STRATEGIES TO IMPROVE RESPIRATORY OUTCOMES IN PREMATURE INFANTS WITH RESPIRATORY DISTRESS SYNDROME

by

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ABSTRACT

STRATEGIES TO IMPROVE RESPIRATORY OUTCOMES IN PREMATURE INFANTS WITH RESPIRATORY DISTRESS SYNDROME

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Infants born prematurely with respiratory distress syndrome (RDS) are at high risk for complications from mechanical ventilation. Strategies are needed to minimize their days on the ventilator. The purpose of this study was to compare extubation success rates in infants treated with two different types of continuous positive airway pressure (CPAP) devices. A retrospective cohort study design was used. Data were retrieved from electronic medical records for patients in a large, metropolitan, Level III neonatal intensive care unit. A sample of 194 premature infants with RDS were selected, 124 of whom were treated with nasal intermittent positive pressure ventilation (NIPPV) and 70 with bilevel variable flow CPAP (SiPAP). Infants in both groups had high extubation success rates (79% of

NIPPV group and 77% of SiPAP group). Although infants in the SiPAP group were extubated sooner, there was no difference in duration of oxygen therapy between the two groups. Promoting early extubation and extubation success are vital strategies to reduce complications of mechanical ventilation that adversely affect premature infants with RDS.

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ABBREVIATIONS

CPAP	Continuous positive airway pressure
FiO_2	Fraction of inspired oxygen
NIPPV	Nasal intermittent positive pressure ventilation
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen

CHAPTER 1

INTRODUCTION

Premature infants are at high risk for complications after birth. Providers seek to minimize complications that are associated with prolonged ventilation. The most effective post-extubation ventilatory strategies are not yet known. A cohort study of extubation success was undertaken to compare the effectiveness of two types of continuous positive airway pressure (CPAP). Background information on the problem of prematurity and therapies known to promote extubation success will be described. A model of extubation success is presented that integrates the physiological foundations of extubation success within a theoretical framework. The chapter will conclude with the study purpose, hypotheses, and assumptions.

Background and Significance

Prematurity is a significant health problem in the United States with 12.3% of all infants born before 37 weeks gestation in 2008 (Martin et al., 2010). Prematurity contributes to the alarming U.S. infant mortality rate of 6.75 deaths per 1000 live births in 2007 (Mathews & MacDorman, 2011). Respiratory distress syndrome (RDS) is a leading co-morbidity associated with prematurity (Rodriguez, Martin, & Fanaroff, 2006). Infants with RDS require ventilatory support at birth. A treatment goal for neonates with RDS is to minimize their time spent on the ventilator. Fewer days on the ventilator mean fewer complications

such as chronic lung disease (Clark et al., 2001) and ventilator-associated pneumonia (Apisarnthanarak, Holzmann-Pazgal, Hamvas, Olsen, & Fraser, 2003). Infants requiring prolonged ventilation are also at risk for poor neurodevelopmental outcomes (Walsh et al., 2005). Minimizing ventilator days may decrease overall lengths of stay (Shiao, Andrews, & Ahn, 2003). Shorter lengths of stay translate into lower costs of hospitalization. The national cost of prematurity is significant with over $50,000 spent for each premature infant per year for a total of $26.2 billion for 2005 (Institute of Medicine, 2006).

Respiratory Distress Syndrome

Respiratory distress syndrome is a disease of surfactant deficiency and diffuse atelectasis (Rodriguez et al., 2006). Surfactant, an endogenous lipoprotein complex, reduces the surface tension within alveoli to prevent their collapse at end expiration (Suresh & Soll, 2003). Atelectasis from collapsed alveoli contributes to the alveolar hypoventilation that is characteristic of RDS (Rodriguez et al., 2006). Work of breathing associated with RDS includes tachypnea, nasal flaring, and retractions. Retractions occur due to the premature infant's compliant rib cage that is prone to collapse as the infant struggles to maintain adequate functional residual capacity, which is the amount of air left in alveoli at end expiration (Wood, 2003).

Infants with RDS commonly require tracheal intubation, surfactant replacement therapy, and ventilatory support at birth to maintain adequate lung volume, which supports oxygenation and ventilation. A treatment goal for infants with RDS is to minimize their time on the ventilator. There are no standard

criteria for extubation readiness (Szymankiewicz, Vidyasagar, & Gadzinowski, 2005). Infants who have weaned to minimal ventilator settings with low FiO_2 requirements and acceptable arterial blood gases are those who may be ready for extubation (Kamlin, Davis, & Morley, 2006).

