THE USE OF ENTERAL STERILE WATER FOR THE TREATMENT
OF HYPERNATREMIA
IN EXTREMELY LOW BIRTH WEIGHT INFANTS
by
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For the degree of Doctor of Philosophy

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<th>Full Form</th>
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<tbody>
<tr>
<td>ADHD</td>
<td>attention deficit hyperactive disorder</td>
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<tr>
<td>ANP</td>
<td>atrial natriuretic peptide</td>
</tr>
<tr>
<td>BPD</td>
<td>bronchopulmonary dysplasia</td>
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<tr>
<td>COX</td>
<td>cyclo-oxygenase</td>
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<tr>
<td>ECF</td>
<td>extracellular fluid</td>
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<td>ELBW</td>
<td>extremely low birth weight</td>
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<tr>
<td>EMR</td>
<td>electronic medical record</td>
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<td>ESWF</td>
<td>enteral sterile water feeds</td>
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<tr>
<td>FeNa</td>
<td>fractional excretion of sodium</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
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<tr>
<td>GI</td>
<td>gastrointestinal</td>
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<td>IWL</td>
<td>insensible water loss</td>
</tr>
<tr>
<td>IVH</td>
<td>intraventricular hemorrhage</td>
</tr>
<tr>
<td>JGA</td>
<td>juxtaglomerular apparatus</td>
</tr>
<tr>
<td>mEq/L</td>
<td>milliequivalent per liter</td>
</tr>
<tr>
<td>mls/Kg/day</td>
<td>milliliters per kilogram per day</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>NEC</td>
<td>necrotizing enterocolitis</td>
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<tr>
<td>NPO</td>
<td>nothing by mouth</td>
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<tr>
<td>PDA</td>
<td>patent ductus arteriosus</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>RBF</td>
<td>renal blood flow</td>
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<td>RCT</td>
<td>randomized controlled trial</td>
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<td>RDS</td>
<td>respiratory distress syndrome</td>
</tr>
<tr>
<td>RVR</td>
<td>renal vascular resistance</td>
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<tr>
<td>SBP</td>
<td>spontaneous bowel perforation</td>
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<tr>
<td>SBS</td>
<td>short bowel syndrome</td>
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<td>VLBW</td>
<td>very low birth weight</td>
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The Use of Enteral Sterile Water for the Treatment of Hypernatremia in Extremely Low Birth Weight Infants

Abstract

by

AMELIA BIEDA

There has been tremendous improvement in the survival rate of extremely low birth weight (ELBW) infants, but as a result, there are associated morbidities. ELBW infants are vulnerable to electrolyte imbalance, particularly hypernatremia (serum sodium value > 150 mEq/L). There are different approaches in the management of hypernatremia but little consensus as to the optimal approach. Liberal intravenous fluid administration is the standard treatment but is associated with comorbidities such as patent ductus arteriosus, bronchopulmonary dysplasia and intraventricular hemorrhage.

The purpose of this prospective, randomized control trial (N=19) was to examine the use of enteral sterile water feeds as an alternative management strategy on the incidence and duration of hypernatremia; patterns in serum sodium values; magnitude of change in serum sodium values, and the relationship between the onset of hypernatremia and onset of diuresis during the first week of life.
Infants in the study were ≤ 27 weeks gestational age and ≤ 1,100 grams birth weight. The study consisted of three groups: the control group (n=8) who received intravenous fluid; the prophylactic group (n=6) who received enteral sterile water feeds when their serum sodium value was ≥ 145 mEq/L and the intervention group (n=5) who received enteral sterile water feeds when their serum sodium value was ≥ 150 mEq/L.

There were no statistically significant differences in the incidence, duration or magnitude of change in serum sodium values in the three groups; nor were there statistically significant differences in the onset of hypernatremia or diuresis. There were statistically significant differences when analyzing patterns of morning sodium values: from day one to two ($p=.008$) and day one to three ($p=0.015$) and from day three to ($p =0.01$) four and four to five ($p =0.005$). There was a statistically significant increase in sodium values found from day one ($p=.000$) to two and day two to three ($p=.051$).

ELBW infants who received enteral sterile water feeds did not have a decrease in the incidence or duration of hypernatremia when compared to ELBW infants who did not receive ESWF. Since the sample size was small, it was not possible to identify cause and effect relationships among variables.
Chapter 1

Approximately 17,000 extremely low birth weight (ELBW) infants are born each year in the United States (National Vital Statistics Report, 2009). An ELBW infant is defined as less than 1,000 grams birth weight and as less than 27 weeks gestational age (Lissauer & Fanaroff, 2006). Advances in medical technology have significantly improved the survival rate of ELBW infants (Lemons, et al. 2001; Wilson-Costello, Freidman, Minich, Fanaroff & Hack, 2005). Concomitant to increased survival rates of these infants are new fluid and electrolyte problems that have not been encountered previously and are associated with major morbidities.

ELBW infants are vulnerable to electrolyte imbalance due to multiple etiologies such as transepidermal water loss and respiratory distress. Small changes in body water and electrolytes represent large proportional changes in ELBW infants. Extremely low birth weight infants have greater body fluid redistribution (Baumgardt & Costarino, 2000) that occurs over a longer period of time (Shaffer, Quimiro, Anderson & Hall, 1987). Changes in fluid volumes contribute to pathophysiologic events such as patent ductus arteriosus (Stephens, et al., 2008), bronchopulmonary dysplasia (Oh, et al., 2005) and intraventricular hemorrhage (Simmons, Adcock, Bard & Battaglia, 1974; Lim, et al. 2010). It is essential that management protocols be developed that reduce the occurrence of these morbidities.

Consequently, fluid and electrolyte homeostasis is a critical component in the care of extremely low birth weight (ELBW) infants during the first week of life (Modi, 2004; Verma, Shibli, Fang & Kamaroff, 2009). Electrolyte imbalance, particularly hypernatremia (serum sodium > 150 mEq/L) can occur rapidly and can lead to seizures
and intraventricular hemorrhage. Hypernatremia may be due to rapid dehydration or excessive administration of intravenous fluids that contain sodium.

During the first 72 hours of extrauterine life, the majority of infants undergo diuresis, which results in contraction of the extracellular space; and therefore, weight loss. During diuresis the glomerular filtration rate of the kidneys increases rapidly and there is loss of extracellular fluid. This normal physiologic process occurs in order to preserve fluid and electrolyte balance. Due to the loss of extracellular fluid, many ELBW infants develop hypernatremia. In order to bring elevated sodium levels to within a normal range, these infants are given intravenous fluids in excess amounts of normal fluid requirements. Rather than expose ELBW infants to large volumes of intravenous fluids, a current treatment for hypernatremia that has been suggested during the first week of life is enteral sterile water feeds (Gaylord, Lorch, Lorch & Wright, 1995).

Enteral sterile water feeds (ESWF) are theorized as an exogenous source of fluids that may decrease elevated electrolytes such as sodium and potassium in premature infants. By giving enteral sterile water to decrease elevated electrolytes, there would be less need for high volumes of intravenous fluids that contribute to the morbidities of bronchopulmonary dysplasia, necrotizing enterocolitis, patent ductus arteriosus and intraventricular hemorrhage (Oh et al., 2005; Bell, Warburton, Stonestreet & Oh, 1980; Stephens et al., 2008; Simmons, Adcock, Bard & Battaglia, 1974). However, there is little empirical evidence supporting the use of enteral sterile water feeds in ELBW infants and there is no consensus among neonatal intensive care units on the management of hypernatremia.
Two small, randomized, controlled trials that investigated the efficacy of enteral sterile water feeds in the treatment of hypernatremia in ELBW infants have been conducted (Gaylord, et al., 1995; Olney, Huseby, Kennedy & Morris, 2005). Gaylord and associates (1995) found that enteral sterile water feeds decreased the need for large volumes of intravenous (IV) fluids to treat both hypernatremia and hyperkalemia, while Olney and associates (2005) did not find any statistically significant change in hypernatremia levels in infants treated with ESWF compared to controls. Consequently, there has been insufficient research concerning whether enteral sterile water feeds reduce the maximum sodium level or the duration of hypernatremia. Further, it is unknown if the timing of the initiation of enteral sterile water feeds impacts the magnitude and duration of hypernatremia. Consequently, there is insufficient evidence to support this treatment modality. The purpose of this proposed study is to investigate the outcomes of enteral sterile water feedings for the management of hypernatremia in ELBW infants.

Problem Statement

There is no consensus in neonatology concerning the volume of fluid administration that is appropriate for extremely low birth weight infants. There are two major schools of thought. The first requires restriction of total fluids to help preserve respiratory function (Costarino, Gruskay, Corcoran, Polin & Baumgart, 1992; Hartnoll, Bétrémieux & Modi, 2000; Oh et al., 2005) and prevent patent ductus arteriosus (Wyllie, 2003; Stephens et al., 2008). The second school of thought advocates liberal fluid administration related to large insensible water losses, dehydration and compromise of renal function (Bell, 1978).
Research has suggested that large amounts of fluids are associated with morbidities such as patent ductus arteriosus and bronchopulmonary dysplasia (Wyllie, 2003; May & Greenough, 2005). Enteral sterile water feeds has been proposed as a method of decreasing the incidence of hypernatremia by providing exogenous water to premature infants thereby avoiding the use of large volumes of intravenous fluids. The proposed randomized control trial will investigate the outcomes of variation in the timing of the introduction of ESWF to infants including the incidence and duration of hypernatremia as well as the magnitude of change in sodium values.

**Purpose**

The purpose of this study was to compare three different fluid management strategies on serum sodium values over seven days among ELBW infants. Subjects were randomized to three different groups. The purpose of this study was addressed by answering the following research questions:

1. What is the pattern of changes in sodium levels over the first seven days of life?
2. What are the differences in the incidence of hypernatremia between extremely low birth weight infants who receive a) intravenous fluids only, b) infants who receive enteral sterile water feeds beginning at 24 hours of life and c) infants who receive enteral sterile water feeds when hypernatremia is diagnosed?
3. Are there differences in the duration of hypernatremia among extremely low birth weight infants who receive a) intravenous fluids only, b) infants who receive enteral sterile water feeds beginning at 24 hours of life and c) infants who receive enteral sterile water feeds when hypernatremia is diagnosed?
4. What are the differences in the magnitude of change in serum sodium levels among extremely low birth weight infants who receive a) intravenous fluids only, b) infants who receive enteral sterile water feeds beginning at 24 hours of life and c) infants who receive enteral sterile water feeds when hypernatremia is diagnosed?

5. What is the relationship between the time of observed onset of hypernatremia and the timing of observed onset of diuresis among extremely low birth weight infants who a) receive intravenous fluids only, b) infants who receive enteral sterile water feeds beginning at 24 hours of life and c) infants who receive enteral sterile water feeds when hypernatremia is diagnosed?

**Background**

Caring for ELBW infants is a very complex and long-term commitment. In order to understand some of this complexity, the following entities will be discussed: length of stay, cost to society and morbidities associated with ELBW infants.

**Length of Stay and Cost to Society**

Advances in medical care and technology that have contributed to the survival of ELBW infants have not occurred without consequences. The care of ELBW infants puts a tremendous strain on allocation of society’s resources including, but not limited to, long-term hospitalization, developmental follow-up, special education and outpatient medical care (Clements, Barfield, Ayadi and Wilber, 2007). In a retrospective study by St. John, et al. (2000) 958 infants born between 24 and 37 weeks gestation were studied in order to examine hospital and physician costs for their first hospitalization, from birth to discharge home. Eighty (8.4%) of these infants were between 24 and 28 weeks
gestational age. This study demonstrated that as gestational age decreased, costs increased, with longer lengths of stays among surviving infants. Longer lengths of stay in NICU’s have increased approximately 10% over the past 10 years (Kornhauser & Schneiderman, 2010). In St. John’s study (2000), the majority of infants that did not survive expired within the first week of life. The estimated cost for neonates in the United States using this data was approximately $10.2 billion annually. Infants between 24 and 28 weeks gestational age accounted for 11.9% of the cost.

Other more recent studies have shown differences from earlier studies in percentage of total newborn hospital costs. Russell et al. (2007), using data from 2001, found that cost for ELBW infants represented 47% of the $12.4 billion total costs for all term and preterm infant hospitalizations (59% of all pediatric hospital costs), while the Institute of Medicine (2007), using data from 2005, found that societal costs of preterm births was a minimum of $26.2 billion dollars which accounted for infants less than 28 weeks gestational age (6% of preterm births). This dollar amount accounted for 38% of total medical costs for all preterm infants born in 2005 (Table 1). Cost analysis studies have also identified preterm infants less than 1,000 grams accounting for 6-16% of total cost of hospitalizations in infants readmitted during the first year of life (Underwood, Danielsen & Gilbert, 2007; Clements et al., 2007).
Table 1

Hospital Cost and Gestational Age of Infant Hospitalization

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<tr>
<th>Author</th>
<th>Gestational Age</th>
<th>Hospital Costs</th>
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<tr>
<td>St. John et al&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24 weeks</td>
<td>$145,892</td>
</tr>
<tr>
<td></td>
<td>25 weeks</td>
<td>$121,181</td>
</tr>
<tr>
<td></td>
<td>26 weeks</td>
<td>$99,362</td>
</tr>
<tr>
<td></td>
<td>27 weeks</td>
<td>$80,264</td>
</tr>
<tr>
<td>Phibbs &amp; Schmitt&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24 weeks</td>
<td>$222,563</td>
</tr>
<tr>
<td></td>
<td>25 weeks</td>
<td>$233,538</td>
</tr>
<tr>
<td></td>
<td>26 weeks</td>
<td>$207,637</td>
</tr>
<tr>
<td></td>
<td>27 weeks</td>
<td>$178,080</td>
</tr>
<tr>
<td>Russell et al&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;28 weeks</td>
<td>$65,000</td>
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<sup>a</sup> Hospital specific costs  
<sup>b</sup> Based on ICD-9-CM codes at discharge


Length of stay has been identified as the only variable related to costs regardless of survival status of the infant (St. John et al., 2000). Length of stay and hospital costs increase exponentially with a decrease in gestational age (Kilpatrick et al., 1997; St. John et al., 2000; Gilbert et al., 2003; Phibbs & Schmitt, 2006). Two studies have shown similar patterns in length of stay in infants born at 24 to 28 weeks gestational age. (Table 2) In a cohort study conducted in California, Phibbs and Schmitt (2006) demonstrated an average length of stay of 66 days for infants born at 28 weeks gestational age as compared to 57.6 days found by St.John et al. (2000). For infants born at 24 weeks gestational age, Phibbs and Schmitt (2006) found an average length of stay to
be 78.9 days, while St. John and associates (2000) demonstrated an average length of stay of 98.7 days for infants born at 24 weeks gestational age.

Table 2

*Length of Stay by Gestational Age of Infants at Birth*

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<td>79 days</td>
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<td>25 weeks</td>
<td>97 days</td>
<td>83 days</td>
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<td>26 weeks</td>
<td>77 days</td>
<td>82 days</td>
</tr>
<tr>
<td>27 weeks</td>
<td>71 days</td>
<td>75 days</td>
</tr>
<tr>
<td>28 weeks</td>
<td>58 days</td>
<td>66 days</td>
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</table>


The decrease in the length of stay for infants at 24 weeks gestational age may be due to changes in neonatal practice. The data from St. John et al. (2000) is prior to widespread use of antenatal steroid therapy and surfactant therapy resulting in a decreased mortality rate, but without changing the morbidity rate (Kobaly et al., 2008), resulting in longer hospitalizations. One way of decreasing length of stay is to develop evidenced-based management strategies to decrease the incidence of morbidities, as is the purpose of this study.

Research on financial expenditures is confusing due to the different analyses used in studying costs for preterm infant hospitalization, coupled with hospitals’ and health care systems’ unwillingness to share billing information. Despite what is known, the total cost to society of preterm infants’ birth, hospitalizations and long term medical care
remains underestimated. There is little research on cost and length of early intervention services for these infants (Clements et al., 2007) or parental out of pocket expenses and costs related to lost productivity of parents (Institute of Medicine, 2007).

Morbidities such as necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD) and intraventricular hemorrhage (IVH), all of which have been associated with hypernatremia, add an additional monetary burden and subsequent increased length of stay. Russell’s group (2007) demonstrated that 25% of the low birth weight infant group had one or more of the above mentioned morbidities, with BPD the single costliest complication. The economic burden of BPD was demonstrated by Happe and colleagues (2008), who examined 1,754 premature infants diagnosed with BPD between 2006 and 2007. BPD was associated with a mean increase in total cost per patient of $48,303.00 ($p<0.0001).

**Morbidities associated with Extremely Low Birth Weight Infants**

Medical advances in neonatology have resulted in the decreased mortality rate of smaller and lower gestational age infants (Fanaroff, Hack & Walsh, 2003; Wilson-Costello, Friedman, Minich, Fanaroff, & Hack, 2005). The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (Fanaroff et al. 2003) reported decreased mortality at three time periods that were investigated: 1987-1988, 1993-1994 and 1999-2000 (Table 3). These time periods were chosen as they represented changes in treatment modalities which decreased mortality in this population. Surfactant and antenatal corticosteroids have been instrumental in decreasing mortality across the last two time periods.
Table 3

Changes in Mortality Rates by Birth Weight for Three Time Periods

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>501-570 *</td>
<td>66%</td>
<td>51%</td>
<td>45%</td>
</tr>
<tr>
<td>751-1,000 *</td>
<td>34%</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>1,001-1,500**</td>
<td>13%</td>
<td>7%</td>
<td>7%</td>
</tr>
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</table>

* Extremely low birth weight infants  **Low birth weight infants


The first time period (1987-1988) was prior to the use of surfactant for respiratory distress syndrome. During the second time period (1993-1994) surfactant was widely used and there was moderate use of antenatal corticosteroids; the third time period (1999-2000) was identified as the ‘post-surfactant era’ because both surfactant and antenatal corticosteroids were widely used. The overall mortality rate decreased from 23% in 1987-1988 to 17% in 1993-1994 and to 14% in 1999-2000 for premature infants weighing 500 to 1500 grams birth weight. Despite the decrease in mortality rate, the morbidities of necrotizing enterocolitis, patent ductus arteriosus, bronchopulmonary dysplasia and intraventricular hemorrhage did not significantly decrease over time (Fanaroff et al., 2003). These short and long-term morbidities impact length of stay and cost to families and society. Each of these morbidities will be discussed briefly in the following sections.

**Necrotizing enterocolitis.** Necrotizing enterocolitis (NEC) is the process of severe inflammation to the large or small intestine that can lead to bowel necrosis (Bradshaw, 2009). The increased survival of smaller and lower gestational age infants has led to an increase in the incidence of NEC (Henry & Moss, 2004). The incidence of NEC
is approximately 10% in ELBW infants (Fanaroff, Hack & Walsh, 2003) with the disease process primarily occurring in immunocompromised infants (Ladd et al., 1998). Prematurity is the most consistent risk factor in the development of NEC (Chwals et al., 2001; Lee & Polin, 2003).

**Etiology.** Despite research in this area for over 30 years, the etiology of NEC remains unknown and is likely to be multifactorial (Bell, 2005; Institute of Medicine, 2007). Three primary factors identified by Santulli et al., (1975) have continued to be the focus of NEC research. They are: (a) pathogenic bacteria colonization (Lin, Nasr & Stoll, 2008; Neu & Walker, 2011); (b) intestinal ischemia and inflammation (Kosloske, 1984; Henry & Moss, 2004; Martin & Walker, 2006; Lin, et al., 2008) and (c) enteral feedings (Kosloske, 1984; Pietz et al., 2007 Hughes, Baez & McGrath, 2009).

Prematurity is the most consistent risk factor in the development of NEC (Lee & Polin, 2003). Prematurity may result in a delay in and abnormal bacterial colonization of the gut, which may lead to aberrant immunity and initiate an inflammatory response (Gregory et al., 2011). Multiple infectious organisms have been implicated, but no one organism has been identified and it is unclear if a bacterial organism is the primary agent precipitating NEC or if injury to the intestinal mucosa allows a pathway for bacterial invasion (Neu & Walker, 2011). Early molecular research suggests that NEC is altered in premature infants who receive prolonged antibiotic therapy (Neu & Walker, 2011).

Intestinal ischemia and inflammation also contribute to NEC. Intestinal motility does not begin until 30-32 weeks gestational age (Blackburn, 2007). Premature infants are at increased risk for intestinal mucosal injury due to immature digestion, poor motility, poor absorption, immune defenses, intestinal epithelial barrier functions and
circulatory regulation events (Gregory, 2011; Neu & Walker, 2011). This gut immaturity, coupled with events such as hypoperfusion, hypoxia and enteral feedings with formula (Gregory et al., 2011), results in an excessive inflammatory response (Berman & Moss, 2011).

The majority of NEC occurs after the initiation of enteral feedings, primarily formula. Introducing enteral feedings into the intestinal lumen causes disruption of mucosal integrity (Kosloske, 1984), blood flow and gut motility (Lee & Polin, 2003; Pietz, et al, 2007) as the intestines try to reduce the osmolarity of the solution. Although the relationship between enteral feedings and NEC has not been delineated, research suggests that a substrate (formula) entering the gastrointestinal tract coupled with bacteria in the intestinal lumen (Kosloske, 1984) results in an excessive inflammatory response (Neu & Walker, 2011), and plays a role in the mucosal injury seen in NEC.

Human breast milk provides protection against NEC due to its anti-inflammatory and antimicrobial properties (Berman & Moss, 2011). Research indicates that providing small amounts of expressed maternal breast milk feedings decreases the incidence of NEC in preterm infants (Gregory, 2008; Sullivan et al., 2010). The difficulty in this type of research is the multiple variations of substrate: maternal breast milk versus donor breast milk; breast milk versus fortified breast milk with powder, liquids or premature formula and alternating maternal breast milk with premature formula. In a recent study by Sullivan and colleagues (2010), 207 premature infants less than 1,250 grams were randomized to either exclusively breast milk feeds or one that included bovine based human milk fortifier added to the maternal breast milk. Infants that received human milk
only had a significantly lower rate of NEC ($p = 0.002$) and NEC requiring surgery ($p = 0.007$).

**Medical consequences of NEC.** In addition to the disease process itself, NEC in a premature infant may result in multiple complications including prolonged ventilatory support which contributes to bronchopulmonary dysplasia (Ladd et al., 1998; Hintz et al., 2005); excess fluid administration which may result in capillary leak syndrome (‘third-spacing’) and sepsis complications (Ladd et al., 1998) including multiple episodes of sepsis (Cole, Hansen, Higgins, Ziegler & Stoll, 2008). Although many premature infants can be medically managed, a small percent require surgical intervention. As a result, with the decreased mortality rate in ELBW infants, there has been an increase in surgical interventions to treat NEC (Chwals et al., 2001).

**Surgical consequences of NEC.** Surgical intervention is reserved for those infants who require an exploratory laparotomy and/or possible bowel resection due to continuous deterioration despite maximum medical support. However, abdominal surgery in a critically ill infant has a unique set of problems post-operatively. The direct complications of surgery may include intestinal strictures, intra-abdominal abscesses, fistula formation, wound infection and dehiscence (Chwals et al., 2001). In addition, these infants have a higher usage of central venous catheters (Wales et al., 2004) because of the need for long-term total parenteral nutrition. Long-term total parenteral nutrition is often necessary because of the slow refeeding process in premature infants after NEC.

NEC is the most common cause of short bowel syndrome (Wales et al., 2004; Cole et al., 2008). Short bowel syndrome (SBS) is the result of loss of functional bowel that occurs after resection of a portion of the small intestine due to necrosis. The severity
of SBS is dependent on the amount of bowel that is left after resection. SBS may result in chronic malabsorption, dehydration, malnutrition, total parenteral nutrition cholestasis and in some cases, liver failure (Wales et al., 2004).

Complications in ELBW infants with NEC result in increased length of stay. In a case controlled study by Bisquera, Cooper and Berseth (2002), the length of stay for infants with NEC who required surgery was $73 \pm 60$ days ($p=.004$) as compared to infants with NEC who did not require surgery. Infants who had surgery in this study had total hospital charges of $448,000 \pm 210,229$ ($p<.001$). An infant who survived surgical NEC added an additional 60 days to the length of stay and additional hospital charges of $186,200$. The additional 60 day length of stay has also been reported by Cole et al. (2008). This added length of stay is partially due to the long recovery process of NEC. The authors adjusted for inflation, estimating additional hospital charges for NEC alone at $7.2$ million per year. This cost was hospital charges alone and did not include physician fees. According to Neu and Walker (2011), it is estimated that caring for infants with NEC in the United States costs between $500$ million and $1$ billion annually.

**Neurodevelopmental morbidities.** Of immense concern is the association between NEC and an increased risk of neurodevelopmental impairment in ELBW infants (Salhab, Perlman, Silver and Broyles, 2004). The NICHD Neonatal Research Network conducted a multicenter, retrospective study of 124 infants treated surgically for NEC and evaluated them at 18 to 22 months postmenstrual age (Hintz et al., 2005). Infants who required surgery to treat NEC were more likely to have a diagnosis of cystic periventricular leukomalacia and BPD compared to infant controls without NEC. The group of surgical
NEC infants in this study were also more likely to have growth failure in weight ($p=.0006$), length ($p=.003$) and head circumference ($p=.002$) when compared to a control group without NEC. These infants also scored lower on the Mental Developmental Index and the Psychomotor Developmental Index compared to infant controls without NEC. Similar results have been previously reported by Walsh et al. (1989). Sonntag and associates (2000) demonstrated significant delay in neurodevelopmental outcomes, with 55% of infants with NEC severely retarded at 20 months postmenstrual age. However, Sonntag, et al. (2000), did not find changes in growth parameters.

