 100 g of lean body per day.	10
Simons et al.	2005	Subjects were allocated randomly. Placebo and morphine effects	Validity and reliability of instrument were not specified. Blood sample was	Continuous morphine infusion decreased plasma epinephrine and norepinephrine in	10

Authors	Yr of Pub	Major Strengths	Major Weaknesses	Conclusions	Level of Evidence
		were compared.	not able to be collected from some subjects (n = 13).	ventilated preterm neonates.	
Terajima et al.	2000	Patients with previous history of metabolic or endocrinologic disorders such as diabetes, excessive obesity or abnormal hepatic or renal function were excluded. Subjects were randomly assigned. Different glucose infusion concentrations were used in this study.	Validity and reliability of instruments were not specified.	The glucose tolerance of patients under general anesthesia is determined by the intensity of surgical stress. Insulin excretion is preserved during minor surgery when glucose infusion was administered at 0.1-0.2g/kg/h under general anesthesia with Sevoflurane.	9
Weale et al.	2004	Four different concentrations of remifentanil infusions were administered. Anesthesia management was standardized for every case. No dextrose infusion was administered during perioperative period.	This study was limited only to pre-bypass stress stimulus; therefore, the release of NPY could have been limited. Nine different cardiac surgeries were performed which could alter the intensity of surgical stress among subjects. Cortisol should have been measured in every	Remifentanil infusion greater than 1.0 ug/kg/min decreases glucose increase and tachycardia related to pre-bypass stress stimulus. Remifentanil may cause bradycardia in neonates.	10

Authors	Yr of Pub	Major Strengths	Major Weaknesses	Conclusions	Level of Evidence
			blood sample to correlate increases with different surgical stimulations.		

APPENDIX E: CODE TABLE FOR REVIEW ARTICLES

Code	**Patient Risk Level**
0	Sepsis, bacteremia or inflammatory injury
1	Hyperglycemia
2	Major abdominal surgery
3	Cardiac surgery
4	Major surgeries
5	Metabolic extrauterine transition
6	Mechanical ventilation
7	Minor surgery
Code	**Care Setting**
1	Neonatal Intensive Care Unit
2	Operating room
3	Preoperative period
4	Intensive Care Unit
5	Pediatric Intensive Care Unit
Code	**Topics Presented**
1	Energy expenditure response in sick surgical infants
2	Hyperglycemia affects mortality in premature infants <1500 g.
3	Changes in whole-body protein flux and metabolism rate after major abdominal surgery.
4	Postoperative protein positive balance
5	Hormonal and metabolic response to stress with deep anesthesia
6	Hormonal and metabolic response after analgesia administer intra and postoperatively period.
7	Cortisol and blood glucose levels in term neonates after mother been induced with etomidate and barbiturate.
8	Glucose infusion effect during minor surgery under general anesthesia.

APPENDIX F: METABOLIC RESPONSE TO SURGERY AND ANESTHESIA DRUGS IN NEONATES

Authors	Yr of Pub	Population Discussed	Risk Level	Care Setting	Topics Presented
Chwals et al.	1995	Sick infants older than 33-67 days old.	0	1	1
Heimann et al.	2007	Low gestational age <27 weeks	1	1	2
Powis et al.	1998	Infants and children (2 days-3 yr old)	2	1	3
Reynolds et al.	2008	36 weeks gestational age, 1-2 days old	2	1, 2	4
Anand et al.	1992	Term neonates from 5-9 days old with congenital heart disease	3	1, 2	5
Barratt et al.	2002	Adults under major abdominal surgery older than 21 but younger than 80 years old.	2	3, 4	3
Bell et al.	2004	From 4-108 months old children	3	2	5
Bouwmeester et al.	2001	Children aged 0-3 years	4	1, 2, 4	6
Crozier et al.	1993	38-40 weeks old neonates	5	1, 2	7
Gruber et al.	2001	Infants < 6 months old	3	1, 2, 5	6
Kussman et al.	2001	Infants 3-4 months	3	2, 8	5
Schricker et al.	2004	Adults 64-80 years old.	2	3, 4	3
Simons et al.	2005	Neonates 27.5-32.1 weeks of gestational age	6	1	6
Terajima et al.	2000	53-62 year old adults	7	2	8
Weale et al.	2004	Children under five years old	3	2	5