Definitions of extubation failure and/or success vary by study. Extubation success is often defined as remaining off the ventilator for at least 7 days, but may range from 24 hours to 7 days. Extubation failure is the need for reintubation and mechanical ventilation. As infants wean from mechanical ventilation, they are at risk for developing atelectasis that can contribute to extubation failure (Whitfield & Jones, 1978; Wyman & Kuhns, 1977). Criteria for extubation failure commonly include respiratory acidosis and apnea, the cessation of respiration for ≥ 20 seconds.

Continuous Positive Airway Pressure

Nasally administered CPAP is a therapy that has been shown to prevent extubation failure (Davis & Henderson-Smart, 2003; Higgins, Richter, & Davis, 1991). All types of CPAP are designed to provide positive pressure to the airways of a spontaneously breathing infant (Wiswell & Srinivasan, 2003). Continuous positive airway pressure aids in maintaining functional residual capacity, which helps to prevent atelectasis. Nasal CPAP is categorized by the type of flow used to generate the positive pressure.

Continuous flow CPAP

Continuous flow CPAP is commonly delivered using an infant ventilator paired with nasal prongs. Continuous flow CPAP is a popular method of

delivering CPAP, as the same ventilator can be used for initial management of the intubated infant as well as post-extubation care. During continuous flow CPAP, the ventilator supplies a continuous flow of pressure during the inspiratory and expiratory phases of the breathing cycle. A limitation of continuous flow CPAP is that the infant must exhale against the continuous flow of gas which increases imposed work of breathing (Klausner, Lee, & Hutchison, 1996).

Variable flow CPAP

Variable flow CPAP has been available in the United States since 1995. Both nasal prongs and a nasal mask can be used to administer variable flow CPAP. Courtney et al. (2001) described the variable flow device:

> It uses jet flows at high velocity, which can entrain gas to assist inspiration on demand and keep the CPAP level constant. On exhalation, the design of the nasal prongs results in gas flow being shunted through an expiratory outlet rather than continue toward the nares, which can increase expiratory work. (p. 307)

Because the variable flow device diverts gas flow away from the infant at exhalation (illustrated in Figure 1), patients receiving variable flow CPAP have decreased work of breathing compared to those treated with continuous flow CPAP (Pandit, Courtney, Pyon, Saslow, & Habib, 2001). In addition, variable flow CPAP has the potential to deliver a more stable mean airway pressure, which can improve alveolar recruitment and minimize atelectasis (Courtney et al., 2001). An increased incidence of nasal trauma has been associated with the use of short prongs, such as those used to deliver variable flow CPAP (Robertson,

McCarthy, Hamilton, & Moss, 1996). The leading manufacturer of the variable flow CPAP device reported that nasal trauma can be minimized with proper fixation of the prongs and selection of correctly sized prongs for each infant (Foster, 1998).

Inspiratory Flow

The flow provided by the Infant Flow SiPAP™ driver is accelerated in the twin injector nozzles of the Infant Flow™ Generator. When the patient makes a spontaneous inspiratory effort, the Infant Flow™ Generator converts the kinetic energy of the flow to pressure, thereby reducing the work of breathing for the patient and maximizing pressure stability at the patient interface.

(a)

Expiratory Flow

When the patient makes a spontaneous expiratory effort, they apply a pressure at the nasal interface of Infant Flow™ Generator. This causes the flow to flip around towards the expiratory limb. Stable NCPAP pressure is maintained throughout expiration with a low work of breathing as flow is diverted away from the patient When expiratory effort stops, the flow instantly flips back to the inspiratory position.

(b)

Figure 1 Flow patterns during variable flow CPAP (a) inspiratory and (b) expiratory. From CareFusion (n.d.). Reprinted with permission.