**Bronchopulmonary dysplasia.** Northway and colleagues (1967) first described bronchopulmonary dysplasia (BPD) in a group of premature infants who developed congruent pulmonary changes on chest radiograph after respiratory failure and long-term mechanical ventilation. These changes included atelectasis, pulmonary fibrosis, and smooth muscle hypertrophy in both the airways and pulmonary vasculature (Bancalari & Claure, 2006). This description has been labeled “classic” BPD which is thought to be a result of prolonged mechanical ventilation and prolonged exposure to oxygen.

In the early 1990’s with the advent of postnatal surfactant, increased use of prenatal steroids and improvement in ventilator technology and management, the clinical presentation of BPD changed (Smith et al., 2004). A new form of BPD emerged in small premature infants who initially had little respiratory distress and spent less time mechanically ventilated (Charafeddine, D’Angio & Phelps, 1999; Bancalari, Claure & Sosenko, 2003). Lung changes in this form of BPD include less pulmonary fibrosis, inflammation and smooth muscle hypertrophy (Husain, 1998); increased lung fluid and damage to vascular development (Bancalari & Claure, 2006). These changes were
thought to be consistent with an interruption in lung development rather than barotrauma from mechanical ventilation (Coalson, Winter & deLemos, 1995; Husain, 1998; Bancalari & Claure, 2006) and were labeled the “new” BPD.

Postnatal surfactant therapy has been instrumental in preventing atelectasis, increasing functional residual capacity and improving oxygenation with resultant decreasing time required for mechanical ventilation. However, the use of surfactant has not resulted in a decreased incidence of BPD which occurs in approximately 33% of ELBW infants (Walsh et al., 2006). BPD remains the most common morbidity of ELBW survivors (Lemons et al., 2001; Vohr, Wright, Poole & McDonald, 2005).

**Etiology.** Oxygen toxicity (Philip, 1975) and long-term mechanical ventilation (Jobe & Bancalari, 2001) are contributing factors to the development of BPD. Pre-surfactant studies have demonstrated a strong association between excessive intravenous fluid volumes during the first week of life and less weight loss with diuresis and BPD (VanMarter, Leviton, Allred, Pagano & Kuban, 1990). Pre-surfactant studies have also demonstrated an association between excess sodium intake and BPD (Costarino, Gruskay, Corcoran, Polin, & Baumgart, 1992; Hartnoll, Bétrémieux & Modi, 2000). Therefore, research has strongly suggested that infants, who receive excessive intravenous fluids and or excess sodium, have an increased incidence of BPD. As a result, fluid restriction and judicious use of sodium were introduced into Neonatal Intensive Care Units (NICU).

As stated previously, the majority of infants undergo a normal physiologic postnatal diuresis with an accompanying weight loss, usually during the first 72 hours of life. There is diuresis of extracellular fluid with expansion of fluid in the intracellular
compartment (Bauer et al., 1991). Diuresis may be delayed in infants with respiratory distress syndrome, the precursor to BPD.

Preterm infants have a limited ability to excrete sodium due to tubular function immaturity (Costarino et al., 1992). If preterm infants are given excessive intravenous fluids or sodium, the diuresis and weight loss may not occur (Stonestreet, Bell & Warburton, 1983; Oh et al., 2005; Wadhawan et al., 2007). If diuresis and weight loss do not occur, there may be an increase in fluids in the pulmonary interstitial tissue resulting in decreased lung compliance (Speer, 2006).

In a retrospective analysis of data from a cohort of 1,382 ELBW infants, Oh, et al. (2005) examined fluid intake and weight loss during the first 10 days of life to determine the risk of BPD. Forty-one per cent (N=573) of this cohort of infants developed BPD and 43% (N=585) survived without BPD. The infants who died (16%) or developed BPD had higher total fluids administered (both intravenous and enteral) from day of life two through day of life 10. Oh and associates (2005) demonstrated that higher fluid intake and decreased weight loss was significantly associated with higher risks of BPD ($p=.006$). There was also a significant association with BPD and male gender ($p=.016$); Grade 3-4 IVH ($p<.0001$); NEC ($p<.0001$); PDA ($p=.043$); days on the ventilator ($p<.0001$) and postnatal steroids ($p<.0001$).

There has been a paucity of research investigating hypernatremia and intravenous fluid volumes in the post-surfactant era and there has been no research conducted to study sodium and intravenous fluid volumes as separate entities. Despite the changes in medical management, there appears to be a subset of ELBW infants that still develop hypernatremia. The administration of large amounts of intravenous fluids and excessive
sodium intake which are precursors to hypernatremia may be additional risk factors for the development of BPD (Oh et al., 2005).

**Medical consequences of BPD.** Infants with BPD are susceptible to respiratory infections and have a high rate of rehospitalization during the first year of life. Smith and associates (2004) examined infants less than 33 weeks gestation in a retrospective cohort study. Of the 1,597 infants, 238 (15%) had BPD. Forty-nine per cent (118) of these infants with BPD were rehospitalized during the first year of life compared to infants that did not have BPD. These findings are consistent with previous studies (Cunningham, McMillian & Gross, 1991; Furman et al., 1996).

**Neurodevelopmental morbidities of BPD.** BPD is a major cause of long term morbidity that has resulted in poor neurodevelopmental outcomes (Kobaly et al., 2008). BPD is a significant risk factor in the development of cerebral palsy and is seen in approximately 10% of ELBW infants who develop BPD (Anderson & Doyle, 2006). Infants with BPD have deficits in gross and fine motors skills compared to very low birth weight (VLBW) infants without BPD (Short et al., 2007). Infants with BPD have general cognitive impairment including lower I.Q. and developmental delay (Taylor et al., 1998; Singer et al., 2001; Short et al., 2007; Anderson & Doyle, 2006). As children with BPD get older there is notable attention impairment. In a study conducted by Short et al. (2003), 15% of former VLBW infants with BPD (N=75) were diagnosed with attention deficit hyperactivity disorder (ADHD) by age eight. This percentage was twice that of former VLBW infants without BPD. Research has also demonstrated that as children with BPD get older, many of them have delayed language and speech (Singer et al., 2001; Lewis et al., 2001); visual perceptual deficits (Taylor et al., 1998; Taylor et al., 2004);
problems with basic school performance (Short et al., 2003; Gray et al., 2004) and behavioral problems (Taylor et al., 1998).

**Intraventricular hemorrhage.** Intraventricular hemorrhage (IVH) is bleeding into the fluid-filled areas (ventricles) surrounded by the brain (Blackburn, 2003). IVH is a serious neurologic insult with a high mortality rate that primarily occurs in infants less than 30 weeks gestational age (Ment, 2000). Approximately 20% of premature infants <1500 grams born yearly in the United States develop some grade of IVH (Bassan, Feldman, Limperopoulos et al., 2006). The risk of IVH is inversely proportional to gestational age (Thorpe, Jones, Clark, Knox & Peabody, 2001) and occurs during the first four to five days of life (Ment, 2000). However, the majority of hemorrhages occur in the first 48 hours of life based on cranial ultrasonography (DeVries, 2005).

The original classification system of IVH is based on the work of Papile and colleagues (1978), which graded IVH into four groups: Grade I, is a hemorrhage limited to the subependymal germinal matrix; Grade II is a intraventricular hemorrhage without ventricular dilatation; Grade III is intraventricular hemorrhage with ventricular dilatation; and Grade IV is a periventricular hemorrhagic with blood extending into the brain parenchyma. Grade IV IVH has been described as being equivalent to a periventricular hemorrhagic infarction (Bassan et al., 2006; Dudink, Lequin, Weisglas-Kuperus et al., 2007).

**Etiology.** Risk factors that have been proposed in the development of IVH are decreased superior vena cava flow (Osborn, Evans & Kluckow, 2003); changes in cerebral blood flow with endotracheal suctioning (Perlman & Volpe, 1983; Kaiser, Gauss & Williams, 2008); pneumothorax (Hill, Perlman & Volpe, 1982; Linder et al., 2003) and
gestational age (Gleissner, Jorch & Avenarius, 2000). Other risk factors proposed in the
development of IVH are hypothermia (Gleissner et al., 2000); early onset sepsis (Linder et al., 2003); respiratory distress requiring mechanical ventilation (Vohr & Ment, 1996) and metabolic acidosis (Synnes, Chien, Peliowski, Baboolal & Lee, 2001; Linder et al., 2003).

Cranial ultrasonography and magnetic resonance imaging (MRI) have helped with visualization of IVH and the damage that occurs. However, the exact etiology of IVH has yet to be determined. IVH may be the result of bleeding from the fragile blood vessels in the germinal matrix (Shalak & Perlman, 2002), venous infarction (Dundink et al., 2007) or reperfusion of an area of the brain that has had ischemic injury (Volpe, 1989).

Neurodevelopmental morbidities of IVH. IVH is another cause of long term morbidity in the ELBW infant. The increased survival rates of ELBW, extremely immature infants has resulted in a multitude of research studies investigating neurodevelopmental outcomes because of the disquieting increased rate of neurologic impairment and developmental delay (Wilson-Costello, Friedman, Minich, Fanaroff & Hack, 2005). Premature infants with a history of IVH have increased rates of cerebral palsy, lower IQ scores and decreased educational performance (Sherlock, Anderson, Doyle & the Victorian Infant Collaborative Study Group, 2005). This group of infants also had a higher risk for speech, language, emotional delay and sensory dysfunction in addition to chronic health conditions that extended into early adulthood (Taylor, Minich, Bangart, Filipek & Hack, 2004; Hack, Taylor, Drotar et al. 2005).
In general, the greater the degree of intraventricular hemorrhage, the poorer the neurodevelopmental outcome (Bassan, et al. 2007; Adams-Chapman, Hansen, Stoll & Higgins, 2008; Luu et al. 2009). Although findings are mixed in studies investigating the impact of Grades I and II IVH on neurodevelopmental outcomes, research suggests that these small hemorrhages may cause cognitive dysfunction and should be investigated further (Vasileiadis, et al., 2004; Patra, Wilson-Costello, Taylor, Mercuri-Minich & Hack, 2006).

**Patent ductus arteriosus.** The ductus arteriosus is a connection from the pulmonary artery to the aorta (Gien, 2008). The function of the ductus arteriosus in utero is to divert blood away from the fetal lungs to the systemic circulation (Blackburn, 2003). During adaptation to extrauterine life, functional closure of the ductus arteriosus in term infants usually occurs between 12 and 15 hours after birth (Gien, 2008). In infants ≥ 1,500 grams birth weight, the ductus arteriosus starts to close within 96 hours of birth (Yu, 1993). In infants ≤ 1500 grams, the ductus arteriosus may remain patent beyond 96 hours of life (Koch et al., 2006).

The incidence of a PDA in infants with birth weights between 501 and 750 grams is approximately 49% (Fanaroff et al., 2003) and for infants between 751 to 1,000 grams the incidence is approximately 38% (Lee, et al., 2000). In general, the more premature the infant, the more likely the infant will develop a PDA.

**Etiology.** A patent ductus arteriosus (PDA) is the failure of this connection to close. PDA’s are classified by the size of the ductal opening and the presenting symptomatology of the infant (Skinner, 2001; Noori, et al., 2009). With a PDA, there is increased left- to- right shunting of blood through the ductus arteriosus and
hyperperfusion to the lung parenchyma, resulting in pulmonary edema (Gien, 2008) and decreased lung compliance (Bancalari, Claure & Gonzalez, 2005). These infants usually require prolonged support on mechanical ventilation. The failure of the PDA to close also results in increased blood flow to the left atrium and left ventricle, resulting in left sided heart enlargement and diastolic volume overload (Alverson et al., 1983). Diastolic volume overload may result in decreased perfusion to the kidneys leading to further volume overload and subsequent congestive heart failure. It has been hypothesized that there is a retrograde diastolic flow when blood flows from the mesenteric arteries back into the aorta and through the PDA, resulting in compromised blood flow to the gut, contributing to NEC (Knight, 2001; Dollberg, Luska & Reichman, 2005). Significant left-to-right shunting through the ductus arteriosus may also predispose preterm infants for increased risk of IVH and death (Noori et al., 2009).

As stated previously, ELBW infants have greater insensible water loss and require increased fluid volume to replace the loss. In addition, these infants are usually sicker and require fluid boluses and pressor support for hypotension, resulting in the need for large volumes of intravenous fluids. Only two prospective studies have demonstrated that large amounts of fluid administration may contribute to PDA. In an early study by Bell and associates (1980), 85 infants were divided into high-volume and low-volume groups. Thirty-five infants (41%) in the high-volume fluid group and 9 infants (11%) in the low-volume fluid group developed a PDA ($p < .001$). However, the infants’ in this study were not ELBW and had an average gestational age of 31 and 5/7 weeks.

In a recent single center retrospective study by Stephens, et al. (2008) 204 infants, ≤ 1250 grams birth weight were grouped into low, intermediate and high fluid
groups. The average birth weight was 937 grams (± 191 grams) and the average gestational age was 27 weeks (± 2 weeks). This study demonstrated that intravenous fluids > 150mls/Kg/day during the first three days of life contributed to the risk of PDA, after controlling for gestational age and illness severity.

**Neurodevelopmental morbidities of PDA.** Patent ductus arteriosus (PDA) is a contributing factor to long term morbidities in ELBW infants. Currently, there is debate if whether the morbidities associated with a PDA are due to extreme prematurity of the infants, the treatment modalities used or the shunting through the ductus arteriosus (Madan et al., 2007; Chorne, Leonard, Piecuch & Clyman, 2007).

Two recent studies evaluated neurodevelopmental morbidities. In 2007, the Trial of Indomethacin Prophylaxis in Preterms (TIPP Study) evaluated whether surgical closure of a PDA is a risk factor for BPD, retinopathy of prematurity and neurosensory impairment in ELBW infants (Kabra et al., 2007). This multicenter prospective study (N=426) examined infants with a symptomatic PDA of which 316 received medical therapy only and 110 underwent surgical ligation. Ninety-five infants survived after surgery and 53% (N=50) had neurosensory impairment (cognition), compared with 34% (N=245) who survived after receiving medical treatment (Kabra et al., 2007). Similar findings suggest that surgical treatment of a PDA place ELBW infants at risk for poor neurodevelopmental outcomes.

A large retrospective study conducted by Madan et al. (2009) examined 2,435 ELBW infants with PDA comparing no treatment, medical treatment and surgical treatment. In this group of infants, 135 (6%) were treated surgically. When compared to medical treatment, surgery was associated with an increased risk of neurodevelopmental
impairment (OR 1.54, CI 98.3%. p=.05). However, these findings should be viewed with caution, as infants requiring surgical intervention for NEC are, by definition, sicker than infants with NEC that does not require surgery.

**Hypernatremia in the pediatric population**

Children of all ages are susceptible to hypernatremia, most commonly through a water deficit exceeding a sodium deficit. Newborns, toddlers and children with renal disorders are at a higher risk for hypernatremia (Moritz & Ayus, 2005). Historically, hypernatremia and brain injury in children has been reported in the German medical literature as early as the 1800’s. Descriptive research of hypernatremia in infants began appearing in the mid-20th century (Rapoport, 1947; Weil & Wallace, 1956). The initial impetus to examine the relationship between hypernatremia and IVH derived from the high mortality and morbidity rate in infants and toddlers who developed diarrhea, hypernatremia and subsequently central nervous system (CNS) sequelae.

**Hypernatremia in premature infants.** A retrospective study by Finberg & Harrison (1955) evaluated 81 children diagnosed with hypernatremia over a seven year period and compared them to children with diarrhea who did not have hypernatremia. All of the children were less than two years of age with 65% of the entire group less than five months of age. Sixty-nine of the subjects were admitted to the authors’ institution with diarrhea. Four other subjects were infants in the hospital nursery who developed diarrhea and eight infants who had respiratory infections and hypernatremia. Hypernatremia was defined as a serum sodium value ≥ 150mEq/L. The purpose of this study was to investigate the possibility of a cause and effect between hypernatremia and CNS injury. Sixty of the 69 subjects had hypernatremia on admission while the other nine subjects
developed hypernatremia after admission. The authors observed that the incidence of hypernatremia was greater in the infants that were born prematurely. However, prematurity was not defined and the number of premature infants with hypernatremia was not reported.

This study demonstrated a correlation between hypernatremia and hypernatremic dehydration with CNS injury. As a result of brain cells shrinking from dehydration, the brain may separate from the meninges damaging the bridging (emissary) veins which run between the surface of the brain and the skull (Musapasaoglu, Agildere, Teksam, Tarcan & Gurakan, 2008), resulting in a subdural, subarachnoid or intracranial hemorrhage. Sixty-six per cent of the infants with hypernatremia in this study demonstrated some form of CNS aberration ranging from lethargy and irritability to increased tone, muscle rigidity, muscle twitching and seizure activity. Two infants with hypernatremia had extensive subarachnoid hemorrhage at autopsy and four infants developed severe neurologic sequelae. Permanent brain damage may result if the brain is not able to adapt to a rapid increase in serum sodium (Arieff & Ayus, 1996; Lim et al., 2010).

A contributing factor to hypernatremia in premature infants is the use of sodium bicarbonate. Since the 1950’s, sodium bicarbonate has been a commonly used pharmacologic therapeutic agent for the treatment of metabolic acidosis in premature infants with RDS (Ashner & Poland, 2008). Hypernatremia is a listed adverse effect of sodium bicarbonate infusion (Neofax, 2009) due to the amount of sodium the solution contains. Simmons et al. (1974) became concerned with the incidence of hypernatremia and subsequent IVH as a result of rapid infusions and large volumes (up to eight mEq/Kg/day) of sodium bicarbonate. In this retrospective study, hypernatremia and IVH
decreased after changing hospital practice to restrict the use of sodium bicarbonate.

Before the restriction, 9% of this group of infants (N=238) developed hypernatremia with 34% of the hypernatremic group developing IVH and a subsequent mortality rate of 81%.

In four years after changing clinical practice, by decreasing sodium bicarbonate volume and decreasing the rate of sodium bicarbonate administration, <1% of infants (N=468) in the second group of infants examined developed hypernatremia, with none of the infants in the hypernatremic group developing IVH and there were no deaths. (Table 4) These authors hypothesized that sodium bicarbonate may cause sudden changes in serum osmolality resulting in shifts of water, electrolyte and acid-base balance.

Although this study was disputed (Volpe, 1974; Robertson & Howat, 1975), Simmons’ and colleagues hypothesis (1974) has since been corroborated (van Alfen-van der Velden et al., 2006). Research continues to show a relationship between hypernatremia, hypernatremic dehydration and IVH (Omar, DeCristofaro, Agarwal & LaGamma, 1999; Mocharla, Schhexnayder & Glasier, 1997; Musapasaoglu et al., 2008).
Table 4

*Incidence and Mortality of Infants with Hypernatremia*

<table>
<thead>
<tr>
<th>Year</th>
<th>1966-1967 (n=238)</th>
<th>1970-1971 (n=468)</th>
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<tr>
<td>Hypernatremia</td>
<td>21 (9%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>IVH</td>
<td>25 (34%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Mortality^a</td>
<td>17/21 (81%)</td>
<td>0 (0%)</td>
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^a Infants with hypernatremia

**Summary**

Fluid therapy has been associated with serious long-term morbidities including NEC, BPD, IVH and PDA. Electrolyte balance is a complex and an on-going issue in caring for premature infants. It is essential that treatment modalities be evaluated to improve the management of hypernatremia.

This study examined the effects of ESWF on the incidence, duration and magnitude of hypernatremia in ELBW infants. This study examined the efficacy of sterile water feeds in the management of hypernatremia, which can change practice and consequently reduce the need to use large volumes of intravenous fluids. Lower volumes of intravenous fluids may result in decreased morbidities such as patent ductus arteriosus and bronchopulmonary dysplasia.
Significance to Nursing

Nursing has a primary, essential role in assessing and managing subtle and acute changes in ELBW infants. Nursing assessment of critically ill infants is a complex process. Therefore, it is vital for advanced practice nurses (APNs) to incorporate nursing research at the bedside in order to identify physiologic instability that may result in rapidly occurring electrolyte imbalance. APNs should assimilate the strength of findings from nursing research along with their clinical expertise to make evidence-based decisions in managing their patients.

Nursing research is essential in order to either provide support of current clinical practice or to demonstrate the need to change clinical practice. This research is important to nursing because it will generate new knowledge and facilitate answers to clinical issues that are seen in caring for ELBW infants.

APNs work collaboratively with a team of health care professionals to manage the care of critically ill preterm infants. It is imperative that APNs extend this collaboration with physicians and other members of the health care team in NICUs to facilitate the research process. All APNs are responsible for evaluating research to guide the care of high risk preterm infants as well as to identify further research. Doctorally prepared APNs are in an ideal position to collaborate with the health care team and conduct research that will improve outcomes in this vulnerable population.

Theoretical Framework

The theoretical framework for the proposed randomized controlled trial is based on William Cannon’s theory of physiologic homeostasis (1929). Physiologic homeostasis provides a framework to investigate biological phenomenon (Richmond, Lipton &
Steinschneider, 1962). Cannon conceptualized that the original condition of the human body is a complex open system with continual modulation of the cells and organs. This occurs in order to sustain the dynamic equilibrium of the internal environment.

Cannon (1929) stated the following:

> The coordinated physiologic processes which maintain most of the steady states in the organism are so complex and so peculiar to living beings-involving as they may, the brain and nerves, the heart, lung, kidneys and spleen, all working cooperatively- that I have suggested a special designation for these states, *homeostasis*. The word does not imply something set and immobile, a stagnation. It means a condition-a condition that may vary, but which is relatively constant.

(p. 24)

In constructing this concept, Cannon made it quite clear that the term *homeostasis* does not imply lassitude (Woods & Ramsay, 2007). Cannon has been customarily misinterpreted by biologists who state that homeostasis is constant and has no variability (Yates, 1982).

Cannon did not use the term *equilibria* because he felt that it implied a ‘constant condition’ in a ‘closed system’ (p.24). Cannon identified homeostasis as a continuous exchange of energy and cellular information in an open system. Equilibrium in a biological system occurs only when there is total cell death (Recordati & Bellini, 2004).

Cannon described the exchange of fluids and electrolytes on the most basic, yet complex level- the cellular level. He emphasized that there are conditions, such as the concentration of dissolved substances in the fluid matrix (extracellular fluid) which may affect cellular activity. When internal or external events occur that disrupt the specified
range of the variable in the body, the internal environment has the mechanisms to respond to and restore homeostasis. These mechanisms were later identified in physiology as negative feedback mechanisms (Carpenter, 2004).

The internal physiologic system is unique with a specific role and is well organized. Physiologic homeostasis is controlled by interdependent regulatory mechanisms (Recordati & Bellini, 2004) that contribute to this organization. Cannon included regulatory mechanisms as an integral component of homeostasis (Carpenter, 2004). Cannon was aware that sodium chloride (Figure A) in the plasma was due to “…the type of homeostatic arrangement” (p.96) provided by regulatory mechanisms that directly affected the balance of sodium chloride and water. This is evident in hypernatremia.

Thirst is part of the regulatory mechanism that contributes to fluid balance (McKinley & Johnson, 2004). This mechanism is stimulated by osmoreceptors in the anterior hypothalamus. The purpose of the thirst mechanism is to replace fluids when a deficiency occurs. However, if there is a rapid addition of sodium to the ECF and/ or a profound diuresis, there is a delay or absence of the regulatory response. This has been seen in animal models (Cserr, Depasquale & Patlak, 1987; Yeong-Hau, Shapiro & Chan, 1990). In most animals, the thirst mechanism helps maintain the ECF concentration (Cannon, 1929; Star, 1990). However, ELBW infants are incapable of responding to the thirst mechanism and depend on their caregivers for fluids.

The largest component of the human body is water. In infants between 26 and 31 weeks gestational age, total body water is approximately 80-85% of body weight (Friis-Hansen, 1983). The majority of this water is in the intracellular fluid compartment with
the remainder in the extracellular fluid compartment. The extracellular fluid space is divided into the intravascular (plasma) and the extravascular (interstitial) spaces (Vokes, 1987). If the body loses water, the water is depleted from both the intracellular and extracellular spaces. However, this depletion may not occur in equal proportions from both spaces (McKinley & Johnson, 2004).

Osmoregulation is the control of the level of water and salts in the blood in order to maintain the proper osmotic concentration of body water (Semama, Bouzaine, Allaert & Gouyon, 2001). The physiologic mechanism required for osmoregulation is dependent on properties of the organism and its environment. A primary concept of homeostasis is that the amount of sodium chloride in the body determines the amount of water in the extracellular fluid (Vokes, 1987). When Cannon discussed the human body as a complex open system with fluctuations occurring that help maintain regulation, he was describing what was later identified in biology as negative feedback mechanisms (Carpenter, 2004). These feedback loops or mechanisms are under the control of the neurologic and endocrine system. (Figure A.)

Despite feedback mechanisms to minimize the effects of changes in body fluid volume, fluid losses must be replaced. By giving enteral sterile water feeds, which is a hypotonic solution, there will be less depletion of water from the intracellular into the extracellular space, with less fluid entering the extracellular space and less sodium. In extremely low birth weight infants the negative feedback mechanisms are not completely understood and may be poorly developed (Lorenz, 2008).

The determinants of plasma sodium values are sodium intake and output and water balance (Reynolds & Seckl, 2005). Fluid shifts that occur in ELBW infants are the
Regulation of body water and sodium concentration in the blood

Figure A.

excretion of sodium and water that occur because of contraction of the interstitial space during the first three days of life (Lorenz, Kleinman, Ahmed & Markarian, 1995) before reaching physiologic homeostasis (Lorenz, 2008). The physiologic relationships of postnatal diuresis have been described (Bidwala et al., 1988; Modi et al., 2000) but the basis for this phenomenon is unknown. See Figure B for diagram of conceptual model.