APPENDIX G: ARTICLES FOCUSED ON METABOLIC RESPONSE TO SURGERY AND ANESTHESIA OF NEONATES

Authors	Year of Publication	Article Focus
Chwals et al.	1995	How preoperative illness determines increases in energy expenditure response to surgical procedures.
Heimann et al.	2007	How repetitive hyperglycemia events in low gestational neonates determines their mortality.
Powis et al.	1998	Changes on whole-body protein and metabolic rate after major abdominal sx in infants and children.
Reynolds et al.	2008	Are 1-2 day old neonates capable to obtain a positive protein balance after parenteral amino acids are administer when they undergo major abdominal sx?
Anand et al.	1992	How deep anesthesia and postoperative analgesia improves mortality and decreases metabolic response to surgical stress.
Barratt et al.	2002	Effects of multimodal analgesia on total body protein loss.
Bell et al.	2004	How analgesia techniques affects stress response.
Bouwmeester et al.	2001	How continuous or intermittent morphine affects the hormonal and metabolic stress responses in 0-3aged years children undergoing major surgeries.
Crozier et al.	1993	Measure the effect of etomidate and barbiturate in metabolic extrauterine transition of full term neonates.
Gruber et al.	2001	Control the metabolic and hormonal response with fentanyl with and without midazolam in infants undergoing cardiac surgery.
Kussman et al.	2001	Compared the BIS reading with the metabolic response of infants undergoing cardiac surgery with different plasma fentanyl levels.
Schricker et al.	2004	How pain control (epidural vs. PCA morphine) in patients undergoing abdominal surgery, suppresses amino acid oxidation.
Simons et al.	2005	Measured the effects of morphine on stress response due to mechanical ventilation.
Terajima et al.	2000	How glucose infusion undergoing minor surgery under general anesthesia may prevent hyperglycemia, elevation of FFA and ketone bodies.
Weale et al.	2004	How remifentanil infusion may alter blood glucose concentration during cardiac surgery stress stimulus.

APPENDIX H: FINDINGS IN REVIEW ARTICLES FOR METABOLIC RESPONSE FOR SURGERY AND ANESTHESIA DRUGS IN NEONATES

Authors	Year of Publication	Findings
Chwals et al.	1995	Preoperative metabolic parameters are a more accurate reflection of injury severity. Postoperative metabolic response
Heinaman et al.	2007	Repetitive hyperglycemia events in low gestational age neonates (<27 weeks) increases mortality.
Powis et al.	1998	Whole-body protein flux and metabolic rate does not change after major abdominal surgery in infants and children.
Reynolds et al.	2008	Neonates undergoing metabolic stress after abdominal surgery shortly after birth are capable of obtain a positive protein balance when parenteral amino acids are administered.
Anand et al.	1992	Physiologic responses in neonates under cardiac surgery are attenuated with deep anesthesia and postoperative analgesia. Also mortality decreases when this stress is attenuated.
Barratt et al.	2002	Multimodal analgesia with IV nutrition preserves total body protein loss.
Bell et al.	2004	Remifentanil and fentanyl/morphine techniques equally control cardiac surgical stress response.
Bouwmeester et al.	2001	Continuous infusion of morphine does not provide any major advantages over intermittent morphine boluses for postoperative analgesia in neonates and infants. Neonates receiving postoperative continuous morphine showed higher blood glucose levels.
Crozier et al.	1993	Etomidate decreased the cortisol and blood glucose levels of neonates that born from emergency C/S.
Gruber et al.	2001	Fentanyl with or without midazolam cannot completely suppress the hormonal and metabolic response in infants undergoing cardiac surgery.
Kussman et al.	2001	There is not relationship between the BIS and hemodynamic, metabolic, or hormonal indices of anesthetic depth.
Schricker et al.	2004	Perioperative epidural analgesia and hypocaloric dextrose infusion suppress postoperative amino acid oxidation.
Simons et al.	2005	Continuous morphine infusion decreases plasma noradrenaline concentration in preterm neonates stressed by mechanical ventilation.
Terajima et al.	2000	The administration of glucose infusion at 0.1-0.2/kg/h