In addition to a baseline of continuous positive airway pressure, infants may be given intermittent, time-cycled positive pressure breaths. These additional breaths may help combat apnea and improve extubation success (Davis, Lemyre, & De Paoli, 2001). Nasal intermittent positive pressure ventilation (NIPPV) is the mode of ventilation that combines continuous flow CPAP with additional positive pressure breaths. The newest generation of variable flow CPAP adds a bilevel mode. In the bilevel mode, infants receive two levels of airway pressure. In addition to the baseline CPAP pressure, the infant

also receives time-cycled breaths at a predetermined rate at a pressure above that set for CPAP. CareFusion (n.d.), manufacturer of the bilevel variable flow Infant Flow SiPAP, reports that this new mode improves oxygenation and ventilation and can help decrease extubation failures and days on the ventilator. At present, insufficient evidence exists to support that claim. Research is needed to identify the most effective post-extubation respiratory strategy so that morbidity associated with prolonged intubation can be minimized.

Framework

A Model of Extubation Success

The model of extubation success (Figure 2) was created using Gibbs' (1972) framework for theory construction. The horizontal dimension of the model is based on the temporal qualifiers described by Gibbs where time zero marks the beginning of the phenomenon. In the model of extubation success, Time 0 (T_0) correlates with the diagnosis of RDS. Patients will be recruited based on their diagnosis of RDS at Time 0. Time 1 (T_1) reflects the time of extubation when infants are placed on either SiPAP or NIPPV. Time 2 (T_2) marks the patient outcome of extubation success and will be measured 7 days after extubation. The vertical dimension of the model represents Gibbs' theory construction process whereby abstract constructs are narrowed to clinical indicators that can be tested.

Theoretical concepts from Roy's Adaptation Model (2009) were chosen to illustrate the process of extubation success. The physiologic needs of oxygenation and ventilation as described by Roy serve as the T_0 construct

because of their relevance to patients with RDS. Premature neonates with RDS have unmet needs for oxygenation and ventilation which can be treated with positive pressure ventilation. These unmet needs are the T_1 construct. Interventions for the unmet needs will be either SiPAP or NIPPV, the T_1 clinical indicator. Roy's levels of adaptation serve as the construct at T_2 with compensatory adaptation reflecting successful extubation and compromised adaptation describing those who require reintubation.