Figure B.

Conceptual Model

IV fluids → Sodium intake → Hypernatremia → Enteral Sterile Water Feeds → Normal serum sodium values

Medications → Hypernatremia → Diuresis
Chapter 2

This chapter will discuss research literature concerning hypernatremia in the premature infant and enteral sterile water feeds in ELBW infants as a treatment modality for hypernatremia. The chapter begins with a section describing renal physiology of the premature infant.

Renal Physiology

The kidney is the primary organ to regulate fluid and electrolyte balance, but has limitations due to immature function when the infant is born prematurely. After birth, the newborn must take over physiologic processes that in utero were predominately a function of the placenta. Consequently, gestational age must be considered in evaluating postnatal renal function (Blackburn, 2003). In an extrauterine environment, there is greater fluctuation of fluid intake and losses than in utero (Lorenz, 2007). During the first week of life, water loss in the ELBW infant are due to contraction of the extracellular space, insensible water loss (IWL) and immature kidney function. It is not uncommon for ELBW infants to lose 10% to 15% of birth weight over two to five days (Shaffer, Quimiro, Anderson & Hall, 1987; Hellerstein, 1993).

Contraction of the extracellular space

The body composition of the ELBW infant is approximately 85-90% water. Approximately two-thirds is extracellular fluid and one-third is intracellular fluid (Hellerstein, 1993). Plasma, interstitial fluid, lymph, connective tissue, bone and transcellular fluid makes up the composition of extracellular fluid (Hellerstein, 1993). Extracellular fluid is approximately 65% of body weight in preterm infants compared to 40% in term infants (Bueva & Guignard, 1994; Modi, 2003). During extrauterine
adaptation, intravascular water initially increases due to redistribution of body water from the interstitial to the vascular space. This shift in fluid between the interstitial and the vascular compartments may be related to withdrawal of maternal hormones resulting in changes in vascular tone or permeability (Blackburn, 2003). Infant kidneys are unable to concentrate urine, resulting in fluid loss and plasma solute concentration. The loss of free water from the vascular compartments produces hyperosmolarity in the vascular system. The intravascular hypervolemia and hyperosmolarity is followed by a physiologic natriuresis and diuresis (Hellerstein, 1993) which increases the sodium level in the body.

**Insensible water loss**

Another source of fluid and electrolyte imbalance in the ELBW infant is through evaporation, primarily through the skin and the respiratory system. Insensible water loss (IWL) is a result of the high surface area to body mass ratio and skin immaturity, notably in infants less than 25 weeks gestation at birth (Lorenz, Kleinman, Ahmed & Markarian, 1995). Evaporation from the skin can contribute up to 70% of IWL in ELBW infants (Baumgart & Costarino, 2000). Table 5 summarizes the sources of IWL. IWL decreases with an increase in gestational and postmenstrual age (Bell & Oh, 1994).

Table 5

**Factors that Influence Insensible Water Loss**

<table>
<thead>
<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>Extreme prematurity</td>
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<tr>
<td>Nonhumidifed oxygen</td>
</tr>
<tr>
<td>Phototherapy</td>
</tr>
<tr>
<td>Respiratory Distress</td>
</tr>
<tr>
<td>Radiant warmers</td>
</tr>
<tr>
<td>Surgical malformations (e.g. gastroschisis)</td>
</tr>
</tbody>
</table>

The epidermal layer that protects against water loss, the stratum corneum, begins development by 18-21 weeks of gestation and is notable on the face, scalp and plantar surfaces of the feet (Agren, Sjörs & Sedin, 1998). By 24 to 25 weeks gestation, the stratum corneum continues developing with complete epidermal development by 34 weeks gestational age (Kalia, Nonato, Lund & Guy, 1998). The epidermal layer is important not only in protecting against water loss, but also protects the infant from bacterial and impedes absorption of medication and cleansing agents such as povidone-iodine (Agren et al., 1998).

**Renal regulation of water and electrolyte balance**

Renal regulation of water and electrolytes is the result of interaction between renal blood flow (RBF), glomerular filtration and tubular function. These three factors are altered in the premature infant, contributing to sodium and water imbalance.

Renal vascular resistance (RVR), which is high initially, begins to diminish as RBF, glomerular filtration rate (GFR) and mean arterial pressure increase (Blackburn, 2003). In preterm infants RVR falls slowly, therefore the increase in the GFR is gradual. However, it is difficult to measure RBF in premature infants; most assumptions are based on animal models (Stefano, 2005). The changes in RBF after birth are due to the development and formation of new glomeruli and vascular remodeling. Autoregulation and hormonal regulation control RBF.

**Renal autoregulation.** Renal autoregulation is a complex phenomenon that prevents abrupt changes in GFR and RBF caused by continuous fluctuations in systemic blood pressure. Renal autoregulation preserves glomerular structure and regulates the
content of sodium chloride and fluid balance (Cuples & Braam, 2007). Renal autoregulation occurs through two mechanisms: the myogenic mechanism and the tubuloglomerular feedback mechanism. The purpose of the myogenic mechanism is to respond to changes in arterial pressure. When pressure is increased, the smooth muscles of the afferent arteriolar vasculature constrict (Holechek, 2003). As a result, there is an increased resistance in both RBF and a decrease in glomerular filtration pressure. In contrast, a decrease in renal perfusion pressure results in relaxation of the afferent arteriolar vasculature with a resultant increased RBF, accompanied by greater glomerular filtration pressure (Figure C).

Figure C

Renal Blood Flow and Glomerular Filtration

**Tubuloglomerular feedback mechanism.** The tubuloglomerular feedback mechanism is a negative feedback mechanism that operates within the juxtaglomerular apparatus (JGA), an anatomic structure at the end of the thick ascending limb of the nephron. Specialized interstitial and renin containing granular cells are located at this site (Arendshort and Navar, 2007). The tubuloglomerular mechanism is activated in the presence of changes in salt concentration and flow in the tubule. In the presence of high levels of salt or low flow at the macula densa, renin is released. The increase secretion of renin activates circulating angiotensin; both act on the arterioles surrounding the glomerulus. The resulting vasoconstriction returns the GFR to normal and stabilizes the salt concentration. Stabilized salt and flow states act to turn off renin secretion (i.e., negative feedback).

In addition to the myogenic and tubuloglomerular feedback mechanisms, autoregulation of renal function is affect by many substances. These substances, classified as hormones are produced either within the kidney or by specialized cells in the cardiovascular and neurohormonal systems.

**Hormonal regulation.** Most hormones affect renal function by acting on systemic or renal blood vessels resulting in either vasodilation or vasoconstriction. These changes in vascular diameter affect blood flow and blood pressure leading to changes in GFR. Vasodilators include atrial natriuretic peptide (and other peptides), nitric oxide, adenosine and bradykinin. Vasoconstrictors include arginine vasopressin, angiotensin II, endothelin and prostaglandins.
**Vasodilators.** Atrial natriuretic peptide (ANP) is a vasoactive natriuretic hormone found in secretory granules in the atrial wall. It has diuretic, natriuretic and vasodilatory effect (Sweeney & Avner, 2004). Although its role has not been clearly delineated, research suggests that ANP plays a role in the regulation of fluid volume by stimulating the excretion of sodium by the kidneys in response to an increase in extracellular volume (Modi, Bétrémieux, Midgley & Hartnoll, 2000). When sodium is excreted natriuresis occurs. Nitric oxide, a vascular endothelium-derived relaxing factor decreases RVR and counteracts excessive vasoconstriction in the premature kidney (Herrera and Garvin, 2005). Adenosine is an intrarenal vasodilator that mediates tubular flow and glomerular filtration rate (Vallon, 2003). It may also play a role in sodium homeostasis during postnatal maturation in the premature infant (Bistritzer, et al., 1999). Bradykinin is a major operative vasodilator that primarily affects pre-tubular renal arteries contributing to an increase in GFR.

Arginine vasopressin, (formerly known as antidiuretic hormone-ADH), is secreted by the posterior pituitary in response to changes in vascular osmolarity and functions as an intrarenal vasoconstrictor. It increases water permeability throughout the collecting ducts; promotes urea permeability in the inner medullary collecting ducts; stimulates active sodium and potassium transport in the cortical collecting ducts and affects the active sodium chloride transport in the thick ascending loop of Henle. Tubular response to arginine vasopressin is decreased in preterm infants (Bonilla-Felix, 2004).

Angiotensin II is the activated form of the potent renal hormone angiotensin I. Renin, released by the juxtamedullary cells in response to renal hypotension, activates Angiotensin I. Angiotensin converting enzyme (ACE) converts Angiotensin I to
Angiotensin II. Angiotensin II contributes to high RVR in the very immature kidney. Angiotensin II stimulates release of aldosterone from the adrenal medullary cells, leading to sodium reabsorption and increased intravascular sodium. Renin and angiotensin II levels subsequently decrease with postnatal age (Gomez, 1998). Immature kidneys have an increased response to angiotensin II, leading to high renal vessel constriction. This hormonal regulation of renal blood flow is known as the renin-angiotensin-aldosterone system.

Endothelin, produced by epithelial cells in most blood vessels, is the second most potent vasoconstrictor peptide (Toth-Heyn, Drukker & Guignard, 2000). It has effects on renal hemodynamic and excretory function. It is elevated during the first few days of life in both term and preterm newborns (Mátyus, et al., 1997).

Prostaglandins are mediators that can either vasodilate (e.g. PGE1, PGE2, and PGI2) or vasoconstrict (e.g. PGF2). Two cyclo-oxygenase (COX) enzymes are present in the kidney: COX-1 and COX-2. These enzymes convert arachadonic acid from cell membranes to different active cell messengers, including prostaglandins. The highest prostaglandin production is in the preterm infant, which decreases with advancing gestational and postmenstrual age (Arant, 1984).

The kallikrein-kinin system modulates RBF. It is involved in the regulation of sodium-water balance, renal vascular resistance and medullary blood flow (Campbell, 2001; Carretero, 2005). The kallikrein-kinin system is also involved in modulating systemic blood pressure and renal blood flow by generating prostaglandins and causing counter-regulation of the vasoconstricting effects of vasopressin.
Glomerular Filtration Rate

The result of renal autoregulation is modification of the glomerular filtrate. Glomerular filtration rate (GFR) is the amount of fluid filtered through all glomeruli in one minute. Changes in GFR at different gestational ages are described in Table 6 (Brion, Fleishman, McCarton & Schwartz, 1986; Bissinger, 1995; Lissauer & Fanaroff, 2006). Initial changes in GFR at birth for all infants are due to the redistribution of placenta blood flow as well as differences in renal blood flow, mean arterial blood pressure, filtration surface area, glomerular permeability and decreased renal vascular resistance (Chevalier, 1996). Nephrogenesis is complete at 36 weeks gestation. Between 36 weeks’

Table 6

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Glomerular Filtration Rate</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 weeks</td>
<td>2</td>
<td>Brion et al.</td>
</tr>
<tr>
<td>28 weeks</td>
<td>10</td>
<td>Lissauer &amp; Fanaroff</td>
</tr>
<tr>
<td>Full term</td>
<td>20</td>
<td>Bissinger</td>
</tr>
</tbody>
</table>

Note. Adapted from “Using Enteral Sterile Water Feeds for Hypernatremia in Extremely Low Birth Weight Infants”, by A. Bieda, D. Dowling and C. Winkelman, 2009, Advances in Neonatal Care, p. 231.

gestation and term, the GFR remains constant due to a stable filtration surface area and then rapidly increases at birth due to vascular changes described previously.

Assessment of GFR is determined clinically by serum creatinine and creatinine clearance. Creatinine clearance (ml/min/1.73m²) is the clearance of creatinine in a volume of plasma or serum in one minute’s excretion of urine. A clinical evaluation of determining approximate GFR in premature infants is by using the Schwartz formula (Brion, et al., 1986).
Estimated GFR = $0.33^k \times \left( \frac{\text{Height [cm]}}{\text{Serum creatinine [ml/min/1.73m^2]} \right}$


$k=$constant 0.33 for premature infants

Creatinine exists in skeletal muscle as creatine phosphate and is a product of muscle metabolism. Creatinine is excreted through glomerular filtration. Creatinine clearance also reflects tubular secretion. The Schwartz formula, devised in the 1970’s estimates GFR using serum creatinine, height and an empirical constant. The purpose of the formula is to determine the rate at which the kidneys are clearing creatinine from the blood. However, these calculations are not always reliable due to inaccuracies of sampling plasma creatinine concentrations in premature infants (Chevalier, 1996), rapidly increasing GFR with postmenstrual growth (Ross, Cowett & Oh, 1997), hydration status of the infant and pathophysiologic events. Due to recent changes in laboratory methods to measure creatinine levels, recent data suggests that this formula may be overestimating GFR (Schwartz et al. 2009).

At birth, creatinine levels in an infant are approximately the same as the mother’s creatinine level (Guignard & Drukker, 1999). The plasma creatinine concentration increases rapidly during the first 48 hours of life in premature infants (Miall, Henderson, Turner & Brownlee, 1999). Gallini and associates (2000) demonstrated that the highest creatinine concentration levels were reached by the third day of life in infants born at 23-25 weeks gestation. In a retrospective study (Auron & Mhanna, 2006), plasma creatinine
levels at birth decreased with increasing gestational age and this decrease is delayed in
infants less than 29 weeks gestational age and less than 1000 grams birth weight.

**Tubular function.** The function of the renal tubules is to modify glomerular
filtrate by transporting water and solutes across the tubular epithelium. The complex cells
of the renal tubule and surrounding blood vessels perform three types of exchange:
reabsorption, secretion and excretion. Tubular reabsorption is the transport of water and
solutes from the tubular lumen to the interstitial fluid or the vasa recta. This exchange
occurs throughout the tubule with over 70% of fluid and sodium returning to the vasa
recta before filtration fluid reaches the distal convoluted tubule. The cells of the renal
tubules distinguish substances essential to fluid equilibrium such as water, glucose,
amino acids and electrolytes, returning these substances to the vascular compartment.
The cells of the renal tubules also contain nonessential substances such as urea, creatinine
and uric acid in the filtrate.

The second type of exchange is secretion. Tubular secretion is the transport of
water and solutes from the capillaries to the tubular lumen. This process removes certain
substances such as hydrogen ions as well as drugs and their metabolites from the plasma
into the filtrate. The third type of exchange is excretion. The conduit of filtrate from the
tubules into the excretery system transports what will ultimately become urine to the
renal ureters and bladder.

**Urine concentration.** The mechanism through which urine is concentrated is
dependent on the counter current multiplier system, which includes the loops of Henle,
the vasa recta, and the collecting tubules. The counter current multiplier system is a
physiologic mechanism that concentrates solutes and regulates water movement. Cells
containing counter current multiplier membranes are found in the renal tubule, with the greatest concentration in the loop of Henle. Sodium, solutes and water move between the tubular lumen, collecting ducts and surrounding interstitial fluid (Blackburn, 2003). The vasa recta acts with the loop of Henle to concentrate solutes in order for the kidneys to excrete concentrated urine. (Figure D)

The premature neonatal kidney has a limited ability to concentrate urine at birth. This increases with gestational and postmenstrual maturation. The limited ability to concentrate urine is primarily related to the immaturity of the distal nephron with a shorter loop of Henle and collecting ducts and immature tubular function (Chevalier, 1996). There is an altered autoregulation via adenosine vasopressin. In addition, premature infants have a limited ability to excrete sodium from the vascular space into the tubules due to tubular function immaturity (Chevalier, 2001). Consequently, these infants are unable to concentrate urine to the degree found in term infants.

**Dilution of urine.** The premature neonatal kidney has the ability to dilute urine. Alterations in the transport of urea change urine concentration through reduced secretion of urea (Bonilla-Felix, 2004). Due to the low GFR in premature infants, there is a decreased ability to excrete a water load with a concurrent solute loss (Blackburn, 2003). Low interstitial fluid also contributes to dilute urine (Costarino, Gruskay, Corcoran, Polin, & Baumgart 1992).

**Fluid and Electrolyte Balance**

The neonatal kidney undergoes three phases during the first week of extrauterine life to preserve fluid and electrolyte balance: a) prediuretic; b) diuretic; and c) postdiuretic (Lorenz, Kleinman, Ahmed & Markarian, 1995). The prediuretic phase is the
first 24 to 36 hours of life in a preterm infant. Independent of fluid and sodium intake, there may be a temporary increase in GFR followed by a decrease in GFR with oliguria (Brion, Bernstein & Spitzer, 1997). In the diuretic phase, GFR increases rapidly with diuresis and natriuresis. Natriuresis during this phase is a result of mobilization of extracellular fluid that is greater in the preterm infant in comparison to the term infant (Auron & Mhanna, 2006). During this phase there is negative water and sodium balance. In the postdiuretic phase between four and five days of life, GFR increases with renal

---

maturation and intake (Lorenz et al., 1995). After these phases, the intake and output of fluids and electrolytes are approximated.

**Sodium balance.** The infant has a poor renal response to a sodium load because of low GFR and high fractional tubular reabsorption of sodium. The premature kidney also has a decreased ability to conserve sodium due to a limited response of the tubules to aldosterone. Most of the RBF in the premature infant goes to the renal medulla that focuses on retaining sodium. The renal cortex, after birth, plays a greater role in regulating sodium. After birth, the fractional excretion of sodium (Fe\textsubscript{Na}) is dependent on gestational age. The Fe\textsubscript{Na} is higher in the newborn infant because of tubular immaturity and intravascular volume expansion. Very low birth weight infants have higher Fe\textsubscript{Na} than term infants. The higher the Fe\textsubscript{Na}, the more sodium is excreted in the urine. The Fe\textsubscript{Na} is an indirect but efficient indicator of tubular function. However, this formula is less reliable with decreasing gestational age. Calculation of the Fe\textsubscript{Na} is used to differentiate prerenal from intrinsic renal failure.

Fractional excretion of sodium calculation:

\[
\text{Fe}_{\text{Na}} = \left( \frac{\text{Urine sodium}}{\text{Serum sodium}} \right) \times \left( \frac{\text{Serum creatinine}}{\text{Urine creatinine}} \right) \times 100
\]

The rapidly changing GFR with normal growth of the infant must be considered when determining the Fe\textsubscript{Na}. In ELBW infants, maturation of tubular function is prolonged if there is fluid and electrolyte imbalance (Al-Dahhan, Haycock, Chantler and Stimmler, 1983). The ELBW infant is at risk for several types of electrolyte imbalances. One common imbalance relevant to this review of renal physiology is hypernatremia.
**Hypernatremia.** The definition of hypernatremia varies from a serum sodium concentration $\geq 145$ mEq/L to greater than 160 mEq/L (Blackburn, 2003; Brion et al., 1997). The serum values for hypernatremia vary among hospitals laboratories with ranges from 150-170mEq/L (Howanitz & Howanitz, 2007). As a result, management of hypernatremia during the first week of life is dependent on the institution’s specific definition of hypernatremia. ELBW infants are at increased risk for hypernatremia during the first week of life. Risk for hypernatremia and the morbidities associated with it have been reviewed in chapter one.

*Management of hypernatremia.* The management of hypernatremia has been to increase intravenous fluids or to reduce the amount of sodium in intravenous fluids (Moritz & Ayus, 2005). There must be consideration of an infant’s weight, electrolytes and pathologic conditions such as PDA or respiratory distress syndrome (Rose, 1994). Despite knowledge of the effects of ambient air temperature, insensible water loss, and advances in neonatal nutrition, the management of hypernatremia remains a combination of experience and intuition. The use of enteral sterile water feeds in the treatment of hypernatremia in low birth weight infants has added to the confusion. Well designed research is imperative to demonstrate if the use of ESWF is an effective treatment modality.

*Hypernatremia studies.* Two retrospective studies (Table 7) have described hypernatremia in premature infants. The study by Harkavy & Scanlon (1983) included 25 very low birth weight premature infants (<1,250 grams birth weight) who developed hypernatremia (serum sodium value >150mEq/L) in the first 39 hours of life. This study determined that there was a negative relationship between weight change and serum
sodium values with sodium values increasing as infants lost weight. However, this finding was not statistically significant. Gawlowski, Aladangady & Coen, (2006) described 46 ELBW infants less than 27 weeks gestational age at birth who developed hypernatremia, defined as a serum sodium >145mmol/L in the first five days of life. This study demonstrated that compared to the control group of infants who did not develop hypernatremia, infants with hypernatremia subsequently had an increase in the incidence of bronchopulmonary dysplasia, patent ductus arteriosus, intraventricular hemorrhage and necrotizing enterocolitis were examined. However, the results were not statistically significant.

Both of these retrospective studies defined hypernatremia differently and examined different variables for different durations as presented in Table 7. Methodological problems in both of these studies included small sample sizes and no identification of confounding variables. In Harkavy and Scanlon’s study (1983) data (chart records) were missing in 12% of the participants and were excluded from the study.

**Enteral sterile water feeding studies.** There are limited data concerning the effects of enteral sterile water feedings (ESWF) on the outcomes of hypernatremia in ELBW infants. The lack of data is due to the paucity of research and mixed results. The initial impetus to investigate the use of sterile water feedings as a therapy was based on an abstract by Gaylord, Lorch, Lorch and Wright in 1992. These authors postulated that feeding premature infants’ sterile water would decrease elevated electrolyte levels such as potassium. Gaylord and associates found that ESWF also decreased sodium levels.
Table 7

Comparison of Hypernatremia Studies

<table>
<thead>
<tr>
<th>Authors/Year</th>
<th>Definition of Hypernatremia</th>
<th>Variables Studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harkavy &amp; Scanlon (1983)</td>
<td>Serum sodium value &gt; 150 mEq/L in the first 39 hours of life</td>
<td>Fluid &amp; sodium intake, NaHCO3 administration, Weight loss, Time under radiant warmer</td>
</tr>
<tr>
<td>Gawlowski, Aladangady &amp; Coen (2006)</td>
<td>Serum sodium value &gt; 145 mEq/L in the first 120 hours of life</td>
<td>Fluid &amp; sodium intake, NaHCO3 administration, Weight loss, Time under radiant warmer, BPD, IVH, NEC, PDA, Phototheraphy, Uree output</td>
</tr>
</tbody>
</table>


Three subsequent studies (Table 8) over the next 17 years, investigated the use of ESWF for the treatment of hypernatremia in infants. All three studies included infants less than or equal to 1,000 grams birth weight. Gaylord, Lorch, Lorch and Wright (1995) and Olney, Huseby, Kennedy and Morris (2005) evaluated the use of ESWF for the treatment of hypernatremia. In 2009, a larger study conducted by Stewart, Morris, Huseby, Kennedy and Moya investigated the use of ESWF for hypernatremia and whether the treatment modality decreased the incidence of patent ductus arteriosus (PDA).
Table 8

Summary of ESWF Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Methods</th>
<th>Findings</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaylord, et al. (1995)</td>
<td>N= 30 10 treated infants 20 historical controls</td>
<td>Retrospective Rescue ESWF in 10 infants vs 20 controls given standard fluid management</td>
<td>Improved electrolyte balance and a decrease in hyperkalemia ($p&lt;0.05$)</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Olney, et al. (2005)</td>
<td>N= 60 &lt;30 wks gestation ≤1,000g birth weight</td>
<td>RCT 10-30 mls/Kg/d ESWF and IVF for 7 days or standard fluid management</td>
<td>No difference in incidence of hypernatremia. Significant reduction in treated PDA in the ESWF group ($p=0.02$)</td>
<td>Lack of control of confounding variables</td>
</tr>
<tr>
<td>Stewart, et al. (2009)</td>
<td>N= 214 &lt;31 wks gestation ≤1,000g birth weight</td>
<td>RCT 10-50 mls/Kg/day ESWF and IVF for 7 days or standard fluid management</td>
<td>ESWF did not reduce incidence of PDA. No adverse outcomes from using ESWF</td>
<td>Interruption of ESWFs in 80% of infants</td>
</tr>
</tbody>
</table>


The retrospective study (N=30) conducted by Gaylord et al, (1995) hypothesized that if sterile water feeds began in the first 24 hours of life there would be improvement in water balance and lower serum sodium and potassium levels, thus preventing hypernatremia and hyperkalemia. Ten ELBW infants received enteral sterile water feeds
of 10-33% of the total fluid intake and were compared to twenty historical control infants with standard fluid management. Gaylord found a statistically significant decrease in both potassium \( p<0.05 \) the first three days of life and creatinine \( p<0.05 \) the first seven days of life. Infants who received the ESWF had significantly lower sodium levels on the third day of life \( p=.015 \) and the fourth day of life \( p=.003 \) compared to the infants who did not receive the ESWF. This study also reported increased urine output for infants receiving sterile water feeds, without receiving an increase in intravenous fluids. They concluded that ESWF were safe, because they did not observe any gastrointestinal complications and the use of enteral sterile water feeds decreased the sodium levels, daily serum creatinine level and the incidence of hyperkalemia.

In 2005, Olney et al. conducted a randomized controlled trial (RCT) to investigate the use of enteral sterile water feeds for the management of hypernatremia in ELBW infants. These researchers hypothesized that ESWF would decrease the incidence of hypernatremia and hyperkalemia in addition to hyperglycemia and hyperbilirubinemia. In this study, 60 ELBW infants were prospectively randomized into two groups. The intervention group received 10 to 30mls/Kg/day of ESWF if their intravenous fluid requirement was \( \geq 120 \) mls/Kg/day for seven days, with total fluids at 150mls/Kg/day. If this group of infants required \( \geq 150 \) mls/Kg/day, the next additional fluid added was intravenous fluid. The control group received conventional IV fluid management as was the standard in their NICU. In contrast to Gaylord et al. (1995), there were no statistically significant differences in the incidence of hypernatremia, hyperkalemia, hyperglycemia or hyperbilirubinemia for infants who received ESWF compared to those who received intravenous fluids. The small sample size and lack of control of confounding variables
are two of the methodological problems found in this study. The investigators however reported an unexpected finding of a reduction in the incidence of treated PDA in the infants who received ESWF ($p<0.05$). Olney et al. (2005) concluded that there were no differences in the outcomes of those infants who were treated with enteral sterile water feeds and intravenous fluids for hypernatremia and those infants who received intravenous fluid therapy for hypernatremia.