Authors	Year of Publication	Findings
		during minor surgery under sevoflurane general anesthesia prevented hyperglycemia.
Weale et al.	2004	Remifentanil may cause bradycardia in neonatal surgical patients. Remifentanil infusion greater than 1.0ug/kg/ min may suppress glucose levels in blood during cardiac surgery in children younger than 5 years old.

APPENDIX I: BACKGROUND ARTICLES

Authors	Yr of Pub	Article Focus	Metabolic Response to Surgery or Anesthesia
Agus & Jaksic	2002	Nutritional support for ill neonates and children.	Surgery
Chwals	2004	Enteral and parenteral nutrition in premature surgical neonates.	Surgery
Eaton	2003	Impaired energy metabolism during neonatal sepsis: the effects of glutamine.	Surgery
Hillier	2004	Neonatal anesthesia management considerations.	Anesthesia
Hulzebos & Saur	2007	Energy requirements for newborn infants.	Surgery
Hume et al.	2002	Developmental disorders of glucose metabolism in premature neonates.	Surgery
Jaksic & Shew	2004	Metabolic Response to illness and operation in full term and premature neonates.	Surgery
Kninouchi	2003	Anesthetic considerations for the management of very low and extremely low birth weight infants.	Anesthesia
Owens & Musa	2009	Nutrition support after neonatal cardiac surgery.	Surgery
Parish & Bhatia	2008	Early aggressive nutrition for the premature infant.	Surgery
Pierro & Eaton	2006	Nutrition in the neonatal surgical patient.	Surgery
Pierro	2002	Metabolism and nutritional support in the surgical neonate.	Surgery
Pierro & Eaton	2008	Metabolism and nutrition in the surgical neonate.	Surgery
Rao	2009	Early introduction of lipids to parenterally-fed preterm infants.	Surgery
Valentine & Puthoff	2007	Enhancing parenteral therapy for the neonate.	Surgery
Yu	2005	Optimizing nutrition in preterm infants, improves extrauterine growth restriction.	Surgery

APPENDIX J: METHODOLOGY MATRIX FOR METABOLIC RESPONSE TO SURGERY IN NEONATES

Author	Yr of Pub	Country	Independent Variables	Dependent Variables	Study Design	Sample Size	Sample Character	Sampling Method	How Data Collected?	Instrument	Valid/ Reliable	Surgery or Anesthesia
Chwals et al.	1995	U.S.	Preoperative sepsis, bacteremia or inflammatory injury.	Measured energy expenditure	Descriptive	12 infants	33-67 days old Critically ill	Convenience sample	CRP concentration measured postop day 2,5,8	Indirect calorimetry	Support by other research studies	Surgery
Heimann et al.	2007	U.S.	27 weeks gestational age	Mortality and hyperglycemia events	Retrospective	252 premature infants	Repetitive hyperglycemia events	Convenience	Review charts	Not described	n/a	Surgery
Powis et al.	1998	England	Major abdominal surgery	Protein flux and energy metabolism	Prospective	10 infants and children (2 days-3 years old)	Major abdominal surgery with operative stress score > 7	Convenience	Energy expenditure calculated with respiratory quotient carbon dioxide production/ oxygen consumption. Indirect calorimeter used with leucine IV infusion.	Computerised indirect calorimeter	Ethanol burned (96% volume) with error less than 3%.	Surgery
Reynolds et al.	2008	U.S.	Gastroschisis abdominal surgery	Immediate postoperative protein	Prospective	13 neonates 2 kg wt 36>weeks gestational age 1-2 days old NTISS-28 SNAP-8	Major abdominal surgery first two days of life.	Randomized	Nitrogen balance was calculated from nitrogen intake minus urine nitrogen output. Blood sample was taken from arterial line for creatinine, BUN, glucose, and ammonia.	Neoscope (indirect calorimeter)	Combustion of absolute ethyl alcohol.	Surgery