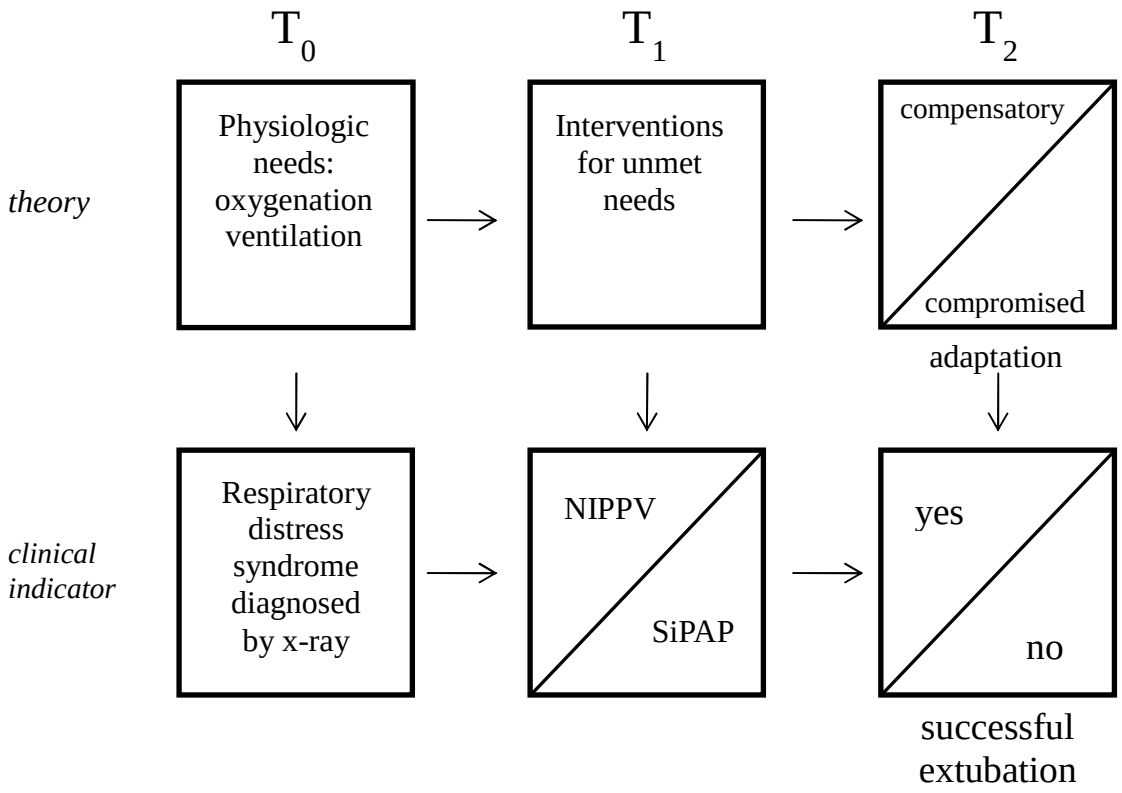

Figure 2 A Model of Extubation Success

Roy Adaptation Model

The Roy Adaptation Model (RAM) has been used as the theoretical framework for numerous studies of infants in the neonatal intensive care unit

(Cheng & Williams, 1989; Garcia & White-Traut, 1993; Harrison, Leeper, & Yoon, 1990; Kitchin & Hutchinson, 1996; Modrcin-Talbott, Harrison, Groer, & Younger, 2003; Raeside, 1997; Shogan & Schumann, 1993). With its focus on the person as an adaptive system, Roy's model serves as a guide for nurses to identify their patients' unmet needs and develop interventions to assist their patients to achieve adaptation. Researchers can use the model to evaluate patient outcomes by their level of adaptation.

Evolution of the RAM

Sister Callista Roy developed the Roy Adaptation Model during her graduate nursing education (Roy, 1988). Her advanced education, including a doctorate in sociology and postdoctoral study in neuroscience, contributed to model revisions. Her theory reflects both her humanistic view related to her life values that were shaped by her religious beliefs, and the knowledge and experience she gained as a pediatric nurse. The scientific assumptions of her adaptation model were based on Helson's adaptation-level theory as well as general system theory (Roy, 2009).

Roy's ideas on adaptation as a conceptual framework for nursing were first published in 1970. The initial concepts outlined at this stage provide the framework for all future versions of the model. Roy explicated her concepts of man as a biopsychosocial being and adaptation as man's response to the stimuli of the changing environment. She viewed man on a health-illness continuum at that time and saw the function of nursing as assisting man to adapt and subsequently move toward the health end of the continuum. Roy identified the

adaptive coping mechanisms (regulator and cognator) at this stage. She defined the regulator mechanism as an autonomic nervous system response to stimuli and the cognator as a conscious response to stimuli (Roy, 1970).

In 1991, Andrews and Roy updated the definition of person to be an adaptive system that copes with stimuli and has behavioral responses. In the RAM, the environment is represented by stimuli, which are classified as focal, contextual, or residual. A focal stimulus, which may be either internal or external, requires immediate attention. Pain in a post-operative patient is an example of a focal stimulus (Roy, 2009). Contextual stimuli are all other stimuli present in the environment. Contextual stimuli affect the way a person responds to a focal stimulus, even if the person is unaware of the contextual stimuli. Patients' cognitive understanding of the temporary nature of post-operative pain is an example of a contextual stimulus that can positively affect adaptation. A residual stimulus is an environmental factor with an unclear effect on the person's current situation. A residual stimulus in a post-operative patient could be a prior negative hospital experience during childhood that the patient does not remember, but which contributes negatively to his adaptation. In combination, the different stimuli contribute to the person's overall adaptation level. This adaptation level marks a point at which the person can respond to the environment positively (Andrews & Roy, 1991).

In the RAM, behavioral responses are the output of the adaptive system (Andrews & Roy, 1991). Roy (2009) defined behavior broadly to include all internal and external reactions to stimuli, including physiological responses. The

four adaptive modes are physiologic, self-concept, role function, and interdependence. The internal control mechanisms, the regulator and cognator subsystems, regulate behavioral output. Andrews and Roy (1991) emphasize the role of nurses in identifying ineffective coping and helping patients to develop adaptive responses to illness.

In her most recent version of the model, Roy (2009) updated her definitions of adaptation, person, environment, health, and the goal of nursing. She expanded her definition of person to include groups of people and emphasized the wholeness of persons in her definitions of person and health. At this time, she also developed three potential adaptation levels. At the integrated level, the functions of life processes are working well to meet the person's needs. In the compensatory level, the control processes of the regulator/cognator have been activated by some disruption. The third level is the compromised level, which occurs when the previous two processes are inadequate and adaptation problems result. The adaptation level determines whether a person or group can respond to a stimulus in a positive way (Roy, 2009).