The subsequent study by Stewart et al. (2009) investigated whether ELBW infants who received ESWF had a reduction in treated PDA and also addressed the tolerance and safety of ESWF with a larger sample size obtained over a one year period. Two hundred and fourteen ELBW infants were randomized by 36 hours of age to receive up to 50 mls/Kg/day of ESWF per day, included in total fluids. This group of infants (N=109) received this intervention for seven days. The control group (N=105) received seven days of routine fluid management per their division’s protocol. Fluid and sodium intake were adjusted to maintain serum sodium levels between 135 and 145 mEq per 100 ml in the control group. If the total fluids per day needed to be increased, it was done by increasing the amount of intravenous fluids.

In the intervention group, intravenous fluids were given at 80 mls/Kg/day with ESWF. The maximum amount of ESWF was 50mls/Kg/day in order to provide total fluids of 130 mls/Kg/day. If an increase in total fluids was needed beyond 130, then the intravenous fluids were increased. All infants enrolled in this RCT were kept in radiant warmers and covered with clear plastic wrap for the seven days of the study to reduce insensible water loss and maintain body temperature.
This study demonstrated that there were no differences between groups in the outcome of treated PDA before 28 days of life (Intervention 64% vs. Control group 63%). The incidence of treated PDA was comparable to their previous study (Olney et al. 2005). The discrepancy in findings between 2009 and 2005 may have been a result of the lower ml/Kg/day of ESWF volumes used in the 2005 study, the small sample size or that the statistically significant finding of treated PDA using ESWF was a secondary occurrence.

**Summary of ESWF Studies.** Both Gaylord’s retrospective study (1995) and the RCT conducted by Olney et al., (2005) demonstrated no differences in serum sodium levels whether the infants received enteral sterile water feeds or not. Infants in both studies who received ESWF received smaller volumes of intravenous fluids. Gaylord’s group determined that there were no differences found in the incidence of PDA, while Olney demonstrated a statistically significant decrease in the incidence of treated PDA ($p <0.05$) in those infants who received enteral sterile water feedings. The study conducted by Stewart et al. (2009) was not conducted primarily to evaluate the use of ESWF for hypernatremia in ELBW infants; it did support that there were no major adverse outcomes associated with its use.

The methods used in these three studies were different. In Gaylord et al. (1995) retrospective study, enteral sterile water feeds were initiated before 24 hours of life and total fluid volume was adjusted to maintain urine output of 2mls/Kg/hr. Enteral sterile water feeds were given for seven days at 10-33% of total fluids based on the infant’s weight. Historical control infants were used, which is a limitation of the study. In the RCT (Olney et al, 2005) the intervention group received enteral sterile water feeds for the
first seven days of life if their total fluid requirement was > 120 mls/Kg/day. If the total fluid volume needed to be decreased, the intravenous fluids were decreased to 150 mls/Kg/day and the enteral sterile water feeds were decreased.

The study by Stewart et al. (2009) used larger volumes of ESWF than Olney et al. (2005). Olney commented that NEC was a theoretical concern, but the use of sterile water feeds was safe for further studies. Stewart and colleagues stated that using the larger volume of ESWF had no effect on the incidence of NEC.

The current study addressed the limitations of the previous studies. It examined the relationship between the timing of the initiation of ESWF on serum sodium levels as well as the duration and magnitude of hypernatremia. The results of this study will indicate that large volumes of intravenous fluids may not be needed to treat hypernatremia. Introducing exogenous enteral sterile water feeds may be an alternative method that may decrease the incidence, duration and severity of hypernatremia.

**Gastrointestinal Tolerance and Safety**

The gastrointestinal (GI) tract digests, absorbs and distributes nutrients to the cells in order to provide energy and promote growth. However, in premature infants, the GI system is limited both functionally and physiologically (Commare & Tappenden, 2007). Due to these limitations, premature infants are at risk for dehydration and electrolyte imbalance (Blackburn, 2007).

**Fetal GI Tract.** The fetal GI tract is similar in form and structure for both term newborns and extremely preterm infants. The function of the GI tract includes suck-swallow coordination, gastroesophageal sphincter tone, gastric emptying and intestinal motility. However, infants born extremely premature have lower esophageal tone; lack
coordination of suck, swallow and breathing (Blackburn, 2007); have delayed gastric emptying (Mezzacappa & Collares, 2005; Neu, 2007) and functional dysmotility (Berseth, 2005; Neu, 2007).

**Functional Motility.** Functional motility is the movement of nutrients through the GI tract (Berseth, Nordyke, Valdes, Furlow & Go, 1992) and is a well-organized mechanism that starts to develop at approximately 29 to 32 weeks gestational age (Blackburn, 2007; Neu, 2007). Functional motility is regulated by the enteric nervous system and endocrine system (Berseth, et al., 1992). Due to the innate immaturity of the enteric nervous system there is delayed processing of food in the stomach and prolonged transit time of nutrients in the upper intestine (Neu, 2007). This is in addition to the immaturity of the intestinal musculature and segmental peristalsis (Blackburn, 2007) complicating digestion and absorption.

The stomach has little permeability to water, but the small intestine is highly permeable to water. Water from the small intestine is transported down the osmotic gradient. The principle determinant of the osmotic gradient in the small intestine is active transport of sodium ions. Chloride ions are absorbed passively down the electrochemical gradient due to sodium reabsorption. Sodium transport occurs throughout the length of the small intestine, with the highest transport of sodium occurring in the duodenum and the lowest in the ileum (Blackburn, 2007).

The functional motility of the GI tract changes in response to water feeds. In a study by Berseth and colleagues (1992), 58 infants were evaluated to examine GI motor activity response to feeding. These infants, 27 to 33 weeks gestational age at birth, were randomly assigned to water or formula feedings. The infants were fed 4 mls/Kg of sterile
water or Similac® formula intraduodenally via a motility feeding tube over two hours by continuous infusion on the fourth day of life. All the infants had been NPO since birth. Motor activity of the intestines was measured using a neonatal manometric system that had been previously validated (Amarnath, et al., 1989). This study demonstrated that preterm infants who were given either water or formula had increased motility indices ($p=0.001$) and decreased periods of inactivity ($p=0.02$) during feeds as compared to fasting. These findings suggested that the very immature intestine can respond to feeding and early feeding may enhance maturation of small bowel motility and improve feeding tolerance.

**Enteral Sterile Water Feeds.** Hypernatremia can represent a water deficit in relation to the amount of sodium content in the body. The study introduced sterile water feeds of 10 mLs/Kg/day via continuous infusion. Giving water by continuous infusion prevents feeding complications and reduces the potential of sudden sodium shifts in fluid compartments. Sterile water is hypotonic and the more hypotonic the fluid, the less volume of fluid is needed to dilute serum hypernatremia (Adrogué & Madias, 2000). Continuous infusions feeds are also preferred because the majority of extremely low birth weight infants have delayed gastric emptying and are not physiologically able to tolerate a bolus feed (Neu & Zhang, 2005).

**Safety of Enteral Sterile Water Feeds.** Few studies have examined the safety of enteral sterile water feeds. A retrospective study by Huston et al. (2007) evaluated the potential for intestinal morbidity in ELBW infants during the first two weeks of life who received ESWF for the treatment of hypernatremia. Retrospectively, infants were divided into three groups. The first group (N=188) were ELBW infants with serum
sodium values < 150 who were normal controls; the second group (N=100) were ELBW infants with sodium values ≥ 150 that were not treated with sterile water and the third group (N=33) were ELBW infants with sodium values ≥ 150 who were treated with enteral sterile water feeds. Huston showed an increased incidence of necrotizing enterocolitis (NEC) and spontaneous bowel perforation (SBP) in the group of infants who received ESWF for the treatment of a serum sodium value ≥ 150. There were statistically significant differences between the group of infants who were fed sterile water for a sodium value ≥ 150, the group of infants who had sodium values ≥ 150 and were not treated with sterile water feeds (p<0.01) and the group of infants who had normal sodium values (p <0.01). The incidence of intestinal morbidity was significantly higher in the high sodium sterile water fed treated group compared to each of the other groups: 13/33 (38%) for high serum sodium value-water treated group verses 16/100 (16%) for the high serum sodium value, not treated group and 18/188 (10%) for the control group. The authors concluded that there was an association between enteral water feeds for the treatment of hypernatremia and intestinal morbidity without controlling for covariates such as lower gestational age and birth weight in the group that received ESWF. In addition, the infants in the group who received ESFW were given different volumes of sterile water, with 19 receiving boluses of 10mls/kg/dose over one hour and ten receiving two to four boluses of indeterminate volume over one hour. Four infants received continuous infusion of 10-30mls/Kg/day over 24 hours. One infant received a 50mls/Kg/dose over 48 hours. The day of life that the feeds were initiated was not reported. Thus, there was a wide variability in the ESWF intervention that occurred, further confounding the findings.
The authors examined intestinal morbidity over a two week time frame. Fifty-four per cent of the infants who had hypernatremia and received ESWF (N=33) were diagnosed with either NEC or SBP while receiving nothing by mouth. Withholding enteral nutrition may have indicated a preceding or underlying gastrointestinal (GI) pathology. Furthermore, 76% of these infants received indomethacin to close a PDA and 45% received hydrocortisone. These powerful medications indicate a high degree of acuity and may have contributed to GI pathology as both medications are associated with NEC and SBP (Fujii, et al. 2002; Aucott, 2005) or the synergistic combination of the two (Gordon & Attridge, 2009). Forty-six per cent received either maternal breast milk, maternal breast milk with a human milk fortifier or a preterm formula at the time of diagnosis of NEC or SBP. (Table 9) In addition to the medications described above, studies have shown that there is a relationship between NEC and feeding premature infants fortified breast milk or formula (Hughes, Baez & McGrath, 2009).

Table 9

*Intestinal Morbidity*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Group (N=188)</th>
<th>High Na group&lt;sup&gt;a&lt;/sup&gt; not treated (N=100)</th>
<th>High Na group&lt;sup&gt;a&lt;/sup&gt; Treated (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed NEC/SBP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 (4%)</td>
<td>10 (10%)</td>
<td>5 (15%)</td>
</tr>
<tr>
<td>Probable NEC/SBP</td>
<td>11 (6%)</td>
<td>6 (6%)</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>29 (15%)</td>
<td>28 (28%)</td>
<td>15 (45%)</td>
</tr>
</tbody>
</table>


<sup>a</sup> Na = sodium

<sup>b</sup> SBP = spontaneous bowel perforation
Seven infants (4%) in the group of infants with normal sodium values had confirmed NEC or SBP and 11 (6%) had probable NEC or SBP while infants in the high sodium group who did not receive ESWF, ten (10%) had confirmed NEC/SBP and six (6%) had probable NEC/SBP. The authors reported a higher incidence in the use of hydrocortisone earlier in the group who received the ESWF (45%), but it was not statistically significant. However, there is research demonstrating a possible relationship between hydrocortisone and GI perforation (Watterberg, et al., 2004; Aucott, 2005).

In conclusion, there is very little empirical evidence supporting or refuting the use of enteral sterile water feedings in ELBW infants for the treatment of hypernatremia. Only two randomized controlled trial (RCT) and one retrospective study have investigated this issue all with differences in methodology. None of the studies addressed the length of hypernatremia or the highest levels of hypernatremia resulting in a significant gap in the literature. This current study is different from Olney et al. (2005) RCT in that it determined the relationship between enteral sterile water feeds, its effect on elevated sodium levels, the timing of the intervention and controlled for more confounding variables.
Chapter 3

The purpose of this study was to compare three different fluid management strategies on serum sodium values over seven days among ELBW infants. This study examined the administration of enteral sterile water feedings to ELBW infants. This chapter described the study design, sampling method, threats to validity, instrumentation and the collection methods that were used in the study. Protection of human rights in a vulnerable population is discussed.

Research Design

The research design for the study was a prospective, repeated measures, non-blinded randomized clinical trial that determined the (a) the changes in sodium levels over the first six days of life (b) the effect of the timing of the introduction of enteral sterile water feeds on the incidence of hypernatremia (c) the effect of the timing of the introduction of enteral sterile water feeds on the duration of hypernatremia (d) the effect of the timing of the introduction of enteral sterile water feeds on the magnitude of change in serum sodium levels (e) a relationship between the timing of the observed onset of diuresis and serum sodium values and (f) the relationship between the timing of diuresis and the magnitude of change in serum sodium levels. The hypothesis for this study was: enteral sterile water feeds will prevent increases in serum sodium values and will reduce the incidence, duration and magnitude of hypernatremia.

The study had three groups of research participants. The first group was the control group who received intravenous fluids only. Infants less than 1,100 grams are given 100 mls/Kg/day of IV fluids on admission to the NICU. Infants in this group who developed hypernatremia received increased intravenous fluids per unit policy and did
not receive ESWF. The second group of infants received ESWF starting at 24 hours of life or after, if their sodium value was \( \geq 145 \text{ mEq} \) (prophylactic group). The third group of infants received ESWF when their sodium value was \( \geq 150 \text{ mEq} \) (intervention group). The definition of hypernatremia used in this study was a serum sodium value of \( \geq 150 \text{ mEq/L} \). Both the second and third group of infants received 10 mls/Kg/day of enteral sterile water based on birth weight. The volume of ESWF was included in the infants’ daily fluid requirements. Serum sodium values and fluid intake and output were documented every 12 hours for the first week of life, starting on admission.

The randomized controlled trial (RCT) was designed to examine both the effect of ESWF on the timing of the intervention and the effectiveness of the intervention. A RCT includes the most control of extraneous variables (Shadish, Cook & Campbell, 2002). Randomly assigning the intervention eliminated the influence of confounding variables. Analysis of the data will demonstrate the effects, if any, on the magnitude, duration and changes in serum sodium values.

**Internal validity**

Threats to internal validity of the study were identified. The first was maturation (Shadish, Cook & Campbell, 2002), or natural occurring changes that take place without treatment. Each 24 hours of life attained by premature infants’ results in one more day of physical/developmental maturation. Maturation is a normal physiologic phenomenon and will be controlled through the inclusion of a control group.

The second threat to internal validity was attrition (experimental mortality). Attrition is failure of enrolled subjects to complete the research study (Shadish, Cook & Campbell, 2002). Attrition in this vulnerable population may occur due to a variety of
reasons, including profound physiologic instability of the infants’ condition or death. If attrition occurred, recruitment continued until the necessary sample size was achieved. The third threat to internal validity was problems with adequate control conditions (Fogg & Gross, 2000). These changes were partially rectified by examining data for associative relationships of variables that were concerning (Shadish, Cook & Campbell, 2002). If the infant developed hypernatremia, it is possible that the collaborative team could initiate enteral sterile water feeds despite an infant’s enrollment in the control group. The study by Olney and associates (2005) addressed this problem by using intent-to-treat analysis in which all research participants randomized are included in the analysis (Shadish, Cook and Campbell, 2002). Intent-to-treat analysis is highly controversial because it may underestimate the treatment effect (Grady, Cummings & Hulley, 2007). If treatments outside of the planned intervention occurred, data were analyzed separately.

Setting

The research study was conducted in the Neonatal Intensive Care Unit (NICU) at Rainbow Babies and Children’s Hospital, Case Medical Center, University Hospitals of Cleveland. Rainbow Babies and Children’s Hospital is an inner city 250 bed children’s hospital with a 38 bed private room NICU and 44 bed NICU step-down/transitional care unit. The NICU staff consists of 17 neonatologists, nine neonatal fellows, 22 neonatal nurse practitioners (NNPs) and 130 registered nurses (RNs). In addition, the NICU has pediatric respiratory therapists, patient care assistants and a dedicated pharmacologist and dietician. Infants in the NICU are managed by two teams of collaborating health care professionals, each composed of a neonatologist, neonatal fellow, one intern, one or two residents, one senior resident and one or two neonatal nurse practitioners. The NICU is a
tertiary referral center for high-risk neonates in northern Ohio and western Pennsylvania.
This hospital was chosen because of its size and demographic structure.

Sample

The sample consisted of preterm infants who met the following inclusion criteria:
(a) less than or equal to 1,100 grams birth weight and (b) less than or equal to 27 weeks
   gestational age at birth. Birth weights of the infants were obtained in the delivery room
   and the infants were reweighed in the NICU on admission. If differences in the weights
   between the delivery room and the NICU occurred, the weight obtained in the NICU was
   used as the birth weight. Birth weight has greater accuracy and precision than gestational
   age (Platt, et al., 2002).

   Exclusion criteria were ELBW infants with (a) congenital heart disease other than
   a patent ductus arteriosus (b) major congenital anomalies (c) a surgical condition (d)
   renal disease (e) hypotension treated with pressor support (f) if emergency medications
   were received in the delivery room other than fluid boluses (g) reverse end diastolic flow
   (h) initial pH <7.2 on the first arterial blood gas and (i) a five minute Apgar score of less
   than five. The first six exclusion criteria were chosen because these groups of infants
   may not receive standard intravenous fluids on admission. Consequently, enrolling these
   groups of infants would have resulted in confounding variables that would not enable the
   study to distinguish between changes that occur as a result of the study intervention and
   changes that occur because of outside influences. The last three exclusion criteria were
   added by the IRB.
Power analysis

Sample size was calculated using G* Power 3.0 (Faul, Erdfelder, Lang, & Buchner, 2007) and entering an a priori effect size of 0.5, power level of 0.80 and a one-tailed alpha (α) of 0.05. For a repeated measures analysis of variance (ANOVA), three groups (one control group and two intervention groups) and five repetitions were entered into the program. An initial sample size of the total number for analysis was calculated at 27. An α of 0.05 indicates there is a 5% possibility that differences in the two intervention groups has occurred as a result of chance rather than as a result of the study intervention. By using repeated measures, there was an increase in the number of time points a response variable was collected, thereby increasing power. Olney et al. (2005) used an effect size of 0.8.

For this study, a more conservative estimate was used and an effect size of 0.5 was chosen. The effect size provided an estimate of the strength or magnitude of the independent variable upon the dependent variable. By calculating the effect size on G*Power, the actual power was 0.811 with a sample size of 27. Forty per cent was added to the calculated sample size after a previous study demonstrated a 40% attrition rate (Olney et al., 2005). Twelve participants were added to the total group for a sample size of 39 with 13 participants in each of the three groups.

Variables

Demographic. Demographic variables were obtained from the maternal record, pediatric delivery room record, the labor and delivery record, resuscitation record and the neonatal intensive care admission form. These variables, as well as the instrument,
indicator, frequency, level of measurement and reliability that were measured are found in Tables 10 and 11.

The expected date of confinement, the date that a pregnant woman is expected to give birth, will be used as the determination of gestational age. Gestational age is defined as the completed weeks and days as determined by the obstetrician. The measurement of gestational age is known to be affected by random and systematic error (Platt, 2002).

Table 10

Demographic Variables-Maternal

<table>
<thead>
<tr>
<th>Variable</th>
<th>Instrument</th>
<th>Indicator</th>
<th>Source/Frequency</th>
<th>Level of Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age</td>
<td>Maternal Record, &amp;/or NICU admission form</td>
<td>Documented on admission record</td>
<td>On admission</td>
<td>Continuous</td>
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<tr>
<td>Race</td>
<td>Maternal Record, &amp;/or NICU admission form</td>
<td>Documented on admission record</td>
<td>On admission</td>
<td>Categorical</td>
</tr>
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<td>Gravida/Parity</td>
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<td>Documented on admission record</td>
<td>On admission</td>
<td>Nominal</td>
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<td>Maternal Medications:</td>
<td>Maternal Record, &amp;/or NICU admission form</td>
<td>Documented on admission record</td>
<td>On admission</td>
<td>Dichotomous</td>
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<tr>
<td>Antihypertensives</td>
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<td>Antenatal Steroids</td>
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<tr>
<td>Delivery Type:</td>
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<td>On admission</td>
<td>Categorical</td>
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<tr>
<td>Caesarean Section</td>
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<tr>
<td>VBAC</td>
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</table>

Note. VBAC=Vaginal birth after caesarean.
To help determine accuracy of gestational age, a Ballard score of maturational assessment (1991) is performed on all infants by the admitting resident or neonatal nurse practitioner. This assessment tool requires a postnatal examination, done within 96 hours of life that measures gestational age or maturation through physical and neuromuscular assessment. If there was a discrepancy of greater or equal to two weeks between the expected date of confinement and the Ballard score, the Ballard score was used for the gestational age.

**Independent Variables**

**Enteral sterile water feeds.** The first independent study variable was administration of enteral sterile water feeds. ESWF provides water enterally so that the water can be absorbed by the digestive tract. Consequently, the enteral sterile water will have a dilutional effect on the sodium level concentration by adding fluid volume to the extracellular fluid compartment and vascular space, thereby decreasing sodium levels. Enteral sterile water is also known as free water because it does not contain any electrolytes. The operational definition for ESWF administration was the provision of sterile water given at 10mls/Kg/day, based on birth weight. This volume of water was determined because, as previously stated, sterile water is hypotonic and the more hypotonic the fluid, the less volume of fluid is needed to dilute serum sodium (Adrogué & Madias, 2000). The volume of sterile water did not change because total fluids were based on birth weight until the infant surpassed birth weight. It was administered by continuous infusion via a nasogastric or orogastric tube. The first intervention group received ESWF until the sodium value was ≤ 140 mEq/L or through six days of life. The
second intervention group received ESWF until the sodium value was \( \leq 140 \text{ mEq/L} \), or through six days of life.

Table 11

Demographic Variables of Infants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Instrument</th>
<th>Indicator</th>
<th>Source/Frequency</th>
<th>Level of Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age</td>
<td>DR note and/or NICU admission form</td>
<td>Weeks and days</td>
<td>On admission</td>
<td>Continuous</td>
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<tr>
<td></td>
<td>Ballard score</td>
<td>Physical exam</td>
<td>At delivery/</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Within 48 hrs. of delivery</td>
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</tr>
<tr>
<td>Gender</td>
<td>DR note and/or NICU admission form</td>
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<td></td>
<td>Categorical</td>
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<tr>
<td>Birth Weight</td>
<td>scale</td>
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<td>Ohmeda In-bed scale</td>
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<td></td>
<td></td>
<td></td>
<td>On admission &amp; daily</td>
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</tr>
<tr>
<td>Race</td>
<td>NICU admission form</td>
<td>Physical exam</td>
<td>On admission</td>
<td>Categorical</td>
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<td>Documented on admission</td>
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<td>DR note and/or NICU admission form</td>
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<td>Rubella</td>
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<td>Resuscitation</td>
<td>NRP</td>
<td>Resuscitation record and</td>
<td>On admission</td>
<td>Dichotomous</td>
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<td>NICU admission form</td>
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<td>Apgar Scores</td>
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<td>Documented on admission</td>
<td>On admission</td>
<td>Continuous</td>
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<tr>
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<td></td>
<td>record</td>
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</tbody>
</table>

*Note. DR= Delivery room; VDRL= Venereal Disease Research Laboratory; GBS= Group \( \beta \) Streptococcus; GC= Gonorrhea; CT= Chlamydia; NRP= Neonatal Resuscitation Protocol.

**Timing of administration.** The second independent variable was the timing of administration of ESWF. The operational definition of timing of administration was the start time of the administration of enteral sterile water feeding in the prophylactic group
at 24 hours of life if the serum sodium value reached 145 mEq/L and for the second intervention group when the serum sodium value was $\geq 150$ mEq/L. It was measured by the documentation on the infants’ bedside record. The starting time in hours of life and the completion time in hours of life for the entire time block of administration of enteral sterile water feeding were measured. The prophylactic group received sterile water feeds when the serum sodium value reached 145 mEq/L and continued until the serum sodium value was $\leq 140$ mEq/L. The intervention group received ESWF starting when hypernatremia was diagnosed for a serum sodium value of $\geq 150$ mEq/L and continued until the serum sodium value was $\leq 140$ mEq.

**Dependent Variables**

*Sodium value.* The dependent variable was the serum sodium value. Sodium is the most abundant electrolyte in the blood and regulates the extracellular fluid levels in the body. It is essential for water balance, regulation of plasma volume and transmission of nerve impulses. Normal neonatal sodium values are generally agreed to be between 135 and 145 mEq/L (Adrogué & Madias, 2000). Preterm infants have a limited ability to excrete a sodium load. Even though preterm infants can excrete sodium due to increased intake through intravenous fluids, they remain at risk to retain sodium (Shaffer, Bradt, Meade & Hall, 1987; Lorenz et al., 1995). The operational definition of sodium was the serum sodium values obtained every 12 hours on each participant as measured by the VIA LVM Blood Gas and Chemistry Monitor or the GEM Premier 4000 Analyzer. (Table 12) These blood sample values were not additional laboratory samples and consequently did not incur additional charges.
Covariate variables

The following covariate variables were controlled for statistically. The *maternal demographic instrument* documented whether there were antenatal steroids administered to the mother prior to delivery. The *percentage of humidity in the isolette* and the set

Table 12

*Instruments for Dependent Variable*

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Instrument</th>
<th>Indicator</th>
<th>Source/Frequency</th>
<th>Level of Measurement</th>
<th>Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Value</td>
<td>VIA LVM Monitor</td>
<td>Printout from monitor</td>
<td>Infant’s bedside record. Documented every 12 hours</td>
<td>Continuous</td>
<td>Monitor self-calibrates every 30 minutes</td>
</tr>
<tr>
<td></td>
<td>GEM Premier 4000</td>
<td>Printout from monitor</td>
<td>Documented on infant’s bedside record and in EMR. Sample obtained as needed</td>
<td>Continuous</td>
<td>Monitor self-calibrates after each blood analysis</td>
</tr>
</tbody>
</table>

*Note.* EMR = electronic medical record.