APPENDIX K: METHODOLOGY MATRIX FOR METABOLIC RESPONSE TO ANESTHESIA DRUGS IN NEONATES

Author	Yr of Pub	Country	Independent Variables	Dependent Variables	Study Design	Sample Size	Sample Character	Sampling Method	How Data Collected?	Instrument	Valid/ Reliable	Surgery or Anesthesia
Anand et al.	1992	U.S.	Halothane-morphine vs. high dose fentanyl	Metabolic response to surgical stress	Experimental	30 neonates	Neonates undergoing cardiac surgery	Randomly assigned	Arterial blood sample collected; before surgery, before CPB, 5 minutes after circulatory arrest ends, end of sx, and 6,12,& 24 hrs postop.	Radioimmnoassay -insulin, glucagon and beta-endorphin Double-isotpe radioenzymatic assay -steroid hormones Specific enzymatic assays-glucose, lactate, pyruvates, acetoacetate, 3-hydroxybutyrate and alanine	Coefficient of variation: Radio-<5%, Radio-enzymatic-<10%, and Specific assays < 3%.	Anesthesia
Barratt et al.	2002	Australia	Multimodal analgesia	Total Body Protein	Experimental	47 adults	22-79 year old adults with upper abdominal surgery	Randomized	Total body protein, nitrogen balance, arterial blood gases, pain scores and	In vivo neutron activation analysis	Coefficient of variation 3%.	Anesthesia
Bell et al.	2004	UK	Remifentanil vs. fentanyl/ morphine	Pain and surgical stress	Experimental	17 children	4-108 months old with cardiac surgery	Randomized	Blood samples for glucose and cortisol from induction-24 hrs postop. HR, MAP, tachycardia and bradycardia were recorded	Not specified	Not specified	Anesthesia
Bouwemmester et al.	2001	Netherlands	Major surgery, effects of continuous and	Hormonal and metabolic surgical stress response	Experimental Double-blind	204 children	Children aged 0-3 years	Randomized	Arterial blood samples to measure Epi, NE, insulin,	Surgical Stress Score, VAS and COMFORT scales for pain, HPLC	Authors only mentioned validation for COMFORT scale	Anesthesia

Author	Yr of Pub	Country	Independent Variables	Dependent Variables	Study Design	Sample Size	Sample Character	Sampling Method	How Data Collected?	Instrument	Valid/ Reliable	Surgery or Anesthesia
			intermittent morphine						glucose and lactate. Urine collected for protein loss test.	(Epi and NE), Insulin IRMA CT kit, standardized labanalyzers (glucose, lactate, total bilirubin and plasma and urinary creatinine) and amino acid analyzer.		
Crozier et al.	1993	Germany	Etomidate and methohexitone administration	Adrenocortical and metabolic adaptation of the neonate	Experimental	40 neonates	Delivered by cesarean section under general anesthesia	Randomized	Blood samples; 1st from umbilical cord, 2h and 6h postpartum from heel.	Radioimmunoassay kit for cortisol measurement. Etomidate measured with gas chromatography.	Radioimmunoassay sensitivity is 5.5 nmol/L. Gas chromatography sensitivity is 2.5ng/mL.	
Gruber et al.	2001	U.S.	Fentanyl bolus, fentanyl infusion, and fentanyl-midazolam infusion.	Stress response	Experimental randomized double-blind	45 infants < 6months	Infants undergoing cardiac surgery	Randomized	Arterial blood samples for epi, NE, cortisol, adrenocortical hormone, glucose, and lactate after induction, sternotomy, 15 min after bypass, at the end of sx and 24 hrs postop.	Single-isotope radioenzymatic assay for NE and Epi levels. Chemilumin-escence for cortisol levels. Immunoradio-metric assay for ACTH levels. STAT profile ultra for lactate and glucose.	Variability/Sensitivity Epi 14.6%/29.2% NE 4.7%/11.2% ACTH 1%/2.5% Cortisol 6.5%/10.1% Variability of lactate 6.0% glucose 5.0%.	
Kussman et al.	2001	U.S.	Stress	Bispectral index (BIS)	Prospective	19	Infants	Randomized	Mean arterial	Single-isotope	Variability/Sensitivity	

Author	Yr of Pub	Country	Independent Variables	Dependent Variables	Study Design	Sample Size	Sample Character	Sampling Method	How Data Collected?	Instrument	Valid/ Reliable	Surgery or Anesthesia
			response and plasma fentanyl levels			neonates and infants<6 mo	undergoing cardiac surgery		pressure, heart rate and arterial blood samples were obtained for NE, Epi, ACTH, cortisol, glucose, lactate and fentanyl levels.	radioenzymatic assay for NE and Epi levels. Chemilumin-escence for cortisol levels. Immunoradio-metric assay for ACTH levels. Chromatography for detection of glucose and lactate.	Epi 14.6%/29.2% NE 4.7%/11.2% ACTH 1.0%/2.5% Cortisol 6.5%/10.1%	
Schricker et al.	2004	Germany	Epidural anesthesia and Dextrose 10% infusion	Amino acid oxydation	Prospective randomized control trial	20 adults 64-68 year old	Adults undergoing hemi-colectomy and sigmoid colectomy	Randomized	Expired breath samples to determine CO2 isotope enrichments and arterial blood gases to determine whole body leucine and glucose kinetics.	Indirect calorimetry, Gas Chromatography Mass Spectrometry, Isotope ratio-Mass Spectrometry, glucose Analyzer2, Synchron CX system(lactate), and Radioimmunoassay (insulin, cortisol and glucagon)	Not specified	
Simons et al.	2005	U.S.	Morphine	plasma adrenaline/noradrenaline concentrations	blinded randomized placebo control trial	126 (<3 days old) neonates	preterm neonates (28.4-32.1 gestational age) on	Randomized	Blood samples were taken before and after administration	High performance liquid chromatography with flurimetric detection was used for measurements on plasma concentration of epi and NE.	Not specified	

Author	Yr of Pub	Country	Independent Variables	Dependent Variables	Study Design	Sample Size	Sample Character	Sampling Method	How Data Collected?	Instrument	Valid/ Reliable	Surgery or Anesthesia
							ventilator <8hrs		of analgesia drug			
Terajima & Ogawa	2000	Japan	Glucose	Usage of energy sources during minor surgery	Experimental	40 adults 53-62 years old	Adults undergoing tympano-plasty or skin grafting under general anesthesia with sevoflurane	Randomized	Blood sample collected 20 min before induction, and 1 and 2 hour after glucose infusion. Urine sample was obtained before induction and 2 hours after glucose infusion was started.	Glucose –oxidase method -glucose Acyl CoA oxidase method -Free fatty acid Williamson's enzyme method -acetoacetate Radioimmunoassay -immunoreactive insulin	Not specified	
Weale et al.	2004	UK	Remifentanil infusion	Stress response during pre-bypass phase of pediatric cardiac surgery.	Experimental	49 infants and children under five years old	Infants and children under 5 years old undergoing cardiac surgery	Randomized	Blood sample was obtained at induction, pre-surgery, 5 min after sternotomy and immediately pre-bypass. Blood glucose was measured with every blood sample taken. Cortisol and	One touch-glucose oxidase method, Chemiluminescence for plasma cortisol Immunoassay kit for neuropeptide Y	One touch coefficient variation % Chemiluminescence variability 6.4% Intra-assay variability less than 5%.	