*temperature of the radiant warmer* were recorded every 4 hours as documented on the infants’ bedside record. The use of *phototherapy* for any infant in the study was documented daily. Percentage of humidity in isolettes and phototherapy are variables directly related to insensible water loss which in turn, influences water balance. Severity of illness at 12 hours of life was measured by the SNAPPE-II instrument.

Diuresis was defined as the physiologic changes in extracellular and intracellular fluid volumes resulting in the largest increase in urine output with documented weight loss and the time frame that these changes occurred. As part of homeostasis, body fluid redistribution is divided into three phases of diuresis: prediuretic, diuretic and post-
diuretic (Lorenz, Kleinman, Ahmed & Markarian, 1995). The operational definition of
diuresis was the hour at life at which urine output was \( \geq 3 \text{ mls/Kg/hour} \) for a 24 hour
period with documented weight loss. This was recorded by documentation of all fluids
taken in, including intravenous flushes and all output including urine output, every 12
hours. Fluid balance is operationalized by daily weights.

**Instruments**

**Bedside data collection instrument.** The bedside data collection instrument used
was developed for use in a pilot study and was revised for this study. The data collection
instrument contained demographic data as well as physiological measures.

Documentation from the nursing flow record for the previous 24 hours was retrieved by
the PI or research assistant each morning and the data was entered into the data collection
instrument. This included total fluids in; total fluids out; total fluids in mls/Kg/day; urine
output in mls/Kg/day. Flashes, fluid boluses and fluids that were piggybacked into the
primary intravenous fluid line were documented. The amount of sodium in the flushes
and fluid boluses, in mEq/Kg/day, was also recorded. The documentation was recorded
from the nursing flow sheet and the electronic medical record (EMR) whose total fluids
are calculated every twelve and 24 hours. All fluid totals were recalculated by the PI or
research assistant and double checked against the numbers recorded by the bedside nurse
before being recorded in the data collection instrument, to insure accuracy. Of concern is
the reliability of the bedside record and if the data are correctly or consistently being
recorded.

**Data collection instruments.** The data collection instruments utilized in the study
were the a) SNAPPE-II, b) SECA Weight Scale, c) VIA LVM Blood Gas and Chemistry
Monitoring System, d) Stat profile critical care xpress analyzer, e) GEM Premier 4000 analyzer and f) Ohmeda Giraffe Omnibed in-bed scale.

**SNAPPE-II.** For this proposed study, the Score for Neonatal Acute Physiology-Perinatal Extender (SNAPPE-II) (Richardson, Corcoran, Escobar & Lee, 2001) was used (Appendix A). The SNAPPE-II is an empirically validated illness severity and mortality risk score for infants in newborn intensive care (Richardson, Khoury, Wedig, Wang, et al. 1993).

The SNAPPE-II was originally developed and validated prospectively with 1643 newborns admitted to three NICUs in the northeastern United States. (Richardson, Gray, McCormick, Workman & Goldmann, 1993). Due to significant variability in birth weight adjusted mortality among NICUs, this instrument was developed to compare mortality outcomes in groups of premature infants across multiple NICUs (Richardson, et al., 1993). It was developed along guidelines similar to the Acute Physiology and Chronic Health Evaluation (APACHE) and the Physiologic Stability Index (PSI). At this time it was known as SNAP –Score for Neonatal Acute Physiology and contained 34 variables that were measured at 24 hours of life for each premature infant.

A follow-up study (Richardson, Phibbs, Gray, et al., 1993) investigated birth weight and illness severity as independent predictors of neonatal mortality. Using logistic regression, six alternative predictive models were tested. The best model was used to develop the addition of three perinatal mortality risks: birth weight ≤ 749 grams and birth weight 750-999 grams; Apgar score less than seven at 5 minutes of life; and if the infant is small for gestational age. Small for gestational age was defined as the cutoff weight for
the 3rd percentile for each gestational age starting at 22 weeks gestation (Kitchen, Bajuk, Lissenden & Yu, 1981).

Table 13

Elements of the SNAP-II and SNAPPE-II

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNAP-II</td>
<td>Lowest mean blood pressure</td>
</tr>
<tr>
<td></td>
<td>Lowest core body temperature</td>
</tr>
<tr>
<td></td>
<td>Lowest serum pH</td>
</tr>
<tr>
<td></td>
<td>Multiple seizures</td>
</tr>
<tr>
<td></td>
<td>Urine output</td>
</tr>
<tr>
<td></td>
<td>FIO2/Pao2 ratio</td>
</tr>
<tr>
<td>SNAPPE-II</td>
<td>Lowest mean blood pressure</td>
</tr>
<tr>
<td></td>
<td>Lowest core body temperature</td>
</tr>
<tr>
<td></td>
<td>Lowest serum pH</td>
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<tr>
<td></td>
<td>Multiple seizures</td>
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<tr>
<td></td>
<td>Urine output</td>
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<tr>
<td></td>
<td>FIO2/PaO2 ratio</td>
</tr>
<tr>
<td></td>
<td>Birth weight</td>
</tr>
<tr>
<td></td>
<td>Apgar score at 5 minutes</td>
</tr>
<tr>
<td></td>
<td>Small for gestational age</td>
</tr>
</tbody>
</table>


Therefore, the SNAP-II represents the six mortality risks of severity of illness and the SNAPPE-II (Richardson, Corcoran, Escobar & Lee, 2001) represents the six mortality risks plus the three perinatal mortality risks that are independent predictors of severity of illness. (Table 13) The SNAPPE-II assigns values for the variables of (a) mean blood pressure, (b) lowest temperature, (c) oxygen level on a recorded blood gas divided by the amount of inspired oxygen the infant is receiving, (d) lowest serum pH, (e) multiple seizures and (f) urine output in mls/Kg/hour. The SNAPPE-II contains nine items.
documented at 12 hours of life. The time of the collection was changed from 24 hours to 12 hours in order to minimize the effect of treatment bias (Richardson, et al., 2001).

The empirical validity of the SNAPPE-II was conducted through a logistic regression model on 14,610 Canadian infants. The authors’ (2001) study showed that the SNAPPE-II had excellent goodness of fit (0.90). Goodness of fit shows how well a statistical model fits a set of observations. The receiver operator characteristic curve (ROC) is a graphical means of assessing the ability of a screening test to quantify the performance of a diagnostic variable (Bewick, Cheek & Ball, 2004). The test must have both sensitivity and specificity. The (ROC) plots test sensitivity against the false-positive rate. The area under the ROC was 0.91. The area under the curve measures discrimination, which is the ability of a test to correctly identify those premature infants who will survive and those who will die. The closer the value of the ROC is to one, the better the accuracy of the test or instrument (Bewick et al., 2004).

The SNAPPE-II was designed to analyze groups of premature infants and compare mortality outcomes among NICUs. It was not designed to predict individual survival or to determine continuation or withdrawal of medical support (Richardson et al., 2001). This instrument has demonstrated predictive validity. Predictive validity refers to the ability of a measurement to theoretically predict future events (Higgins & Straub, 2006) and is a type of criterion-related validity. An instrument needs to be validated to confirm that it can predict future events, preferably in a different dataset with adequate calibration (accuracy). Accuracy can be investigated by using the Hosmer-Lemeshow goodness of fit test. Predictive validity depends on longitudinal measurement. For scores
to be clinically useful, the predicted and observed event rates should correlate (Altman & Royston, 2000). Information about the SNAPPE-II is found in Appendix A.

**SECA 856 scale.** The volume of urine collected in each diaper is quantified by weighing them on a SECA scale (SECA Corporation, North America East, Hanover, MD) that is calibrated prior to each diaper being weighed. Behind this method is the principle that one ml of urine weighs approximately one gram (Fox, 1992; Amey et al., 2008). After calibration of the scale a dry diaper is weighed and the dry weight is recorded. When the wet diaper is changed the scale is again calibrated and the wet diaper is weighed. The difference in weight in grams is equal to the urine output in mls. Calibrating the scale prior to weighing each diaper and weighing the diaper as soon after voiding as possible, helped reduce systematic error. The bedside nurses routinely followed this procedure. Urine output was recorded in total amount of urine voided every 12 and 24 hours and urine output in mls/Kg/day. These totals were recalculated by the PI before being recorded in the data collection instrument to insure accuracy. Information about the SECA scale is found in Appendix B.

Stool output in premature infants is less than five per cent of output. Delayed passage of the first stool is a common occurrence in extremely premature infants. In a study by Verma and Dhanireddy (1993), 114 infants with a birth weight of ≤ 1,000 grams were studied for the timing of passage of the first stool. The authors found that in this group of infants the first stool occurred anywhere from 24 hours to 22 day of life with the median age of the passage of first stool by three days of life.

**VIA LVM blood gas and chemistry monitoring system.** The VIA LVM Blood Gas and Monitoring System (International Biomedical, Austin, TX) is an FDA-approved,
Class II, Clinical Laboratories Improvement Act (CLIA) - exempt medical device (Widness et al., 2000). It is a closed system that consists of a monitor with sterile, disposable components that are directly connected to the infants’ umbilical artery catheter (Appendix C). The disposable components include small diameter tubing, tubing connectors that decrease line turbulence and a low volume presample flush of the infant’s UAC fluid to improve accuracy. The monitor also increases accuracy because it reduces specimen preparation and error (Billman et al., 2002).

The VIA LVM Monitor and sensor undergoes an in vitro two-point calibration before being attached to the infant. Once the system is attached to the infant, one-point calibrations are performed automatically every 30 minutes with a sterile, isotonic, heparinized calibration solution. This supports reliability, ensuring that the same test is stable over time and decreases random error.

Two studies have investigated the VIA LVM Blood Gas and Chemistry Monitoring System in critically ill infants. Widness et al. (2000), in a single cohort study evaluated bias and precision based on standard laboratory procedures. A total of 229 paired-sample and split blood samples (N=16) were analyzed. In a multicenter study conducted by Billman et al. (2002), bias and precision were also evaluated. One thousand, four hundred and fourteen paired-sample and split blood samples (N=100) were analyzed. Both studies compared electrolyte and blood gas results using both the VIA LVM Monitor and a standard bench top laboratory instrument. The infant population in Widness et al. (2000) study was between 32 and 42 weeks gestational age. The infant population in Billman et al. (2002) study was less than eight months of age.
Widness and associates (2000) demonstrated that the monitor’s precision results for sodium using the paired-sample technique on the standard bench top laboratory instrument was less precise than the results obtained using the split sample technique. Correlation coefficients ($r$) between the monitor and standard laboratory instrument for sodium was $> .90$. However, overall results exceeded the CLIA testing performance criteria. Billman and associates (2002) determined the mean difference (standard deviation from differences) and correlation coefficients. For sodium the $r = 0.87$ and the standard deviation of differences was 2.89 for paired-sample in vivo testing.

**Stat profile critical care xpress analyzer.** Sodium, potassium, chloride, bicarbonate, blood urea nitrogen and creatinine were measured using the Stat Profile Critical Care XPress analyzer (NOVA Biomedical, Waltham, MA). This analyzer is calibrated daily by a laboratory supervisor according to federal guidelines. Concurrent validity has been determined by a hospital conducted method comparison study of the analyzer on site in the neonatal intensive care unit with standard laboratory analysis performed in the main laboratory (Personal communication, P. O’Shaughnessy, CLT, October, 2007). This instrument has demonstrated both precision and sensitivity. During the study this analyzer was replaced by the GEM Premier 4000 Analyzer. Information about the stat profile critical care xpress analyzer is found in Appendix D.

**Gem Premier 4000 Analyzer.** The Gem Premier 4000 (Instrumentation Laboratory, Bedford, MA) is a blood gas/electrolyte/co-oximetry analyzer recognized by the Clinical and Laboratory Standard Institute and their guidelines. It analyzes whole blood samples at the point of care delivery in either a clinical setting or a central laboratory. The special feature of this analyzer is an Intelligent Quality Management
which is used as the quality control and assessment system for this instrument. This system performs continuous monitoring of the analytical process with real-time, automatic calibration at regular schedules including a one point calibration after every sample and every 30 minutes after the last sample run; automatic error detection, automatic correction of the system and automatic documentation of all corrective actions, replacing the use of an external quality control instrument. (Appendix E)

In a study conducted by Bénéteau-Burnat and colleagues (2008), the analytical performance of the GEM Premier 4000 was compared to three routinely used laboratory blood gas analyzers in two hospital laboratories. The authors evaluated for precision, linearity and accuracy by method comparison using patient samples. The results of the study showed good coefficients of variations for all parameters.

*Ohmeda Medical Giraffe Omnibed.* The Giraffe® Omnibed (General Electric Healthcare, GE) is a neonatal microenvironment. It has multiple features (Appendix F) that help decrease the stress that premature infants may be exposed to in the NICU. The ability to convert from a radiant warmer to an isolette, decreased the need to transfer a medically fragile infant to another piece of equipment, thereby promoting thermoregulation and decreasing stress. The feature that it has that was relevant to the study was the built-in scale to weigh the infants. The scale, according to the manufacturer, weights infants between 300 grams (0.661 pounds) to eight Kilograms (17.6 pounds) and has an accuracy of ± 10 grams. The scale is digital and stores up to 14 weight. It also has memory in order to obtain weight gain recall. Electronic capture of weights will ensure that data are not lost. The scale is also designed to use tare weighing. This method allows placing a blanket on the scale and the weight of the blanket is
deducted by pressing the tare key. Therefore, the infants’ actual weight can be measured. According to the manufacturer the scale needs to be calibrated annually. Calibration improves accuracy and helps reduce systematic error. However, studies have shown that there is always the potential for error with scales and test weighing (Dowling, Madigan & Siripul, 2004). The ability of this instrument to perform tare weighing supports internal validity. However, there are no documented studies on the reliability of this instrument.

Instrumentation can occur and are therefore a threat to internal validity if the measurement instrument does not have established accuracy. Despite the fact that the in-bed scale used in the study to weigh the infants only had to be calibrated annually, the changes in weight could be attributed to changes in the scale and not be related to the weight of the infant. Although the precision of the instrument may be high, the accuracy of the instrument may decrease. This threat is more pronounced in a repeated measures design (Buckwalter, Maas & Wakefield, 1998). Also of concern is human error when weighing the infant. Examples of this include, the person weighing the infant not following the study protocol, being tired, distracted and or not tare the scale before weighing.

**Procedures**

The study was submitted to the NICU Research Committee at Rainbow Babies and Children’s Hospital. After approval, the study was submitted to University Hospitals Case Medical Center Institutional Review Board for approval. Approval was received nine months after the initial submission. Potential participants were identified daily through two different logs: the neonatal consultation log and the NICU neonatal admission log. The first log, the neonatal consultation log which is kept in the NICU, is a
copy of official physician consults done by a neonatologist or a neonatal fellow at the request of the referring obstetrician. These consultations were completed for those antepartum mothers who are hospitalized at MacDonald Hospital for Women, part of University Hospital, Case Medical Center. The referring obstetrician requested a consultation for issues such as premature delivery, a known defect of the fetus or if the mother was high-risk due to a maternal health issue. The second log, the admission NICU log is kept in the NICU and contains all the identifying information for all neonates admitted to the NICU including date of birth, time of birth, weight, race and gestational age.

The primary investigator (PI) or research assistant determined eligibility of each infant and met with the parents. The study was described to them in the infant’s room or in the mother’s room on the postpartum unit at McDonald’s Women’s Hospital after delivery of the infant. However, if the infant was transferred from another institution, the study was explained to them in the infant’s room. All consents were obtained before 24 hours of life. Prior to enrollment the PI or designated research assistant determined if the participant met inclusion criteria and obtained written informed consent. A copy of the consent form was placed in the infant’s chart, a copy was given to the parent and the original consent form is kept in the research consent log in the locked research file cabinet in the PI office. The PI obtained the demographic data and the research assistant randomly assigned the participants using permuted block assignment.

**Permuted Block Assignment.** A permuted block design, also known as block randomization, is an alternative design to complete randomization (Rudy, Vaska, Daly, Happ & Shiao, 1993). Permuted block designates each block containing one possible
combination of treatment distribution with the distribution balanced at the end of each block and balanced groups at the end of the research study. Separate randomization lists for each combination of strata are required at the beginning of the block (Conlon & Anderson, 1990; Doig & Simpson, 2005).

Permuted block has the advantage of promoting balance over time. The disadvantage of this method is the theoretical concern that this method is susceptible to selection bias and easy to predict future block assignment.

While it was originally intended that a permuted block randomization procedure would be done it was not possible because of a communication error with a research assistant. However, it is established that ELBW infants of a certain gestational age have a specific weight range.

After parental consent, two manila envelopes were marked with weight stratification: \( \leq 750 \) grams birth weight and \( \geq 751 \) grams birth weight. After obtaining parental consent, the PI or research assistant asked a random staff member in the NICU to choose a paper out of the envelope, based on the subject’s weight stratification to determine what group the infant was enrolled in: control, prophylactic or intervention.

**Procedure after consent.** Once consent was obtained, a data collection packet and the demographic sheet (each packet was number coded) was filled out with randomization of the infant by weight strata. The participant’s assignment and code number was placed in a log book. All documentation was placed in the data collection packet. The data collection packet was placed in the research binder which was kept in a locked office by the NICU. Documentation of the SNAPPE-II score was based on the values recorded in the infants’ flow sheets by the bedside nurse at 12 hours of life. For all
groups the infant was weighed daily by the bedside nurse on the Ohmeda Giraffe® Omnibed built-in scale. Weight was documented daily in the data collection instrument.

The majority of infants are initially cared for under radiant warmers and then transferred to humidified, convectively heated double-walled isolettes. Due to birth weights ≤ 1,100 grams, the infants in this study were admitted directly to the Giraffe® Omnibed. Recorded in the data collection instrument was the highest humidity percentage in the isolette in a 24 hour period and the set isolette temperature. If the infant received phototherapy, the number of banks of phototherapy lights was recorded. The total bilirubin levels and the age of the infants in hours of life at the time of the blood draw were also recorded.

The prophylactic group, who received enteral sterile water feeds starting at 24 hours of age had the same documentation as described above. In addition, documentation of the initiation of sterile water feeds when the serum sodium value was ≥ 145 mEq/L and cessation of feeds when the serum sodium value was ≤ 140 was recorded. Also recorded was a documented serum sodium value <135 mEq /L or if the feeds were stopped by the NICU team for any reason and the time in the infant’s hours of life that it was done. In the event that an infant was randomized to the prophylactic group and their sodium level did not reach ≥ 145 mEq/L, the infant remained in the study and all documentation was recorded for the 144 hours. This also included an infant randomized to the intervention group and who did not develop hypernatremia. The sodium level, chemistries and the times of the draws were recorded.

The intervention group of infants received ESWF for documented hypernatremia. The data collection method followed that of the control group and the prophylactic group.
In addition, documentation was recorded for the start of the initiation of enteral sterile water feeds for a documented hypernatremia in hours of life, the volume of ESWF and the sodium level. Documentation continued through six days of life. If the infant developed hypernatremia anytime from 96 hours of life through 144 hours of life, documentation continued for 48 hours after resolution of the hypernatremia.

Each management team was told that the infant was in the study and their group assignment was designated by a color coded study protocol, approved by the IRB, which was posted in the front of the infant’s medical chart. Completed documentation instruments were placed in a locked file cabinet in the PI office.

**Data Management**

The primary investigator set up an electronic database using PASW 20.0 software package prior to the study implementation. The database was password protected and was known only to the investigator and to the dissertation advisor.

Emphasis was placed on the protection of participants records. Faculty members, who are not affiliated with the study, monitored data content. Members of the data safety board are: Christopher Burant, PhD, Elizabeth Damato, PhD, RN and Gulgun Yalcinkaya, MD. Maintenance of data safety was monitored at 50 % of collected sample. Any serious events related to study procedure were to be reported to the IRB within 24 hours. However, there were no serious events related to the study.

All study variables were created and a codebook specifically developed for this study was used to code variables. Data was collected every 24 hours. The data was kept in a locked file in the PI’s office. All quantitative data was entered by the investigator after each subject completed the study. The data was cleaned prior to analysis.
All data was deidentified after completion of the study. After completion of the study all research documents remains in the possession of Case Western Reserve University for five years, per the School of Graduate Studies.

**Data Analysis**

Each subject’s data after completion of the study was entered into the computer by the investigator. After all data was entered, the data was cleaned by first, running frequencies and testing descriptive statistics for: missing data, normality, outliers and variance.

**Data Cleaning**

*Missing data.* Missing data was examined to see if there was a pattern that exists. This may be done by in several ways. First, a list wise deletion may be done by omitting the subjects with the missing scores from that variable, if less than five per cent of the data are missing. Secondly, a mean substitution may be done. This entails calculating the means of the available data for the variables with the missing values. Those mean values replace the missing values prior to analysis. This will work when very few data are missing. However, this procedure does not add any new information and it may underestimate error. A third possible method that can be used to examine missing data is running a regression to determine predictive value. This is conducted by taking several independent variables to predict the value on a dependent variable. The dependent variable becomes the variable with the missing values. However, the regression may inflate the predicted scores so the scores appear better than they actually are. The final possible alternative is maximum likelihood. Maximum likelihood chooses values as estimates. If the values as estimates are true, the probability increases of what you have
observed is actually true (Allison, 2002). This statistical method is available in SPSS as Expectation-Maximization (EM) algorithm or as Full Information Maximum Likelihood (FIML) in AMOS.

Missing data needs to be addressed because it can threaten both the internal and external validity of the study. Missing data may lead to a decrease in sample size, loss of statistical power and contribute to bias in parameter estimates such as group means, betas and slope coefficients.

**Normality.** The second test is to check for normality, to determine if the observations for a variable are normally distributed. This can be done by checking the skewness and kurtosis coefficients which will determine if the data is normally distributed. Skewness is the measurement of the symmetry of a frequency distribution (Field, 2005). If the absolute value is less than three (-3 to 3), the data is normally distributed. Kurtosis is a measurement of the flatness of a distribution. If the absolute value is less than eight (-8 to 8), the data is normally distributed.

**Outliers.** The third primary influence that must be examined is outliers. These are subjects that have extreme values and may be caused by error in data entry, subjects who are not truly representative of the sample population or a subject who actually may be different from the rest of the sample. If the sample size is small, outliers can be determined by examining the frequency distribution. The subjects’ data record needs to be checked to determine if there was data entry error. Models can be tested with and without outliers. If the influence on the results is very small, the outlier may be omitted. If the outlier is a genuine result, it is important because it may indicate an extreme of behavior of the process under study. In that case, the data will be examined with and
without the outlier and results of both analyses will be presented to alert the readers that
the points may be questionable. If an outlier is genuine and is to be kept in the sample, all
the variables can undergo data transformation. Data transformation is a mathematical
procedure that is applied to the data in order to meet the assumptions (Mertler &
Vannatta, 2005), thereby reducing the impact of an extreme value. If there are
multivariate outliers, a regression may be run and a Mahalanobis distance statistical test
or Cook’s D can be performed. Both of these tests are used to calculate the distance or
leverage, which specific cases may exert on the predicted value of the regression line
(Tabachnick & Fidell, 2000). The crucial value depends on the number of predictors and
the sample size (Field, 2005).

Variance. The final primary influence to be examined is variance. Variance is the
estimate of the average variability or ‘spread’ of a data set. The variance represents the
average squared deviation from the mean or the spread of the values around the central
tendency. Variance takes into account both the deviation of data (away from the mean)
and how frequently these deviations occur. The spread of values around the center gives a
sense of what kinds of deviation from the center are common. In general, the higher the
variance, the more spread out the data is. By analyzing the data using descriptive
statistics you can examine the mean, range, variance and standard deviation.

Statistical Analysis

Research question 1: What are the patterns of changes in sodium levels over the
first seven days of life? This research question was answered by constructing a graphic
representation to examine the patterns of changes in sodium levels over the first seven
days of life in all three groups. Also included is maternal and infant descriptive statistics including frequencies, percentages and measures of central tendency.

Research Question 2: What are the differences in the incidence of hypernatremia among extremely low birth weight infants who receive intravenous fluids only, infants who receive enteral sterile water feeds beginning at 24 hours of life and infants who receive enteral sterile water feeds when hypernatremia is diagnosed?

This research question was answered by using the statistical analysis Chi-Square. Chi-Square statistic compares the differences of categorical data between two or more independent groups that do not have an inherent order. Categorical data may be entered as raw scores or as weighted cases. Frequencies and percentages will be reported in contingency table. After running the statistical test, a check of the assumption for Chi-Square will be determined. The assumption is that all expected frequencies will be > 5 in the contingency table. If it is < 5, a Fisher exact test will be performed. The level of significance will be set at .05. If the results are highly significant this indicates that the pattern of responses (those infants with hypernatremia and those infants without) is significantly different. The Chi-Square results are reported along with the degrees of freedom and the significance level.

Research Question 3: Are there differences in the duration of hypernatremia among extremely low birth weight infants who receive intravenous fluids only, infants who receive enteral sterile water feeds beginning at 24 hours of life and infants who receive enteral sterile water feeds when hypernatremia is diagnosed?

This question was answered by using the statistic test, repeated measures analysis of variance (rmANOVA). This statistical method is used to analyze data from the same
subject over multiple points in time and tests if there are mean differences across the same variable measure at multiple points in time. The data from the different experimental conditions will be related. Repeated measures also tests mean differences for the same variable measured multiple times across groups. Before checking for significance, it must be determined if the assumption for sphericity was met. Sphericity is the equality of variance of the differences between treatment levels and equal correlation between periods (Fields, 2000). Examining Mauchly’s test statistic for sphericity will determine if there are or are not significant differences between the variances of the differences. If Mauchly’ test is significant, \((p<.05)\), the assumption of sphericity has been violated. This violation can be corrected by using the Greenhouse Geisser correction, the Huynh-Feldt correction or multivariate MANOVA.

Research Question 4: What are the differences in the magnitude of change in serum sodium levels among extremely low birth weight infants who receive intravenous fluids only, infants who receive enteral sterile water feeds beginning at 24 hours of life and infants who receive enteral sterile water feeds when hypernatremia is diagnosed?

This question was answered by using the statistic test, repeated measures analysis of variance. \((\text{rmANOVA})\). This statistical method is used to analyze data from the same subject over multiple points in time and test if there are mean differences across the same variable measure at multiple points in time. Repeated measures also tests mean differences for the same variable measured multiple times across groups. Before checking for significance, it must be determined if the assumption for sphericity was met. Sphericity is the equality of variance of the differences between treatment levels and equal correlation between periods (Fields, 2000). Examining Mauchly’s test statistic for
sphericity will determine if there are or are not significant differences between the
variances of the differences. If Mauchly’s test is significant, ($p < .05$), the assumption of
sphericity has been violated. This violation can be corrected by using the Greenhouse
Geisser correction, the Huynh-Feldt correction or multivariate MANOVA.

Research question 5: What is the relationship between the timing of the observed
onset of hypernatremia and the timing of observed onset of diuresis among extremely low
birth weight infants who receive intravenous fluids only, infants who receive enteral sterile water feeds beginning at 24 hours of life and infants who receive enteral sterile water feeds when hypernatremia is diagnosed? This research question will be answered by running a simple linear regression.

A simple linear regression is a statistical test to analyze data and predict an
outcome (highest sodium values) from a single predictor variable (timing of diuresis). A regression fits a predictive model to the data and the model is used to predict values of the dependent variable. Regression requires testing for primary and secondary assumption of both descriptive and inferential statistics. Descriptive statistics is quantifying the basic features of the data in a study. The three primary assumptions test for effects on descriptive statistics: variance among the variables, outliers (influential cases) and linearity. The secondary assumptions tested in a regression are for effects on inferential statistics. These secondary influences are constant error variance and normality of error.

After running descriptive statistics for frequencies and normality which tests the first primary assumption, a regression is run and several statistical tests are used to
measure influential cases: Cooks D (distance), Mahalanobis distance, studentized deleted residuals, standardized DF Betas and covariate ratios.

The Cook’s D (distance) is a statistic that examines the effect of a single case on the ability of the model to predict all cases. A Cook’s D greater than one on the x and y axis is the cutoff value for influential cases. The Mahalanobis distance is related to leverage values. Leverage values examine the influence of the observed value of the outcome variable over the predicted value. The Mahalanobis distance measures the distance of cases from the means of the predictor variables on the x axis. Due to the small sample size, cases with the highest values will be examined using Barnett and Lewis’s (1978) table of critical values.

Studentized residuals and Studentized deleted residuals are used to look for outliers that have high leverage. The Studentized residual is the observed residual divided by the standard deviation. The Studentized deleted residual is the observed residual divided by the standard deviation with the outlier omitted from the analysis.

Another test that measures influential cases is the Standardized DF Beta. The DF Beta is a new variable for each term in the regression model and examines the difference between a parameter estimated using all cases in the analysis and estimated when one case is excluded. The Standardized DF Beta contains the DF Beta value divided by the estimate of its standard error. By using the Standardized DF Beta, standardized values produce a universal cut-off point. Absolute values greater than one indicates cases that influence the model parameters.

The last test to check for primary influences of influential cases is the covariate ratio. This statistic measures the impact of each observation on the variances and standard
errors of the regression coefficients and their covariances. Values close to one have little impact on the variances of the model parameters (Fields, 2000).

The third assumption to test in regression that may influence descriptive statistics is linearity which shows relationships among the variables. This is examined by producing partial plots from the regression. Partial plots are used to visually assess linearity. Lines of best fit are added for linear, quadratic and cubic. The coefficient of determination ($R^2$) associated with the line of best fit will be compared for differences of two percent or more.

The two secondary assumptions to test in regression which affect inferential statistics are constant error variance and normality of errors. Constant error variance (homoscedasticity) is necessary to make valid statistical inferences about population relationships. Constant error variance indicates that the variance around the regression line is the same for all values of the predictor variable (Osborne & Waters, 2002). Constant error variance is tested by plotting Studentized deleted residuals on the X axis by standardized predicted scores on the Y axis and adding a fit line for Loess (locally weighted scatterplot smoothing) and checking for variance scatter. This scatter should be approximately 3:1 with lowest variance scatter to highest variance scatter.

Normality of errors tests for normality of residuals. This is done by assessing a normal probability plot of studentized deleted residuals for skewness and kurtosis. Skewness is the measurement of the symmetry of a frequency distribution (Field, 2005). If the points on the plot fall close to the diagonal line, the distribution is normal. If the absolute value is less than three (-3 to 3), the data is normally distributed. Kurtosis is a
measurement of the flatness of a distribution. If the absolute value is less than eight (-8 to 8), the data is normally distributed.

**Protection of Human Subjects**

**Issues related to enrolling newborns in research.** Federal regulations mandate that research in children, because they are a vulnerable population, must be based on analysis of probable risks, possible benefits and possible discomforts (Shamoo & Khin-Maung-Gyi, 2002). Infants may only be enrolled in research if there is minimal risk, or if there is a possibility that the infant will directly benefit from the research study (Singhal, Oberle, Burgess & Huber, 2002).

Individuals should not be used in research without their voluntary and informed consent. The protection of human subjects, especially a vulnerable population such as premature infants, is problematic because these infants are unable to give consent. A parent or guardian must give informed written consent for their infant to be admitted into a research study. Controversy surrounds the conjecture that parents are truly giving informed consent. In order for informed consent to be valid, the parent(s) must not just understand the purpose of the study, but also the risks and benefits. Parents’ perception of research in infants plays a role (Singhal, et al.,2002) and some studies have demonstrated that a proportion of parents would like their physician to advise them if they should enroll their infant in a research study (Zupancic, Gillie, Streiner, et al.,1997) or actually make the decision for the parent(s) (Singhal, et al. 2002).

Consent is often obtained under stressful conditions due to (a) parents emotional shock in having a critically ill premature infant, (b) the research study may actually be an emergency intervention, (c) the research study may be complicated and difficult for the
parent(s) to understand and (d) consent may need to be decided in a very short amount of
time (Allmark, Mason, Gill & Megone, 2003). The results of research looking at these
problems in this area are mixed.

In a study by Ballard, Shook, Desai and Anand (2004), 64 parents were asked 20
open-ended questions to determine their level of understanding about a study in which
they had enrolled their infant, 3 to 28 months prior. The purpose of the study was to
determine the validity of informed consent obtained from parents of infants between 23
and 33 weeks gestational age who were enrolled in a multicenter RCT investigating
neurologic outcomes and preventative analgesia in the newborn. The results of this study
indicated that eight percent had no recollection of the study or signing consent; 68%
understood the purpose of the study and of those who understood the purpose of the
study, 95% were able to verbalize the benefits, but only five percent understood the
potential risks. No parent(s) reported feeling coercion to consent to the study. In a similar
retrospective study (N= 29) conducted by Burgess, Singhal, Amin, McMillan and
Devrome (2003), 93% of parents reported that they understood the purpose of the study;
55% understood the benefits of the study and 52% understood the potential risks. Thirty-
four percent did not remember receiving a copy of the consent. However, of concern is
that 31% of the parents felt coercion in giving consent.

A recent study focused on parents’ perception of consent and decision making in
neonatal research. Freer and colleagues (2009) conducted a RCT in Scotland and the
United States investigating various information styles on parents’ understanding of a
research study. Although the study itself was hypothetical, it demonstrated that
understanding of the research study proposed was better in those parents who received a
concise information sheet rather than a lengthy one and that those parents who received additional verbal explanation had increased understanding.

Parents must often decide whether to enroll their critically ill infant into a study in a short amount of time while under duress. Hoehn, Nathan, White et al. (2009) investigated the parental perception of time and its relationship to when to decide to participate in a neonatal research study. This study conducted interviews with 37 parents of 19 neonates with congenital heart disease who were eligible for three different studies. Several themes emerged. The primary theme was that parents did not have enough time to make an educated decision (N=10). Many of these parents wanted to discuss the research with their infant’s physician before making a decision. Quantitative analysis was performed between those parents who reported adequate time to make a decision and those parents who felt they did not. The authors found that the relationship between parental perception of time allowed to make a decision to participate in the research and those who consented to enroll were statistically significant in all three research studies proposed.

Integrity of informed consent must be ensured in order to continue to conduct ethical research. Trust in the researcher and frequent communication between the researcher and parents is an important component for conducting research in a vulnerable population. These principals were used in this study.

**Human subject procedures**

The study was submitted to the Human Subjects Review Board of University Hospitals, Case Medical Center where the study took place. After approval, potential subjects were identified through the neonatal consultation log or the NICU admission log.
The PI or research assistant read the consent form to the parent(s) whose premature infant met the study criteria and explained the study to them. The parents were told that a) the study concerned infants who may develop hypernatremia during the first week of life, b) the study will take place during the first six days of life starting at 24 hours of life, c) study participation is voluntary and d) the parents may withdraw their infant from the study at any time without consequences. If the mother was a patient on the postpartum unit at McDonald’s Women’s Hospital, she and the father of the baby were given time to decide if they wanted to participate in the study. The difficulty was that the parents needed to decide before the infant was 24 hours old because the study began at 24 hours of life.

If the parent(s) agreed to participate, they signed a consent form guaranteeing confidentiality per unit policy. A copy of the consent form was placed in the infant’s chart; a copy of the consent was given to the parents and the original consent was kept by the PI. Included in the consent form was the HIPAA consent, (Health Insurance Portability and Accountability Act, 1996) which safeguards patients’ right to privacy and protects individually identifiable information.
Chapter 4

This chapter describes the sample and the results for each research question. The purpose of this study was to compare the effects of three different fluid management strategies on serum sodium values over the first seven days of life among ELBW infants. Ninety infants were assessed for eligibility over a 24 month period of time. Thirty families declined to participate. Seven infants were lost to enrollment because they could not be enrolled by 24 hours of life. Five families were not approached for consent due to attending physician refusal. Seventy one infants did not meet inclusion criteria including one infant with congenital anomalies and one infant who had reverse end diastolic flow. Twenty-seven of the infants who did not meet inclusion criteria included 21 infants with Apgar scores of five or less at five minutes of life and six infants with an initial arterial blood gas pH of less than 7.20. The final sample size was 19 (Figure E).

The data from four infants enrolled in the study were analyzed with intention to treat (Polit & Gillespie, 2009). Three of these infants were started on breast milk feeds at the discretion of the attending physician before completion of the study. One infant (20%) in the intervention group never reached a serum sodium value of 150 mEq/L and did not receive ESWF.
Figure E.

Flow of Subject Recruitment through each Stage of Research

- Assessed for eligibility (N=90)
- Excluded (n=71)
  - Did not meet inclusion criteria (n=29)
  - Declined to participate (n=30)
  - Other (n=12)
- Randomized (N=19)
- Allocated to control group (n=8)
- Allocated to prophylactic group (n=6)*
- Allocated to intervention group (n=5)*
- Analyzed (N=19)

Note. *ITT= intent to treat. This flowchart is an adaptation of the flowchart offered by the CONSORT group (Altman et al., 2001; Maher, Schulz & Altman, 2001) Journals publishing the original CONSORT flowchart have waived copyright protection.
Demographics

Maternal demographics.

Descriptive analysis was conducted for both maternal and infant data. Ninety-five per cent of the mothers were African American. Maternal age ranged from 18 to 39 years with a mean of 25.0 years. For 11% of the mothers (n=2), this was their first pregnancy. Twenty six per cent of the mothers (n=5) delivered vaginally and 74% (n=14) of the mothers delivered via caesarean section. Ninety per cent of the mothers had prenatal screening done, including screening for syphilis, gonorrhea, chlamydia, rubella and hepatitis B surface antigen. Only 47% of mothers had *Group B streptococcus* (GBS) screening as GBS screening is generally done between 35 and 37 weeks gestational age for first pregnancies, which is greater than the gestational age of the infants in this study. Forty-two percent of mothers were screened for HIV and 16% were tested for trichomonas. At delivery, 17% of mothers had premature rupture of membranes and another 17% had prolonged premature rupture of membranes (>18 hours prior to delivery). There was no maternal fever or documented chorioamnionitis for any of these mothers. Only one mother (5%) did not receive any medication at or prior to delivery. The majority of mothers received antibiotics (53%) and 63% received betamethasone. Thirty-two per cent of mothers received medication to control blood pressure. Table 14 describes demographic data concerning maternal medications given prior to or at delivery.
Table 14

*Demographics of Maternal Medications prior to or at Delivery (N=19)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No medications</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>10</td>
<td>53</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>12</td>
<td>63</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>37</td>
</tr>
<tr>
<td>Prometrium</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Zofran</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Nubain</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Ativan</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Percocet</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Methadone</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Depo-Provera</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

**Infant demographics.**

Table 15 depicts the race, gender, weight, mean gestational age of the infants and type of delivery. The majority of the subjects were African American (95%). The mean gestational age was 184 days (26 and 2/7 weeks). The mean birth weight was 847.0 grams (1 lb. 9 oz.) Forty-seven per cent of the infants were male and 53% were female.
Table 15

Demographics of Infant Characteristics at Delivery (N=19)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>18</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>-</td>
<td>-</td>
<td>847.0 grams (153.5)</td>
</tr>
</tbody>
</table>

Gestational Age

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>185 / 26 3/7 weeks</td>
<td>874 grams (1 lb. 9.2 oz.)</td>
<td></td>
</tr>
<tr>
<td>Prophylactic</td>
<td>190 / 27 1/7 weeks</td>
<td>867 grams (1 lb. 9 oz.)</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>183 / 26 1/7 weeks</td>
<td>779 grams (1 lb. 7 oz.)</td>
<td></td>
</tr>
</tbody>
</table>

Gestational age.

Table 16 depicts the mean gestational age for the control, prophylactic and intervention groups as well as the mean birth weight for each group.

Table 16

Infant Mean Scores of Gestational Age and Birth Weight with Randomization by Groups

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>Gestational Age (days/weeks)</th>
<th>Birth Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>185 / 26 3/7 weeks</td>
<td>874 grams (1 lb. 9.2 oz.)</td>
</tr>
<tr>
<td>Prophylactic</td>
<td>190 / 27 1/7 weeks</td>
<td>867 grams (1 lb. 9 oz.)</td>
</tr>
<tr>
<td>Intervention</td>
<td>183 / 26 1/7 weeks</td>
<td>779 grams (1 lb. 7 oz.)</td>
</tr>
</tbody>
</table>
**Apgar scores.**

The median Apgar scores (Table 17) were four, seven and eight at one, five and ten minute of life, respectively. Only 21% ($n = 4$) of the infants had Apgar scores recorded 10 minutes of life.

Table 17

*Median Apgar Scores by Groups (N=19*)

<table>
<thead>
<tr>
<th>Apgar Scores by Randomization Group</th>
<th>Total Group</th>
<th>Control</th>
<th>Prophylactic</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 minute</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5 minutes</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>10 minutes</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

An infant born at home was assigned Apgar scores by Emergency Medical Technician (EMT).

**Snappe-II scores.**

The infant SNAPPE-II Scores, computed at 12 hours of life, are empirically validated illness severity and mortality risk scores. Table 18 describes the mean SNAPPE-II scores for each group of subjects.

Table 18

*Mean infant SNAPPE-II Scores and Risk of In-hospital Mortality*

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean Score (SD)</th>
<th>Range$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8</td>
<td>30.5 (17.85)</td>
<td>0-50</td>
</tr>
<tr>
<td>Prophylactic</td>
<td>6</td>
<td>21.2 (15.19)</td>
<td>10-49</td>
</tr>
<tr>
<td>Intervention</td>
<td>5</td>
<td>22.0 (7.085)</td>
<td>15-33</td>
</tr>
</tbody>
</table>

*Note. $^a$SNAPPE-II scores range from 0-80 with lower scores representing a lower mortality risk.*
A one-way analysis of variance (ANOVA) followed by Bonferroni’s post-hoc comparison test was conducted to examine group differences for gestational age and birth weight, Apgar scores at one and five minutes of life and SNAPPE-II scores documented at 12 hours of life. There were no statistically significant differences between groups either for gestational age, birth weight, Apgar scores or SNAPPE-II scores. These findings are summarized in Table 19.

**Delivery room support.**

Table 20 describes the delivery room support provided the infants. All the infants were given oxygen and any infant in the study who required positive pressure ventilation was scored as needing support during delivery. One infant, born at home, was given positive pressure ventilation by the Emergency Medical Technician. Any infant who received chest compressions or resuscitation medications were excluded from recruitment per the exclusion criteria. Fifty-eight percent (n=11) of the total group did not require support in the delivery room and 42% (n=8) required support.
Table 19

*Infant Gestational Age and Birth Weight by Groups* (N=19)

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>SS</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>2</td>
<td>129.79</td>
<td>64.89</td>
<td>1.101</td>
<td>.356</td>
</tr>
<tr>
<td>Within Groups</td>
<td>16</td>
<td>942.83</td>
<td>58.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>1072.63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Birth Weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>2</td>
<td>31555.29</td>
<td>15777.64</td>
<td>.643</td>
<td>.539</td>
</tr>
<tr>
<td>Within Groups</td>
<td>16</td>
<td>392628.70</td>
<td>24539.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>424184.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apgar Scores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 minute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>2</td>
<td>5.081</td>
<td>2.541</td>
<td>.354</td>
<td>.707</td>
</tr>
<tr>
<td>Within Groups</td>
<td>16</td>
<td>114.708</td>
<td>7.169</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>119.789</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>2</td>
<td>3.939</td>
<td>1.970</td>
<td>1.016</td>
<td>.384</td>
</tr>
<tr>
<td>Within Groups</td>
<td>16</td>
<td>31.008</td>
<td>1.938</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>34.947</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>2</td>
<td>.900</td>
<td>.450</td>
<td>.900</td>
<td>.449</td>
</tr>
<tr>
<td>Within Groups</td>
<td>7</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SNAPPE-II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>2</td>
<td>268.472</td>
<td>134.236</td>
<td>.599</td>
<td>.561</td>
</tr>
<tr>
<td>Within Groups</td>
<td>16</td>
<td>3585.633</td>
<td>224.102</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A Chi-Square test was conducted to examine differences in the incidence of support required in the delivery room between groups. There were no statistically significant differences in the need for support in the delivery room ($\chi^2 = 2.557; p = 0.139$) between the three groups.

**Research Question One**

For the first three to four days of life, blood sampling is approximately every twelve hours in infants admitted to the NICU. If the infant is critical ill and having multiple medical issues, blood sampling may occur as often as every four to six hours. Due to the blood conservation protocol used in the NICU and with improvements in the infants’ medical status, fewer blood samples were required to obtain electrolyte values over the last three days of the study. As a result, there were missing sodium values over these last three days. For the purpose of this study, the average sodium value was considered to be between 135 and 145 mEq/L; therefore, missing sodium values were recoded as 140 in order to conduct the analysis.

The first research question was: What are the patterns of changes in sodium levels over the first seven days of life? The most variation and the highest sodium levels
was seen in the first 72 hours of life. Figure F is a graphic representation of the patterns of mean sodium levels over the first seven days of life for the total sample with each time point representing a 12 hour interval.

Figure F

*Mean sodium values over 7 days (12 hour intervals)*

Analyses were conducted to examine patterns of sodium values over the first seven days of life for the total sample. Five paired-sample t-tests differences of mean sodium values at different twelve hour time frames were conducted. The first paired t-test compared the first morning sodium value with each subsequent morning sodium value over seven days. There was a statistically significant mean difference in the sodium values from day one morning sodium value to day two morning sodium value and from day one morning sodium value to day three morning sodium value (Table 21). However,
there were no statistically significant differences in sodium values between day one morning sodium value and days four, five, six and seven morning sodium values.

Table 21

*Mean differences between day one morning sodium level and subsequent morning sodium levels (N=19)*

<table>
<thead>
<tr>
<th>Day of life</th>
<th>M</th>
<th>SD</th>
<th>df</th>
<th>t</th>
<th>p (one-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 am/Day 2 am</td>
<td>-5.052</td>
<td>8.256</td>
<td>18</td>
<td>-2.668</td>
<td>.008</td>
</tr>
<tr>
<td>Day 1 am/Day 3 am</td>
<td>-4.736</td>
<td>8.767</td>
<td>18</td>
<td>-2.355</td>
<td>.015</td>
</tr>
<tr>
<td>Day 1 am/Day 4 am</td>
<td>-1.947</td>
<td>9.652</td>
<td>18</td>
<td>-0.879</td>
<td>.195</td>
</tr>
<tr>
<td>Day 1 am/Day 5 am</td>
<td>0.631</td>
<td>9.334</td>
<td>18</td>
<td>0.295</td>
<td>.385</td>
</tr>
<tr>
<td>Day 1 am/Day 6 am</td>
<td>0.368</td>
<td>9.759</td>
<td>18</td>
<td>0.165</td>
<td>.435</td>
</tr>
<tr>
<td>Day 1 am/Day 7 am</td>
<td>1.210</td>
<td>9.168</td>
<td>18</td>
<td>0.575</td>
<td>.286</td>
</tr>
</tbody>
</table>

The next set of paired t-test analysis compared the mean differences in sequential morning sodium values (Table 22). There was a statistically significant mean difference in the sodium values from the day one morning sodium value to the day two morning sodium value, day three morning sodium value to the day four morning sodium value and day four morning sodium value to day five morning sodium value.

The third set of paired-sample t-test analysis compared mean differences in the first evening sodium value with each subsequent evening sodium value for seven days. There were no statistically significant differences in the sodium values at these time points. The fourth set of paired-sample t-test analysis compared the mean differences in
the first morning sodium value to each evening sodium value; there were no statistically
significant differences in the sodium values at these time points.

Table 22

*Mean differences in sequential morning sodium values* (N=19)

<table>
<thead>
<tr>
<th>Day of life</th>
<th>M (SD)</th>
<th>df</th>
<th>t</th>
<th>p (one-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 am/Day 2 am</td>
<td>-5.052 (8.256)</td>
<td>18</td>
<td>-2.668</td>
<td>.008</td>
</tr>
<tr>
<td>Day 2 am/Day 3 am</td>
<td>.315 (4.203)</td>
<td>18</td>
<td>.327</td>
<td>.373</td>
</tr>
<tr>
<td>Day 3 am/Day 4 am</td>
<td>2.789 (4.837)</td>
<td>18</td>
<td>2.514</td>
<td>.011</td>
</tr>
<tr>
<td>Day 4 am/Day 5 am</td>
<td>2.578 (3.948)</td>
<td>18</td>
<td>2.847</td>
<td>.005</td>
</tr>
<tr>
<td>Day 5 am/Day 6 am</td>
<td>-.263 (5.635)</td>
<td>18</td>
<td>-.204</td>
<td>.420</td>
</tr>
<tr>
<td>Day 6 am/Day 7 am</td>
<td>.842 (3.516)</td>
<td>18</td>
<td>1.044</td>
<td>.155</td>
</tr>
</tbody>
</table>

The fifth set of paired t-test analysis (Table 23) compared mean differences in the
first evening sodium value on day one to the following morning sodium value on day two
over the entire seven days. There was a statistically significant mean difference between
the evening sodium value on day one and the morning sodium value on day two. There
was also a statistically significant mean difference between the evening sodium value on
day two compared to the morning sodium value on day three. The mean difference
between day four evening sodium value and day five morning sodium value approached
significance (p =.060). No statistically significant mean differences were found for the
remainder of the time points.
Table 23

*Mean differences in sodium values between evening and morning sodium values by day of life (N=19)*

<table>
<thead>
<tr>
<th>Day of life</th>
<th>M (SD)</th>
<th>df</th>
<th>t</th>
<th>p (one-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 pm/Day 2 am</td>
<td>-5.421 (6.238)</td>
<td>18</td>
<td>-3.787</td>
<td>.000</td>
</tr>
<tr>
<td>Day 2 pm/Day 3 am</td>
<td>-1.631 (4.139)</td>
<td>18</td>
<td>-1.718</td>
<td>.051</td>
</tr>
<tr>
<td>Day 3 pm/Day 4 am</td>
<td>-.1578 (3.484)</td>
<td>18</td>
<td>-.198</td>
<td>.423</td>
</tr>
<tr>
<td>Day 4 pm/Day 5 am</td>
<td>1.421 (3.790)</td>
<td>18</td>
<td>1.634</td>
<td>.060</td>
</tr>
<tr>
<td>Day 5 pm/Day 6 am</td>
<td>-.1052 (4.724)</td>
<td>18</td>
<td>-.097</td>
<td>.462</td>
</tr>
<tr>
<td>Day 6 pm/Day 7 pm</td>
<td>.3157 (4.150)</td>
<td>18</td>
<td>.332</td>
<td>.372</td>
</tr>
</tbody>
</table>

Data were analyzed using repeated measures ANOVA to examine mean sodium values within subjects over the first seven days of life. Mauchly’s test indicated that the assumption of sphericity had been violated (p=.000), Therefore, degrees of freedom were corrected using the Greenhouse-Geisser estimates of sphericity (ε=.299). There were no statistically significant differences within subjects F (1, 3.891) = 6.099, p=0.128. The main effect of change over time was not statistically significant.