Author	Yr of Pub	Country	Independent Variables	Dependent Variables	Study Design	Sample Size	Sample Character	Sampling Method	How Data Collected?	Instrument	Valid/ Reliable	Surgery or Anesthesia
									neuropeptide Y were measured in first and last sample. Heart rate and mean arterial pressure were recorded.			

APPENDIX L: UCF IRB APPROVAL

University of Central Florida Institutional Review Board
Office of Research & Commercialization
12201 Research Parkway, Suite 501
Orlando, Florida 32826-3246
Telephone: 407-823-2901 or 407-882-2276
www.research.ucf.edu/compliance/irb.html

Approval of Human Research

From: **UCF Institutional Review Board #1**
FWA00000351, IRB00001138

To: **Zulay H. Ritrosky** and Co-PIs if: **Steven R. Talbert**

Date: **April 02, 2010**

Dear Researcher:

On 4/2/2010, the IRB approved the following human participant research until 4/1/2011 inclusive:

Type of Review:	UCF Initial Review Submission Form
Project Title:	Prevalence of and Risk Factors for Intraoperative Non-Euglycemia Events in Premature Neonates <2500 grams
Investigator:	Zulay H Ritrosky
IRB Number:	SBE-10-06878
Funding Agency:	Florida Hospital for Children(FHC)
Grant Title:	The Florida Hospital for Children Nursing Doctoral Student Mentoring Award.
Research ID:	n/a

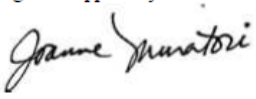
The Continuing Review Application must be submitted 30days prior to the expiration date for studies that were previously expedited, and 60 days prior to the expiration date for research that was previously reviewed at a convened meeting. Do not make changes to the study (i.e., protocol, methodology, consent form, personnel, site, etc.) before obtaining IRB approval. A Modification Form **cannot** be used to extend the approval period of a study. All forms may be completed and submitted online at https://iris.research.ucf.edu .

If continuing review approval is not granted before the expiration date of 4/1/2011, approval of this research expires on that date. When you have completed your research, please submit a Study Closure request in iRIS so that IRB records will be accurate.

In the conduct of this research, you are responsible to follow the requirements of the Investigator Manual.

On behalf of Joseph Bielitzki, DVM, UCF IRB Chair, this letter is signed by:

Signature applied by Joanne Muratori on 04/02/2010 09:43:20 AM EST



IRB Coordinator

APPENDIX M: LMHS IRB APPROVAL

LEE MEMORIAL
HEALTH SYSTEM
Cape Coral Hospital
Gulf Coast Medical Center
HealthPark Care Center
HealthPark Medical Center
Lee Convenient Care
Lee Memorial Hospital
Lee Physician Group
Regional Cancer Center
The Children's Hospital
The Rehabilitation Hospital

Institutional Review Committee
636 Del Prado Boulevard
Cape Coral, Florida 33990

Phone: 239-772-6383
Fax: 239-772-6388
Email: pam.fowler@leememorial.org

March 5, 2010 VIA EMAIL

Ms. Zulay Ritrosky, CRNA

RE: – Prevalence of and Risk Factors for Intraoperative Non-Euglycemic Events (IONEE) in Premature Infants <2500 Grams

Dear Ms. Ritrosky:

The Lee Memorial Health System Institutional Review Committee met on March 3, 2010.
At that meeting the Committee reviewed your request for approval of the above-mentioned protocol and request for waiver of informed consent and waiver of authorization.