In the between subjects analysis (Figure G), there were no statistically significant differences in mean sodium scores over time between groups (p = .608). Figure G represents the mean sodium values by group over 14 time points with each time point representing a 12 hour period of time.
Figure G

*Mean sodium values by group over 12 hour time points/seven days (N=19)*

**Research Question Two**

The second research question was: What are the differences in the incidence of hypernatremia among extremely low birth weight infants who receive a) intravenous fluids only (control group), b) infants who receive enteral sterile water feeds beginning at 24 hours of life (prophylactic group) and c) infants who receive enteral sterile water feeds when hypernatremia is diagnosed? (intervention group) For the purpose of this study, the incidence of hypernatremia is defined as a one occurrence of a sodium value of $\geq 150$ mEq/L.

Eight infants of the total group (42%) had 12 episode of hypernatremia over seven days when hypernatremia was defined as a serum sodium value $\geq 150$ mEq/L: three
of the eight infants (16 %) were in the control group, one infant (5 %) was in the prophylactic group and four infants (21%) were in the intervention group. A Chi-Square test was conducted to examine the differences in the incidence of hypernatremia by groups. There were no statistically significant differences in the incidence between groups ($x^2 = 1.667; p = 0.398$).

When using a serum sodium value of $\geq 146$ mEq/L as the definition of hypernatremia, 19 subjects (100 %) had 19 episodes of hypernatremia over seven days: eight infants (42 %) in the control group, six infant (32 %) in the prophylactic group and five infants (26%) in the intervention group. There were no statistically significant differences in the incidence between groups ($x^2 = 8.233; p = 0.384$).

**Patterns of hypernatremia.**

Thirty eight per cent of the infants in the control group (n=3) had sodium values $\geq 150$ mEq/L (Table 24). Two of these infants had single documented sodium values: one at 12 hours of life and one at 36 hours of life. The third infant had two documented sodium values $\geq 150$ mEq/L: from 48 hours of life to 60 hours of life.

In the prophylactic group, one infant (17%) had a sodium value $\geq 150$ mEq/L occurring at 12 hours of life. Eighty per cent of the infants in the intervention group (n=4) had sodium values $\geq 150$ mEq/L. Two of the infants had single documented sodium values at 12 hours of life. One infant had two episodes and one infant had three episodes of hypernatremia separated by a 12 hour period of normal serum sodium.
Table 24

*Episodes of hypernatremia (Sodium value ≥ 150mEq/L) by groups (n=8)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Single episode/Sodium value</th>
<th>Multiple episodes/Sodium values</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2 (150 &amp; 155)</td>
<td>1 (152-154)</td>
<td>3</td>
</tr>
<tr>
<td>Prophylactic</td>
<td>1 (151)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Intervention</td>
<td>2 (150 &amp; 151)</td>
<td>2 (151-152)</td>
<td>4</td>
</tr>
</tbody>
</table>

**Research Question 3**

The third research question was: Are there differences in the duration of hypernatremia among extremely low birth weight infants who receive a) intravenous fluids only, b) infants who receive enteral sterile water feeds beginning at 24 hours of life and c) infants who receive enteral sterile water feeds when hypernatremia is diagnosed?

For the purpose of this study, a one-time episode of hypernatremia was considered to be ≤ 12 hours in duration. Figure H show the duration of episodes for the eight infants who developed hypernatremia. All of the episodes in the control group were single episodes ≤ 12 hours except for one infant that had two episodes of hypernatremia for ≤ 24 hours and one infant in the intervention group who had three episodes of hypernatremia ≤ 12 hours separated by a 12 hour periods of normal sodium values.
Figure H

*Duration of hypernatremia (Sodium ≥ 150mEq/L) by time values (n=8)*

![Duration of hypernatremia graph](image)

*Note: T stands for time value: each value represents 12 hours of life, sequentially. Blue represents control group, green represents prophylactic group and yellow represents intervention group.*

**Research Question Four**

The fourth research question was: What are the differences in the magnitude of change in serum sodium levels among extremely low birth weight infants who receive intravenous fluids only (control group), infants who receive enteral sterile water feeds beginning at 24 hours of life (prophylactic group) and infants who receive enteral sterile water feeds when hypernatremia is diagnosed (intervention group)?

In the control group, 63% (N=5) of the infants had the lowest sodium values with a range of 131-134mEq/L. One infant in this group had a serum sodium value of 151 at six hours of life. The other infants in this group did not develop hypernatremia. In the
prophylactic group, sodium values ranged from 127-151 mEq/L. One infant (12.5%) had a serum sodium value of 151 at 12 hours of life with the lowest sodium value of 140 mEq/L at 72 hours of life. In the intervention group, of which 80% of the infants developed hypernatremia, the sodium values ranged from 130 to 152 mEq/L.

Table 25

**Magnitude of change in serum sodium values by groups** (N=19)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Sodium Value Range</th>
<th>Hours of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8</td>
<td>131-155</td>
<td>12-144</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time periods of highest sodium</td>
<td>12-96</td>
</tr>
<tr>
<td>Prophylactic</td>
<td>6</td>
<td>127-151</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time periods of highest sodium</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time periods of lowest sodium</td>
<td>12</td>
</tr>
<tr>
<td>Intervention</td>
<td>5</td>
<td>129-152</td>
<td>12-72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time periods of highest sodium</td>
<td>120-145</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time periods of lowest sodium</td>
<td>120-145</td>
</tr>
</tbody>
</table>

**Research Question 5**

Research question 5 was: What is the relationship between the time of observed onset of hypernatremia and the timing of observed onset of diuresis among extremely low birth weight infants who a) receive intravenous fluids only, b) infants who receive enteral sterile water feeds beginning at 24 hours of life and c) infants who receive enteral sterile water feeds when hypernatremia is diagnosed?
Figure I represent the closest sodium value at the time of diuresis in the eight infants who had episodes of hypernatremia.

Eleven infants did not have hypernatremia. For this study, diuresis was defined as a urine output $\geq 3.0$ mls/Kg/hr in a 24 hour period. One of the infants in the control group

Note: Triangle represents control group, rectangle represents prophylactic group and circle represents intervention group.
did not have a diuresis by this definition throughout the seven days of the study. Figure J represents the hours of life at the time of diuresis in the infants without hypernatremia.

Figure J

*Hours of life at time of diuresis (n=10)*

*Note.* *One infant did not have diuresis.*

**Diuresis.**

Three infants in the control group developed hypernatremia. One infant had an initial sodium value of 155 mEq/L at 12 hours of life and a second sodium value of 148 mEq/L at 20 hours of life. This infant had a diuresis at 24 hours of life. The second infant had a sodium value of 147 mEq/L at 24 hours of life. The sodium value at 36 hours of life was 154 mEq/L, at which time diuresis occurred. At 55 hours of life the sodium
value was 152 mEq/L. The third infant in the control group had a sodium value of 150 mEq/L at 24 hours of life, 138 mEq/L at 19 hours of life and 146 mEq/L at 32 hours of life. Diuresis occurred in this infant at 72 hours of life.

There was only one infant in the prophylactically treated group of infants who developed hypernatremia. The initial sodium value was 151 mEq/L at 12 hours of life with a sodium value of 149 mEq/L at 24 hours of life when diuresis occurred.

Four infants in the intervention group were given ESWF when their sodium value was ≥ 150 mEq/L. The first infant had a sodium value of 148 mEq/L at 46 hours of life which increased to 151 mEq/L at 61 hours of life, 13 hours after diuresis occurred. ESWF were started at 61 hours of life and the sodium value was 140 mEq/L at 69 hours of life.

Table 26 examined the magnitude of change in serum sodium values before and after diuresis in all three groups. Two of the three infants in the control group had hypernatremia after diuresis. The third infant had hypernatremia with the first sodium value at 12 hours of life, before diuresis occurred at 24 hours of life. The infant in the prophylactic group who had hypernatremia at 12 hours of life (before receiving ESWF), had a lower sodium value after diuresis at 24 hours of life.

In the intervention group, two infants had higher sodium values after diuresis. One infant had a minimal change in serum sodium value after diuresis. The one infant who had three separated episodes with serum sodium values ≥ 150 mEq/L diuresed at 48 hours of life, with a serum sodium value of 148 mEq/L at 79 hours of life. All four of these infants were received ESWF from the time hypernatremia was diagnosed.

A t-test was conducted to examine the mean time onset of diuresis in both the infants who had hypernatremia and those that did not. There were no statistically
Table 26

*Sodium values immediately before and after diuresis in infants who developed hypernatremia (n=8)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Sodium value/HOL</th>
<th>Diuresis/HOL</th>
<th>Sodium value/HOL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>155/12 hours</td>
<td>24</td>
<td>140/52 hours</td>
</tr>
<tr>
<td>2</td>
<td>147/24 hours</td>
<td>36</td>
<td>154/49 hours</td>
</tr>
<tr>
<td>3</td>
<td>138/19 hours</td>
<td>24</td>
<td>150/32 hours</td>
</tr>
<tr>
<td><strong>Prophylactic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>151/12 hours</td>
<td>24</td>
<td>145/26 hours</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>148/46 hours</td>
<td>48</td>
<td>151/61 hours</td>
</tr>
<tr>
<td>2</td>
<td>151/28 hours</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>151/39 hours</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>149/49 hours</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>152/67 hours</td>
<td></td>
<td>148/79 hours</td>
</tr>
<tr>
<td>3</td>
<td>144/29 hours</td>
<td>48</td>
<td>148/52 hours</td>
</tr>
<tr>
<td>4</td>
<td>140/48 hours</td>
<td>72</td>
<td>138/78 hours</td>
</tr>
</tbody>
</table>

*Note:* HOL is the acronym for hours of life.

significant differences in the onset of diuresis in infants who were treated for hypernatremia and those infants who did not have hypernatremia, t(16)= .941, p =0.180.

In the eight infants who had hypernatremia, two infants had a diuresis at 24 hours of life, three had diuresis at 36 hours of life, and one infant each diuresed at 48, 60 and
72 hours of life, respectively. In the 11 infants who did not have hypernatremia, two infants had a diuresis at 24 hours of life, four infants had diuresis at 48 hours of life, three infants diuresed at 60 hours of life and one infant had diuresis at 72 hours of life. As previously stated, one infant who did not have hypernatremia, did not diuresis. The maximum urine output for this infant was 2.8mls/Kg/hr at 96 hours of life.
Chapter 5

This chapter presents a discussion of the findings of this study. Limitations of the study in relation to sampling, methodological and instrumentation issues will be addressed. Implications of the findings for practice will be discussed as well as recommendations for future research.

Introduction.

Hypernatremia is a physiologic occurrence often seen in ELBW infants and is related to high insensible water loss with substantial contraction of the extracellular space (Lorenz, 1997). The administration of large amounts of intravenous (IV) fluids to decrease high sodium levels may have grave consequences for these infants and contribute to the comorbidities of PDA (Stephens, et al., 2008), BPD (Oh, et al., 2005), IVH (Lim, et al. 2010) and NEC (Wyllie, 2003).

It has been hypothesized that the administration of exogenous fluids, such as sterile water, may decrease high sodium levels in ELBW infants with hypernatremia and decrease the need for intravenous (IV) fluids that contribute to the previously described comorbidities. However, there is little empirical evidence supporting the use of enteral sterile water feeds in ELBW infants. The purpose of this prospective, randomized control trial was to compare the effects of three different fluid management strategies on serum sodium values over seven days among ELBW infants. The three strategies were a) standard care (the use of changes in intravenous fluid volumes if hypernatremia was diagnosed), b) initiation of enteral sterile water feeds at 24 hours of life if the sodium value was $\geq 145$ mEq/L (prophylactic group) and c) the initiation of ESFW if the serum sodium value reached $\geq 150$ mEq/L (intervention group). The study examined the patterns of sodium values, incidence of hypernatremia, duration of hypernatremia,
magnitude of change of serum sodium levels and the relationship between the onset of hypernatremia and the onset of diuresis.

This study was different in several aspects when compared to previous studies. First, the infants enrolled in the study were ≤ 27 weeks gestational age and ≤ 1,100 grams birth weight whereas Olney et al. (2005) enrolled infants < 30 weeks gestational age and Stewart et al. (2009) enrolled infants < 31 weeks gestational age in their RCT. In Gaylord’s et al. (1995) retrospective study, 10 infants treated with ESWF were compared to 20 control infants given standard fluid management. All three studies enrolled infants’ who were ≤ 1,000 grams birth weight. Older infants may have improved renal function which would augment the regulation of fluid balance.

Secondly, this is the first study to have a prophylactic group who received ESWF beginning at 24 hours of life for a serum sodium value ≥ 145 mEq/L and continued to receive ESWF until their sodium value reached 140 mEq/L. Also different was the volume of ESWF given. This study used 10 mls/Kg/day of ESWF, included in the total fluids/Kg/day, to be given by continuous infusion feeds. There was no increase or decrease in the ESWF volume, compared to the RCT conducted by Stewart et al. (2009) whose intervention group received 80 mls/Kg/day total fluids with an adjusted ESWF maximum volume of 50 mls/Kg/day in order to keep urine output > 2 mls/Kg/hr. Olney’s et al. (2005) intervention group received 10-30 mls/Kg/day of ESWF if their total IV fluid requirement was > 120 mls/Kg/day.

Finally, in Gaylord’s et al. (1995), Olney’s et al. (2005) and Stewart’s et al. (2009) studies, infants were kept under a radiant warmer and covered with clear plastic wrap during the seven days of the study. All infants in the current study were placed in
Giraffe Omnibeds (GE Health Care, USA), on admission per NICU protocol. The Omnibed is a type of hybrid humidified incubator (Appendix F) which increases humidification, thereby decreasing insensible water loss (IWL) and this may contribute to improved electrolyte balance. These differences will be addressed in the discussion of the findings of this study.

**Findings.**

*Demographics.* There were no statistically significant differences in gender, birth weight, gestational age or Apgar scores between the three groups. Infant group assignment was done by stratification by weight: ≤ 750 grams and ≥751 to 1,100 grams birth weight. There were six infants ≤ 750 grams, three in the control group, one in the prophylactic group and two in the intervention group. For infants ≥750 grams, five were in the control group, five were in the prophylactic group and three were in the intervention group. There were no statistically significant differences in birth weight between the three groups. These findings indicate that randomization resulted in the three groups being balanced on potentially confounding variables.

*Patterns of sodium values.* This was the first study to examine pattern of changes in sodium values over the first seven days of life. There were no statistically significant differences ($p = 0.128$) in mean sodium values within subjects over the seven days of the study. Additionally, there were no statistically significant differences in mean sodium scores over time between groups ($p = .608$) indicating the main effect of change over time was not statistically significant at any of the 14 time points. It is interesting to note that at 36 and 60 hours of life the mean sodium values in the intervention group were higher than those for the other two groups and approximated sodium values that were
used to define hypernatremia in this study. This most likely reflects normal variations in sodium levels. However, there is little consensus on the definition of hypernatremia or the management of hypernatremia and because of these variations it is possible that infants may be treated for hypernatremia when, in fact, they do not need treatment.

To further describe variations in sodium levels over the first seven days of life, changes in sodium levels between different time points were examined. There was a statistically significant decrease in the morning sodium value from day one to day two ($p = .008$), and a statistically significant increase in morning sodium values from day three to day four ($p = .011$) and day four to day five ($p = .005$). When examining differences between evening and next morning sodium values, there were statistically significant decreases in sodium values found from day one ($p = .000$) to day two and day two to day three ($p = .051$).

These findings may be due to variations in fluid shifts that occur during the first 72 hours of life or may be due to the inability of premature infants to regulate insensible water loss (IWL) (Lorenz, 2008). These decreases, followed by increases in sodium values, is possibly related to the fact that IWL is highly variable (Hammarlund, et al., 1983) and is inversely proportional to gestational age and postnatal age. IWL primarily occurs through the skin and respiratory system (Bieda, Dowling & Winkelman, 2009) and decreases with increased maturation of the stratum corneum (Chiou & Blume-Peytavi, 2004).

Another possible reason for these patterns of sodium values is the limited ability of the immature kidney to compensate for changes in water and electrolyte intake (Lorenz, 2008). ELBW infants have a reduced capability to both retain and excrete
sodium (Hartnoll, 2003) which results in a narrow margin for sodium homeostasis (Modi, 2003). Glomerular filtration rate (GFR) increases rapidly for a few hours after birth due to increased blood flow (Blackburn, 2007), but is not influenced by post-conceptional age as is, for example, skin maturation.

**Incidence.** This study examined differences in the incidence of hypernatremia between the three groups. Forty-two per cent (N=8) of the total group had 12 episodes of hypernatremia over seven days when hypernatremia was defined as a serum sodium value ≥150 mEq/L: 16 % (N=3) were in the control group, 5% (N=1) were in the prophylactic group and 21% (N=4) were in the intervention group. There were no episodes of hypernatremia after 72 hours of life. There were no statistically significant differences in the incidence of hypernatremia between groups. This is consistent with the studies done by Olney et al. (2005) and Stewart et al. (2009) who also did not find any statistical significance between groups in the incidence of hypernatremia. However, in both Olney et al. (2005) and Stewart et al. (2009) studies, it is only known that ESWF were started after enrollment which occurred after 36 hours of life. However, only one infant in the prophylactic group developed hypernatremia while three in the control group and four infants in the intervention group developed hypernatremia, when the definition of hypernatremia was ≥ 150 mEq/L., suggesting that initiation of ESWF at 24 hours of life, in the presence of a sodium value of 145 mEq/L may be beneficial.

It is of interest that in a pilot study conducted at the study setting, (Bieda, 2009), 17% (n=15) of ELBW infants developed 37 episodes of hypernatremia over the first seven days of life, as compared to 42% (n=8) of infants in the current study, having 12 episodes. In the pilot study, one infant had two 48 hour episodes of hypernatremia with
24 hours of normal serum sodium values in between and a second infant had two episodes of hypernatremia starting at 36 hours of life and again developed hypernatremia at 136 hours of life. Three of the infants (3%) had hypernatremic episodes through 84 hours of life compared to this study, where there were no episodes of hypernatremia after 72 hours of life.

The pilot study used data from infants hospitalized from January 1, 2006 through December 31, 2007. The infants in the pilot study and the current study were of comparable gestational age and weight. Also, there were no differences in the percentages of infants in the pilot study and current study who received antenatal steroids, 61% and 63%, respectively. In a study conducted by Omar, DeCristofaro, Agarwal & LaGamma (1999), antenatal steroids were shown to accelerate skin maturation, thereby decreasing the incidence of hypernatremia. Consequently, a major difference in the management of the two groups of infants was the use of the hybrid incubator which began after the time period of the pilot study.

During the pilot study, infants were managed in standard double-walled incubators with a specific humidity protocol, based on the infant’s weight and the humidity was adjusted based on the infant’s skin temperature. The use of the hybrid humidified incubator (Giraffe Omnibed) resulted in a different environmental management than the previous cited studies. In a more recent study conducted by Kim, Lee, Chen & Ringer (2010), 95 ELBW infants were placed in a hybrid humidified incubator compared to 87 ELBW infants who were first placed in radiant warmers, then placed in incubators without humidity. Kim, et al. (2010) demonstrated that less fluid intake was required and there was decreased IWL in the infants who were placed in the
hybrid incubator. Kim, et al. (2010) also demonstrated a statistically significant decrease in the number of hypernatremia episodes \( (p = .014) \) during the first week of life in the ELBW infants placed in the hybrid incubator compared to those infants placed in standard incubators without humidity. Also statistically significant were the decreased episodes of hypernatremia in ELBW infants ≤ 749 grams birth weight \( (p = .003) \) who were placed in the hybrid incubator when compared to infants of the same weight stratification in the regular isolette. Consequently, it is possible that the use of the hybrid incubator in the current study contributed to the decreased number of hypernatremic episodes when compared to the pilot study.

What also needs to be taken into consideration are the changes made in total parenteral nutrition (TPN) over the past 10 years. Infants in the current study are started on ‘starter’ TPN on admission to the NICU, which contains three Gms/Kg/day of protein. There is no sodium chloride in TPN for 24-48 hours of life and then both sodium chloride and protein are incrementally increased. This is in comparison to TPN ordered in 2006-2007 where initial protein in TPN was 1 Gm/Kg/day without sodium chloride for 24 hours and then both sodium chloride and protein were incrementally increased.

There is no consensus between NICUs on the definition of hypernatremia. Although the majority of NICUs define hypernatremia as a serum sodium value \( \geq 150 \) mEq/L, many units define hypernatremia as a serum sodium value \( \geq 145 \) mEq/L. When using a serum sodium value of \( \geq 146 \) mEq/L as the definition of hypernatremia, 19 subjects (100 %) had 19 episodes of hypernatremia over seven days: eight infants (42 %) in the control group, six infants (32 %) in the prophylactic group and five infants (26%) in the intervention group. This may create a predicament when treating hypernatremia
because ‘treatment’ may be occurring in infants who do not need to be treated. In extremely premature infants there is a very narrow range in which the immature kidney can accommodate changes in water and electrolytes (Lorenz, 2008) which is being compromised if treatment isn’t necessary.

**Duration.** This is the first study to examine duration of hypernatremia in infants who received ESWF. The definition of duration was determined by the NICU constraint of unit protocol blood draws which are done approximately every twelve hours. Consequently, the exact duration of a hypernatremic episode could not be determined. Therefore, a single episode of hypernatremia was considered to be ≤ 12 hours. Two infants in the control group had single episodes of hypernatremia ≤ 12 hours and one infant had a 24 hour episode of hypernatremia.

One infant in the prophylactic group (17%) developed hypernatremia and this occurred ≤ 12 hours of life before ESWF were started. The source of the one episode may be laboratory instrument error or may be reflective of maternal electrolyte values. However, there is no support in the literature that infant electrolyte values in the first 24 hours of life reflect maternal values. However, the low incidence of hypernatremia in the prophylactic group compared to the other groups suggests that ESWF may be beneficial in preventing hypernatremia, although this finding was not statistically significant.

In the intervention group, three infants (60%) had single episodes of hypernatremia and one infant had three episodes of hypernatremia ≤ 12 hours in duration separated by 12 hour periods of normal sodium values. This may be a result of the fact that this group of infants was not treated until their sodium values were ≥ 150 mEq/L.
There were no prolonged durations of hypernatremia. The infant in the intervention group who had the three episodes of hypernatremia, separated by periods of normal sodium values may have benefited from an increase in the volume of ESWF administered as has been done in other studies. In the current study, infants received 10 mls/Kg/day of ESWF. However, previous studies allowed for variations in the amount of ESWF used that were greater than the amount used in this study (Berseth and Nordyke, 1993; Gaylord, et al., 1995; Olney, et al., 2005; Stewart, et al., 2009) with volumes from 10-50 mls/Kg/day.

**Magnitude of change.** This study also examined the differences in the magnitude of change in serum sodium levels between the three groups. In the control group 63% had the lowest sodium values and did not develop hypernatremia. The one infant in the prophylactic group had one episode of hypernatremia at 12 hours of life. In the intervention group, the sodium values ranged from 130 to 152 mEq/L. The infants in this study who received ESWF did not have lower sodium values on day of life three and four (sodium values 138-149) compared to infants who did not receive ESWF (sodium values 133-147).

These results are in contrast to results found by Gaylord et al. (1995) who found lower sodium values on the third and fourth days of life in infants who received ESWF compared to the infants who did not receive ESWF. This may be due to the difference in ESWF volumes that were administered. However, lower values during the first week of life may be due to excess free water that results in a dilutional hyponatremia although total body sodium may be decreased, normal or increased (Modi, 1998). The differences in the results of lower sodium values speak to the issue of the definition of
hypernatremia. The medical literature varies on the definition of hypernatremia which is usually reported as either $\geq 146$ mEq/L or $\geq 150$ mEq/L. Based on the findings of this study, the definition of hypernatremia should be 150 mEq/L. The reason for this is the issue in clinical practice of treating a number (e.g., sodium value) and not the infant. If members of a medical team treat a sodium value $\geq 146$ mEq/L, many infants could be treated for hypernatremia when in fact they do not need to be. This in turn may create further electrolyte issues that are iatrogenic.

**Diuresis.** This study also addressed the relationship between the time of observed onset of hypernatremia and the timing of observed onset of diuresis in the three groups. The differences in the mean time onset of diuresis in both the infants who had hypernatremia and those who did not have hypernatremia was not statistically significant ($p = 0.180$). Diuresis occurred both in the infants with hypernatremia and those who did not develop hypernatremia between 24 and 72 hours of life. These findings are different from the diuresis at 72 hours of life reported in Gaylord’s (1995) study, with another increase in urine output at 120 hours of life without an increase in total fluids per day. However, the findings in this study are consistent with the hypothesis that ELBW infants undergo the same three phases of fluid homeostasis: prediuretic, diuretic and post-diuretic during the first week of extrauterine life in order to preserve fluid and electrolyte balance, despite fluid intake (Lorenz, Kleinman, Ahmed & Markarian, 1995).

The accuracy of weighing diapers to determine urine output may play a role in the calculation of urine output and therefore, diuresis. With the use of high-absorbency cellulose/polyacrylate diapers in humidified isolettes, the accuracy of urine output is questionable. In an observational study conducted by Oddie, Adappa and Wyllie (2004),
preweighed diapers with five mls of 0.9% normal saline were placed in isolettes with no humidity or different settings of 40%, 65% or 80% humidity. The diapers were weighed three to six times in a six hour time frame. The rate of weight change for each diaper was calculated to assume linear rate weight loss over time. Oddie et al., (2004) found statistically significant differences ($p < 0.05$) in each humidity setting between the rates of weight change. In a study by Amey et al., (2008) dry diapers were placed in different levels of humidity, between 55% and 90%. There was a statistically significant ($p < 0.05$) increase in the weight of the dry diapers for each humidity level the diaper was placed in. If the humidity was $\geq 80\%$, the diapers continued to gain weight and if the humidity was $\leq 65\%$ humidity, the diapers lost weight.