After careful review of the information provided, the Committee recommended revisions to your protocol reflecting the following: Page 2 – 1st paragraph under Background, 7th sentence, remove extraneous comments (I thought the citation for books….), Page 3 under Relation of study to NRC focal area, sentence 3, change manage to manage(d). The LMHS IRC office has received your revised protocol addressing the committee's recommendation. After review of the revisions, approval of your protocol has been granted.

This protocol has been approved for a period of one year, from 3-3-2010 through 3-2-2011 and you have been granted a waiver of informed consent requirements and a waiver of authorization. The informed consent waiver request qualifies for approval under 45 CFR 46.116 (d). (1)The research involves no more than minimal risk to subjects, (2). The waiver or alteration will not adversely affect the rights and welfare of the subjects, (3) the research could not practically be carried out without the waiver. The committee also grants approval of the waiver of authorization as the request qualifies for waiver of authorization under 45 CFR 164.512 (ii) waiver criteria. Under this waiver you are allowed to collect only the following information*: patient demographics, medical history, medications, Operative characteristics, Preoperative Glucose levels, Immediate Post Op Glucose levels, PreOperative Events, Intraoperative Events, PostOperative Events and laboratory data (all data included on your data collection form)* .

You must not release the PHI collected under this waiver to any other individual or entity other than those stated in your initial application. You must destroy any individual identifiers at the earliest possible opportunity consistent with your explanation of such as stated in your application.

If this protocol is to be continued for more than one year, please remember to request yearly reapproval from this committee.

The Lee Memorial Health System Institutional Review Committee policy requires reporting of any serious or unexpected adverse event within five days of discovery. This Committee must approve any protocol, informed consent, or research activity changes prior to their implementation. Please be reminded that study renewal is due annually. A final report is required upon study completion.

Sincerely,

Pam Fowler, RN, BS, CIM
IRB Administrator
Lee Memorial Health System,Institutional Review Committee

APPENDIX N: PREVALENCE OF AND RISK FACTORS FOR INTRAOPERATIVE NON-EUGLYCEMIA EVENTS IN PREMATURE NEONATES <2500 GRAMS

Data Collection Tool

Subject Code #

Demographic Data:

Gestational Age on the day of surgery: _____weeks Gender: (1) Male (2) Female

Ethnicity: (1) Caucasian (2) Black (3) Hispanic (4) Asian (5) Other

Weight on the day of surgery: (1) < 2,500 grams (2) < 1,500 grams (3) < 750 grams

Gestational age at birth: _____weeks

Exclusion criteria:

Surgical procedures immediately after birth (1) Yes (2) No

Mother treated with following drugs during third trimester:

a. Beta-sympathomimetics (1) Yes (2) No
b. Beta-blockers (1) Yes (2) No
c. Chlopropamide (1) Yes (2) No
d. Benzothiazide diuretics (1) Yes (2) No
e. Tricyclic antidepressants (1) Yes (2) No
f. Neonatal metabolic disorders:
g. Type I glycogenesis storage disease with glucose-6-phosphate deficiency (1) Yes (2) No
h. Beckwith-Wiedemann Syndrome (1) Yes (2) No
i. Nesidioblastosis (1) Yes (2) No

Exclusion criteria:

a. Islet Cell Adenomas (1) Yes (2) No
b. Adenomatosis (1) Yes (2) No
c. Adrenal insufficiency (1) Yes (2) No

Operative characteristics:

a. Length of surgery _____minutes
b. Type of surgery:
    1. Cardiac_____
    2. Abdominal_____
    3. EENT_____
    4. Thoracic_____
    5. Neuro_____
c. Length of anesthesia_____minutes
d. Type of anesthesia:
    1. General anesthesia_____
    2. TIVA_____
    3. Regional anesthesia_____

Neonatal physiological characteristics:

Preoperative underlying medical history of premature neonates

1. Sepsis
2. Necrotizing enterocolitis
3. Respiratory distress
4. Bronchopulmonary dysplasia
5. Intraventricular hemorrhage
6. Pulmonary hypertension