The results of these two studies have clinical implications in the care of premature infants. Clinicians base daily fluids and electrolytes in premature infants on all fluids taken in and all fluid outputs. The variations in fluid shifts that occur and the inability of ELBW infants to regulate IWL are taken into consideration. However, the inaccuracy of urine output may result in inaccurate IV fluids being ordered and lead clinicians to contemplate pathophysiologic occurrences that may be based on inaccurate intake and output. In addition, attention must be paid to the density of the fluid being weighed and the accuracy and precision of the scale being used (Dowling, Madigan & Siripul, 2004).

TPN may also play a role in diuresis. The increased protein currently found in TPN promotes protein synthesis, prevents catabolism (Poindexter, Langer, Dusick & Ehrenkranz, 2006) and allows weight gain similar to that seen in utero (Maggo, et al., 2007; Velaphi, 2011). A study by Elstgeest, Martens, Lopriore, Walther and TePas
(2010) found diuresis but at lower volumes in the first three days after birth in 70 infants ≤ 28 weeks gestational age who were started on 3Gms/Kg/day of protein in TPN versus 73 infants ≤ 28 weeks gestational age who were started on 1Gms/Kg/day of protein in TPN. Also noted were less of a decrease in body weight as a percentage of birth weight in the group of infants who received the 3Gms/Kg/day of protein in the TPN.

**Limitations.**

The major limitation of this study was the small sample size. It had been anticipated that 39 subjects (13 in each group) would be needed for a power of 0.8 and an α of 0.05. This sample size was not achieved despite a recruitment period of 24 months and consequently a post hoc power analysis found a power of 0.67 with a medium effect size. One reason for non-entry of eligible infants was physician refusal (N=5). The other factors contributing to the small sample size are discussed below.

**Sample.** It can be very difficult to enroll extremely low birth weight infants in clinical research trials and it is not uncommon for parents to be asked to consent for their infant to participate in more than one study (Morley, Lau, Davis & Morse, 2005), which has the potential for adding to the stress of having an ill infant (Stenson, Becher, & McIntosh, 2004). Thirty percent (n= 30) of the parents approached for participation in this study declined, and as a result it was necessary to recruit for 12 months longer than had been anticipated.

Additionally, recent research indicates that those who are enrolled may not accurately represent the population being studied (Wade, Finer, Gantz, Newman, Hensman, Hale, et al., 2012). Interestingly, 95% of the participants were African American. The general racial characteristics at the study site are 65% African American
and 35% Caucasian (R. Martin, personal communication, November 24, 2012). Twenty-
four of the families that declined to participate were Caucasian, five were African
American and one family was Asian. One mother declined to participate because only
one of her twins was eligible for the study.

Historically, minorities are difficult to enroll and are underrepresented in
research. A lack of trust has been identified as a factor in the decision by African
American parents to consent for their child’s participation in research (Shaw, Morrell,
Corbie-Smith, & Goldsmith, 2009) and consequently, building a trusting relationship is a
hallmark of enrolling minorities in research studies (Coleman, 2011). This is reflected in
a spontaneous comment from a mother who agreed to enroll her infant in this study, “I
know this hospital and have come to this hospital since I was little myself and trust what
they do here”.

An additional factor that limited enrollment and extended the duration of
recruitment was the requirement mandated by the IRB that was infants could not be
enrolled in the study if they had a five minute Apgar ≤ 5 at five minutes of life. Twenty-
one infants were unable to be enrolled due to this limitation. The Apgar scoring system
was developed in the 1950’s as a physiologic evaluation of an infant’s transition to
extrauterine life, based on heart rate, respiratory rate, color, muscle tone and reflex
irritability at one minute and five minutes of life, for the purpose of identifying infants
needing resuscitation and evaluating the infant’s response to intervention. The Apgar
scoring system has excellent face validity but poor inter-rater reliability (Clark and
Hakanson, 1988). However, in the 1950’s few preterm infants of the gestational age and
birth weight of infants in the current study survived past delivery.
Catlin et al. (1986) found that one and five minute Apgar scores were directly related to gestational age, and with the exception of heart rate, the components of the Apgar score improved with increasing gestational age, making its use limited for preterm infants (Hegyi et al. 1998). As all five components of the Apgar score are weighted equally, the effect of physiologic immaturity on various components creates a bias in the scoring of premature infants (Bharti & Bharti, 2005; AAP, 2006). Consequently, this requirement was most likely unrealistic for this population and contributed to the difficulty in requiring a sufficient sample.

**Research Design.**

Subjects needed to be recruited before 24 hours of life in order to initiate ESWF in the prophylactic group and seven potential subjects were not able to meet this requirement. Fifty-seven per cent of these infants unable to be enrolled were due to maternal illness and the mother not having seen their infant. It is very difficult to enroll infants within the 24 hours after birth. Parents are emotionally overwhelmed and have difficulty assimilating the birth of a critically ill premature infant. Consequently, it is very difficult for parents to process complex information to participate in neonatal research (Cartright, Mahoney, Ayers & Rabe, 2011) under time constraints (Hoehn, Nathan, White, Ittenbach, Reynolds, Gaynor et al. 2009).

**Methodological.** A methodological limitation of the study were three infants that were lost during the study due to attending physicians stopping the intervention and feeding the infant maternal or donor breast milk. A fourth infant who was randomized to the intervention group never had a sodium value >148 mEq/L and never received ESWF. A fifth infant, while receiving ESWF, had a bilateral intraventricular hemorrhage at 46
hours of life and was placed NPO. This complication has not been reported in the literature with respect to ESWF but occurs in approximately 10% of extremely premature infants. It is associated with injury of the premature lung due to treatment of respiratory distress syndrome, mechanical ventilation and disturbances in pulmonary circulation (Berger, Allred, VanMarter, 2000).

These infants were included through intention-to-treat analysis (ITT). The use of ITT is controversial because it may underestimate the treatment effect (Grady, Cummings & Hulley, 2007). However, other researchers consider this approach as the gold standard strategy for preserving the integrity of randomization (Altman, et al., 2001).

**Instrumentation.** Eleven months into data collection, the hospital system changed from paper to electronic charting. As a result, a learning curve ensued for all employees of the institution where the study was conducted. Saline flushes are an important component of an infant’s fluid intake, and were routinely charted on paper. After changing to the electronic system, flushes were not being charted in EMR. This was despite the efforts by the PI and members of the data collection team reminding the staff nurses to add a column in the intake and output section of EMR to record the composition and volume of flushes. As a result, flushes were not being documented consistently making the accuracy of fluid intake questionable.

In addition, fluid intake (intravenous and nasogastric/orogastric feeds) and outputs (urine output) were calculated at 12 hour intervals per unit policy at the time. The intake and output variables of the study were designed according to the 12 hour interval on paper. Due to changes in charting, the computer calculated intake and output totals every eight hours. As a result, the members of the research team would have to
scroll through all the intake and outputs and recalculate the intake and outputs for 12 hour intervals. This may have resulted in human error of data entry. Every calculation was checked by the PI to ensure inter-rater reliability before data entry.

Another limitation of the study was the use of blood analysis instruments. During this study, there were three different instruments that measured arterial blood gases and electrolytes including sodium: the Stat Profile Critical Care Xpress analyzer (NOVA Biomedical, Waltham, MA), the Gem Premier 4000 (Instrumentation Laboratory, Bedford, MA), and the VIA (International Biomedical, Austin, TX). In addition to reporting blood gas values, the VIA analyzer prints out sodium and potassium values on a paper scroll. However, the analyzer is not interfaced to a computer system and the values must be written down in the patient’s chart. On several occasions, the arterial blood gas was written down, but not the electrolytes and the VIA paper roll had been discarded.

During data collection, the stat profile critical care xpress analyzer was replaced with the Gem Premier 4000 analyzer. This instrument was preferred by hospital administration because of the automatic error detection and had an internal quality control instrument to enhance accuracy and decrease systematic error. However, a change in the instrument itself may have altered the pattern of electrolyte results from one instrument to another.

Due to the three different instruments used to interpret laboratory results and these instruments having different error ranges, there was concern for the possibility of misinterpreting electrolyte values. Electrolyte results vary between hospital laboratories and point of care testing (POCT) instruments used in the NICU. A recent study by King, Mackay, Florkowski & Lynn (2011) demonstrated that sodium values measured in the
main laboratory were higher than those serum sodium value results using point of care testing (POCT) instruments in the NICU. The authors found that hypernatremia was overestimated in those infants who had a corresponding hypoalbuminemia (1400/2420 paired samples). Serum albumin values were not addressed in this study.

**Implications for Future Research.**

This study should be replicated as a prospective, multi-center RCT. This design would allow the representation of multiple geographic areas and a more diverse racial representation of the United States. The study design would also include all infants to be in hybrid incubators or in an incubator with humidification. The design would include variations in volume per kilogram per day of ESWF depending on sodium values. It would be interesting to learn if prophylactic ESWF could prevent hypernatremia with the study requirements of a set amount of total fluids per day. Also, serum sodium values would be determined by one point of care testing (POCT) instrument per site, to avoid multiple serum sodium value results and to have set times for laboratory blood analysis depending on the serum sodium value. Urine output calculations would be done at four hour intervals to better capture the time frame of diuresis. Most importantly, in order to have generalizability of the findings of the study, a large cohort of subjects would be required.

Another area of research is to develop models for predicting optimal water intake in ELBW infants based on birth weight, gestational age, postnatal age and ambient humidity in hybrid isolettes. What needs to be identified are the physiologic fluid requirements of ELBW infants without symptoms of dehydration and/or electrolyte imbalance. Restricted water intake increases the risk of postnatal weight loss but also
decreases the risks of PDA, NEC and BPD. However, there is a much smaller margin of error for ELBW infants due to variable IWL and immature renal function.

Research also needs to be replicated in the area of the effects of prenatal steroids on sodium and water homeostasis. There have been only two research studies (Omar, DeCristofaro, Agarwal and LaGamma, 1999; Dimitriou, Kavvadia, Marcou and Greenough, 2005) that investigated this hypothesis. Both studies determined that prenatal steroid treatment was associated with a decrease in IWL. Omar et al. (1999) study also demonstrated a decrease in hypernatremia. However, the subjects were not randomized and the sample size was small (N=30). Dimitriou, et al. (2005), examined 96 infants ≤ 33 weeks gestation in a secondary analysis and also found a lower IWL (\( p =0.01 \)). Replication of these studies with the inclusion of hybrid isolettes may provide valuable information that would assist in identifying the physiologic fluid requirements of ELBW infants in light of new technology.

**Implications for Nursing Practice.**

The knowledge generated from this study expands our knowledge about the rapidly changing physiology that occurs in critically ill premature infants and the delicate balance of fluid and electrolytes required during the first week of life. This is directly related to sustaining the dynamic equilibrium of the internal environment posited by Cannon (1929) in his theory of physiologic homeostasis.

Nursing research is an essential component of nursing practice in optimizing nursing care and to ensure that infants have better outcomes. An important aspect of nursing research is to communicate findings to the bedside clinician. The knowledge obtained from this study will make nurses more cognizant of the diligence needed in
accurately documenting fluid administration. This study will contribute to current nursing research and assimilate the strength of findings to aid advanced practice nurses and physicians in making evidence-based decisions in the management of ELBW infants.

**Summary**

The purpose of this study was to examine three different fluid management strategies on serum sodium values among ELBW infants during the first week of life. These infants require expert care and due diligence. The homeostatic control of fluids and electrolytes in these infants during the first week of life are an integral component of their survival.

Hypernatremia occurs in ELBW infants. The current use of large volumes of intravenous fluids to control hypernatremia contributes to the comorbidities of BPD, IVH, PDA and NEC. Although this study did not show the statistical significance it had hoped to, it did show clinical significance in a small subset of the infants who received ESWF prophylactically.

Fluid and electrolyte balance in ELBW infants is complicated by this population’s small size, the transition from fetal to extrauterine life and the rapid fluctuations in fluids and electrolytes that may occur. The purpose of research in this area is not to radically change fluid administration, but to assist ELBW infants through the judicious administration of fluids they need in order to have a successful transition to extrauterine life.
### Scoring systems for ICU and surgical patients:

**SNAP-II** and **SNAPPE II** (Score for Neonatal Acute Physiology and SNAP Perinatal Extension)

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**SNAP II**: 0

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**SNAPPE II**: 0  

*In-hospital mortality: see below* Data are collected within the first 12 hours after admission to the NICU

Ref: D K. Richardson et al. SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. *J Pediatr* 2001; 138: 92-100
Appendix B

seca 856:
Precision for safety and health.

Medicine is precision work. Doctors and medical staff must be able to rely on the precision and functionality of their measuring devices. The organ and nappy scale seca 856 is the perfect assistant. The reliable determination of the weight of organs is indispensable in many medical sectors. For example, the specific weight of an organ must be determined precisely in the pathological sector for scientific purposes or in forensic medicine when professional reports have to be drawn up. In paediatrics (especially in neonatology) weighing soiled nappies makes it possible to control the vital food intake of newborn and premature infants down to one gram. Also in aesthetic and reconstructive surgery, the precise weight of tissue and other elements can be extremely important for the success of an operation.

High reliability with protected electronics.

The seca 856 is as safe and easy to clean as is required in its area of application. As the display is slightly raised, it cannot be soiled by possible leaking fluids. And the battery compartment and feet on the base have been sealed off in such a way that no fluid can seep into the scale and damage the electronics.

Reliable measurement of the net weight.

The pre-TARE function makes possible: The specific weight of organs or tissue can be measured safely and reliably, even in a container. When the function is activated, the additional weight of the container is first measured and stored and then automatically deducted from the combined weight value.

Meets all hygienic and economic requirements.

The seca 856 has a robust surface of stainless steel which is easy to clean and thus meets all the hygiene demands made on a medical device. As the scale is battery operated, it can be used anywhere. To make sure that the battery lasts as long as possible, the automatic switch-off function guarantees low power consumption.

The stainless steel surface is tough and easy to clean.

Technical Data

- Capacity: 5,000 g / 11 lbs
- Graduation: 1 g < 3,000 g > 2 g /
  0,05 oz < 6,6 lbs > 0,1 oz
- Dimensions (W x D x H):
  285 x 53 x 285 mm
- Weight: 1.9 kg / 4.2 lbs
- Power supply: Batteries
- Functions: Automatic switch-off,
  Pre-TARE, TARE, HOLD,
  kg/lb switch-over
- Material: Cover - stainless steel,
  base - black plastic material

Seca (2010). Digital organ and nappy scale. Retrieved from:
Appendix C

VIA BLOOD GAS AND CHEMISTRY MONITOR

REAL-TIME ANALYSIS The VIA Blood Gas and Chemistry Monitor connects to an existing arterial or venous line where it withdraws a small blood sample, performs eleven of the most commonly requested blood chemistries and then reinfuses the sample – all in about one minute.

PATIENT ATTACHED, NO MORE MANUAL SAMPLES The changing face of healthcare puts your time at a premium. The current method of manual blood gas sampling and analysis involves many steps – increasing the chance for errors and delays. The VIA Patient Attached Blood Gas and Chemistry Monitor combines automation with proven electrode technology to meet your clinical needs in a variety of critical care settings.

FAST, SAFE, SIMPLE The VIA Blood Gas and Chemistry Monitor combines state-of-the-art technology with safety. This simple closed system eliminates blood loss and blood handling, reducing the risks to both patient and clinician.

ACCURATE RESULTS AND COST EFFECTIVENESS Analysis can now be performed at the bedside – automatically or on demand. Accurate test results can now be reported every 10 minutes over a 72-hour period – all with one VIA Blood Gas and Chemistry Sensor. Your cost goes down with each test.

RAPID RESPONSE TO CHANGING PATIENT STATUS You can now observe dynamic and sometimes rapid changes in patient blood gases and chemistries absolutely a critical clinical advantage, which may lead to improved patient outcomes and shorter hospital stays.

VIA Blood Gas and Chemistry Monitor

Analysis Time Approximately 1 minute

Flow Rate KVO Rate to 5 ml/hr
Purge Rate: 900 ml/hr
Purge per Sample: 8 ml

Volume Limit 1-1000 ml in 50 ml Increments

Infusion Set VIA Infusion Set

Measured Values VIA Sensors & pH, pCO₂, pO₂, K+, Na⁺, Hct

Calculated Values Hgb, BE, HCO₃, TCO₂ and Oxygen Saturation

Calibration Solution Use only fluids and additives designated by Via Medical for measurement of blood gases and chemistries

Calibration Method Initial two-point calibration with each new sensor plus automatic calibration with infusable calibrant every 10 minutes

Alarm Audible tones and diagnostic messages for alarms and advisories

Maximum Output Pressure 600 mm/Hg (11.6 psi)

Dimensions and Weight
Width: 9.8 inches (25.0 cm)
Depth: 9.0 inches (22.8 cm)
Height: 8.5 inches (21.6 cm) monitor and Autosampler/printer
Weight: 16 pounds (7.3 Kg) monitor and Autosampler/printer

Case Aluminum alloy

Battery Rechargeable Ni-Cd battery. A new, fully charged battery will operate the monitor for approximately 2 hours.

Power Requirements 90-125V, 50/60 Hz, 0.75A, three-wire grounded

Ground Current Leakage at 110V line, maximum 15 μA rms ungrounded; Tested to UL Standard 544 for medical equipment

Solution Spillage Resistance Drip Proof (per IEC 601-1)

Operating Temperature 65° to 85°F (18° to 30°C)

Stat Profile Critical Care Xpress from Nova Biomedical

Nova Biomedical Corporation: 200 Prospect Street, Waltham MA, 02254-9141. USA

Description

Stat Profile Critical Care Xpress is a consolidated stat analyzer with up to 20 measured whole blood tests plus 29 calculated tests on board. Thirteen standard menus provide a choice of popular critical care assays.

Beyond these standard menus, a Critical Care Xpress can be configured with any custom test menu that is created from the Critical Care Xpress menu choices.

Features:

- Color Touchscreen Operation
- Automated, On-Board QC
- SmartCheck Automated Maintenance
- No Gas Tanks
- On-Board CO-Oximeter
- Small Sample Volume
- Low Maintenance Biosensors

Innovative and special features particular to this analyser/series of analysers

- Single snap-in combined reagent/waste pack for liquid calibration, no gas tanks.
- Compact design giving largest whole blood test menu: pH, pCO2, pO2, Na+, K+, Cl−, Ca++, Mg++, glucose, lactate, creatinine, tHb, Hct, O2Hb, HHb, MetHb, COHb
- Automatic QC system using snap-in QC pack.
- Full password protection
- Remote control of analysers from laboratory workstation (PDM)
- Small sample size, automatic microsample

Appendix E

Introducing the New GEM Premier 4000.
The new whole blood analyzer that’s so revolutionary and advanced, it makes life simple for everyone.

- Exceptionally easy to use with basic operation and virtually no maintenance
- Remarkably flexible analyte menu, including a full CO-Oximetry panel for every testing need
- iQM, IL’s proprietary Intelligent Quality Management system, provides continuous, real-time monitoring and quality control
- Assures quality results and helps reduce errors, enhancing patient safety and patient care

PAKs contain all the components required for patient testing, are replaced every 30 days, and require no refrigeration.

Bringing the lab to the bedside

- **Easy-to-use** touch-screen displays with clear and concise menus make it simple to select and customize parameters and view results.
- **Self-contained** cartridge PAKs incorporate all components for patient testing and are maintenance-free, maximizing uptime and eliminating staff time.
- **Onboard CO-Oximetry** and a full complement of parameters for every testing need increase flexibility.
- *iQm* automates test quality control and continuously detects, corrects and documents errors and corrective actions...24 hours a day, seven days a week.
- **GEMweb® Plus**, a unique suite of software, enables remote access to any networked analyzer for real-time status updates and supervision of remote locations.
**GEM Premier 4000. Simple. Flexible.**

Assures universal staff training, consistent test results, easy customization and ultimate monitoring and control.

- Basic operation—simply press ‘GO!’ and present sample
- Onboard training videos and screen prompts assure maximum operator familiarity
- Select options at the touch of a button, including micro sample and analyte panels
- Easy access to patient history, including automatic delta calculation between the current and last sample of same sample source

**A broad range of measured analytes and onboard CO-Oximetry, with a full complement of derived parameters, provide a complete clinical assessment from a single sample.**

- Convenient self-contained cartridge PAK in a wide choice of cartridge configurations:
  - High- and low-volume testing
  - Multiple analyte menu configurations
  - Minimal setup with easy front loading and no maintenance
  - Accepts a syringe, capillary tube or ampoule
  - Stored at room temperature
- Optional GEM PCL Plus portable coagulation module

**Customizable for every setting**

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</tr>
<tr>
<td>Blood Gas, Electrolytes, Hct, tHb, O₂Hb, COHb, HHb, MetHb, sO₂</td>
<td>75 150 300 450</td>
<td>30 days</td>
</tr>
<tr>
<td>Blood Gas, Electrolytes, Glu, Lac, Hct, tHb, O₂Hb, COHb, HHb, MetHb, sO₂, BUN*, Creat*, Total Bilirubin*, HCO₃*</td>
<td>75 150 300 450</td>
<td>30 days</td>
</tr>
</tbody>
</table>

*In development.

Easy and intuitive—simply press ‘GO!’ and present sample.
iQM—IL’s patented, real-time, automated, continuous quality assurance system helps ensure optimal test results...regardless of location or operator.

- Continuously monitors and checks all critical components in real time to assure accurate results
- Immediately detects and corrects errors, unlike traditional or auto quality control systems
- Automatically performs and documents system events and corrective actions
- Assures that each patient test result meets established quality specifications and prevents reporting of results when instrument tolerance limits are exceeded
- Is based on the measurement of internal solutions and independent external materials

iQM Delta Chart Reports are automatically generated for each Process Control solution, assuring documentation compliance.

Measured, temperature-corrected values and derived (calculated) test results are prominently displayed; view patient history and enter notification information with one button touch.
Appendix F

Technical Specifications

Dimensions
- Maximum Height: Compan down: 70 in (178 cm)
  Compan up: 94 in (239 cm)
- Minimum Height: Compan down: 58 in (147 cm)
  Compan up: 82 in (208 cm)
- Footprint: 45 in x 26 in
  (114 cm x 66 cm)
- Weight: 294 lbs (129 kg)
- Floor to mattress height: 32 in to 44 in (81 cm to 111 cm)
- Mattress size: 26 in x 15 in (66 cm x 48 cm)
- Access door size: 9 in x 31 in (23 cm x 78 cm)
- Dower size: 19 in x 20 in (48 cm x 50 cm)
- Dower depth: 6 in (20 cm)

Physical Characteristics
- Mattress lift angle: 12°, continuously variable
- Microfilter: 0.5μ. 99.98% efficiency (SM Filtertec™)
- Tubing access ports: 8

Electrical Power Requirements
- 9A @ 115V – 50/60 Hz
- 4.5A @ 220-230/240V – 50/60 Hz

Standards Compliance
- IEC 60601-1 (amendment 1 and 2)
- IEC 60601-1-2
- IEC 60601-2-19 (amendment 1)
- IEC 60601-2-1 (amendment 1)
- Federal Regulation 21 CFR CH-1
  (4-1-92 Edition)
  Section 1020.3(m) – X-ray Attenuation

User Control settings
- Baby (bivacal) temperature control
  35-37.5°C in 0.1°C increments
  (Regulates baby temperature in both
  open and closed bed model)
- Manual Radiant Power Control:
  0-100% in 5% increments
- Air temperature control:
  20-39°C in 0.1°C increments
- Servo humidity control range:
  30-95% rel. humidity in 5% increments
- Alarm sound level: Adjustable audible levels

System Performance
- Microprocessor-based control system
  Self-test functions are performed at
  power-up and during normal operation.
- Open Bed Performance Radiant
  Heater Mode: Radiant Heater
  Element: 450-480 watts
- Closed Bed Performance, Incubator
  Mode: Temperature variability and
  distribution. Exceeds IEC-60601-2-19
  incubation standard
- Patient measurement accuracy:
  ±0.3°C between 30°C to 42°C
- Air Velocity:
  <10 cm/sec Whisper Quiet™ Mode
  closed bed, measured 10 cm above
  the center of the mattress
- Sound level:
  <50 dBa Whisper Quiet™ Mode
  closed bed, measured 10 cm above
  the center of the mattress

In-Bed Scales Performance
- Accuracy: ±10 g (0.35 oz)
- Range: 300 g to 9 kg (6.6 lbs to
  17.6 lbs)

Servo Oxygen Control Performance
- Control Range: up to 65%
- Display Range: 0 to 99%
- Recovery Time:
  <10 minutes to 5% below set point
  after open door
- Alarms: ±3% from set point
- Offset: ±5% average O2 to display

Humidifier Performance
- Recovery time:
  <15 minutes typical recovery to
  75% RH with 38°F set temperature
- Operating time between fills:
  >12 hours at 65% RH control setting
  in a 25°C / 50% RH ambient
- Reservoir capacity: 1000 ml
- Accuracy:
  ±10% for settings up to 85%,
  minimum 75% for settings >85%

Operating Environment
- Temperature: 20 to 30°C
- Humidity: 10 to 95% RH
  (non-condensing)
- Air Velocity: Up to 0.5 m/sec

Storage/Shipping Information
- Temperature: -25°C to 60°C
- Humidity: 0 to 95% RH
  (non-condensing)

Service and Maintenance
- Battery: 9V NiMH
- Recommended Calibration:
  Preventative Maintenance Period:
  Annually
- Limited Warranty:
  One year parts and service

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