Preoperative glucose level:

1. ACCUCHECK value_____ or Serum value
2. Normal (glucose level 40-150 mg/dL): _____mg/dL

a. Normoglycemia (glucose level 40-150 mg/dL) (1) Yes (2) No

3. Abnormal (glucose level < 40 or > 150 mg/dL): _____mg/dL
    a. Hypoglycemia (glucose level <40 mg/dL) (1) Yes (2) No

       Hyperglycemia (glucose level > 150mg/dL) (1) Yes (2) No
4. Site for blood collection
    a. Heel stick
    b. UAC
    c. UVC

Intraoperative blood glucose level:

1. ACCUCHECK VALUE___ or Serum Value_____
2. Normal (glucose level 40-150 mg/dL): _____mg/dL
3. Normoglycemia (glucose level 40-150 mg/dL) (1) Yes (2) No
4. Abnormal (glucose level < 40 or > 150 mg/dL): _____mg/dL
    a. Hypoglycemia (glucose level <40 mg/dL) (1) Yes (2) No
    b. Hyperglycemia (glucose level > 150mg/dL) (1) Yes (2) No
5. Site for blood collection
    a. Heel stick___
    b. UAC___
    c. UVC____

Proxy measure of intraoperative blood glucose level:

1. ACCUCHECK VALUE_____ or Serum Value_____
2. Normal (glucose level 40-150 mg/dL): _____mg/dL
    a. Normoglycemia (glucose level 40-150 mg/dL) (1) Yes (2) No
3. Abnormal (glucose level < 40 or > 150 mg/dL): _____mg/dL

a. Hypoglycemia (glucose level <40 mg/dL) (1) Yes (2) No

Hyperglycemia (glucose level > 150mg/dL) (1) Yes (2) No

4. Site for blood collection

a. Heel stick___

b. UAC___

c. UVC____

Preoperative events:

Preoperative acidosis: pH < 7.30 (1) Yes (2) No

Preoperative hypobicarbonatemia: Bicarbonate < 19mEq/L (1) Yes (2) No

Preoperative hypercarbia: PCO2 > 45 mmHg (1) Yes (2) No

Neonatal physiological characteristics

Intraoperative events:

1. Intraoperative hypothermia: <37˚C (1) Yes (2) No
2. Intraoperative desaturation: SaO2 < 90% (1) Yes (2) No
3. Intraoperative acidosis: pH < 7.30 (1) Yes (2) No
4. Intraoperative hypobicarbonatemia: Bicarbonate < 19mEq/L (1) Yes (2) No

5.Intraoperative hypercarbia: PCO2 > 45 mmHg (1) Yes (2) No

Postoperative events:

1.Postoperative acidosis: pH < 7.30 (1) Yes (2) No

2. Postoperative hypobicarbonatemia: Bicarbonate < 19mEq/L (1) Yes (2) No

3. Postoperative hypercarbia: PCO2 > 45 mmHg (1) Yes (2)

4. Postoperative complications during first 24h postoperative period

a. bleeding

b. sepsis

c. Necrotizing enterocolitis

d. Bronchopulmonary dysplasia

e. Pulmonary hypertension

f. Intraventricular hemorrhage

Anesthesia provider resuscitation measures

1. Intraoperative endotracheal tube placement: (1) Yes (2) No
2. Intraoperative crystalloids administration: (1) Dextrose (2) Saline
3. Intraoperative colloids administration: Albumin 2.5% (1) Yes (2) No
4. Intraoperative blood product administration: (1) PRBCs (2) platelets (3) FFP
5. Intraoperative vasopressor administration: (1) Epinephrine (2) Ephedrine (3) Neosynephrine, (4) Dopamine

Anesthesia provider resuscitation measures:

6. Intraoperative anticholinergic administration: (1) Atropine (2) Glycopyrrolate

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