Previous research in neonates using the RAM

A search of the *CINAHL* database using the major subject "Roy Adaptation Model" paired with the keyword "infant" yielded 61 articles. Seven of those demonstrated use of the RAM as the theoretical framework for the study of infants in the neonatal intensive care unit (NICU). All of the researchers investigated the effects of a stimulus on the adaptive response of the neonate.

Some researchers investigated the effects of environmental stimuli. Others assessed the effects of specific nursing interventions that act as stimuli.

Several nurse researchers found the RAM to be a useful framework on which to base their research of environmental stimuli in the NICU (Harrison et al., 1990; Kitchin & Hutchison, 1996; Raeside, 1997; Shogan & Schumann, 1993). The RAM provided a foundation for Raeside's (1997) mixed-methods study of environmental stimuli that are stressful to infants in the NICU and their mothers. She used Roy's four adaptive modes to collect and describe NICU stressors. She created a stress scale from the data she collected.

In another study of environmental stimuli, Shogan and Schumann (1993) measured oxygen saturation levels as a clinical outcome in their study of the effects of environmental lighting in the NICU. They viewed high light levels (compared to low light levels) as potential stressors that may act as contextual stimuli as described by Roy. They explained that high lighting, as a contextual stimulus, could trigger the regulator subsystem in the neonate and be associated with decreased oxygenation. They recorded infant oxygen saturation at low and high lighting levels. They found that 22% of the infants in their study experienced a drop in oxygen saturation of 4 to 7% after lights were increased. The researchers concluded that high lighting was a source of stress in the NICU.

Kitchin and Hutchinson (1996) studied both human and mechanical touch that act as stimuli during infant resuscitation in the delivery room. They used the RAM as the theoretical framework for their qualitative study. They categorized the types of touch that occur in a resuscitation using Roy's categories of stimuli

(focal, residual, and contextual). They stated that Roy's model also provided a framework for nursing assessment of both the stimuli and the behavioral responses in the infants and the development of nursing interventions to help infants manage stimuli.

Roy's model served as the conceptual framework for the study done by Harrison et al. (1990) on the effects of parental touch on physiologic adaptation of preterm infants. They utilized Roy's concept of focal stimuli to categorize parental touch. Oxygen saturation and heart rate served as the clinical indicators of physiologic adaptation. They found that 45% of infants had lower oxygen saturation levels with parental touch, while 19% of the infants had higher saturation levels. On the second outcome variable of heart rate, they reported that 17% of infants had lower heart rates during parental touch, while 43% had higher heart rates. Harrison et al. (1990) concluded that the variable responses of infants to parental touch necessitate individual plans of care for premature infants.

Unlike the study of parental touch as an environmental stimulus done by Harrison et al. (1990), Modrcin-Talbott et al. (2003) designed a study of gentle human touch (GHT) as an intervention for premature infants in the NICU. They used the RAM as a theoretical framework that illustrated premature infants' responses to stimuli. Because of their immature neurological system, premature neonates demonstrate exaggerated regulator activity. Evidence of this activity can be seen in behaviors such as elevated heart rate and hyperactivity. These behaviors signal adaptive concerns that can be monitored and treated by the

nurse. Modrcin-Talbott et al. (2003) found evidence of adaptive responses in behavioral output such as stabilization of oxygen levels and heart rate after the GHT intervention. They explained that their findings support the proposition that the regulator and cognator mechanisms can contribute to coping in the preterm infant.

Garcia and White-Traut (1993) used the RAM as the framework for their study comparing tactile stimulation to an experimental oral stimulation intervention to treat apnea in premature infants. They hypothesized that their experimental intervention of oral tactile stimulation would promote optimal physiologic adaptation as explained by Roy. They found that both interventions were effective in re-establishing respiration during an apneic episode, the clinical indicator of adaptation in the study.

Cheng and Williams (1989) used Roy's theory as a framework to investigate the effects of chest physiotherapy (CPT) on oxygenation in the very low birth weight infant (less than 1500 grams). They demonstrated that the interventions of CPT and subsequent suctioning may either promote adaptation or cause a maladaptive response. Based on their findings, they recommended close monitoring of oxygenation during these procedures to promote effective adaptation of the neonate.

In summary, nurse researchers have used the RAM as a theoretical framework to study the effects of stimuli on the adaptation of premature infants. Roy's model provides a framework to categorize stimuli that may be focal, contextual, or residual. The RAM illustrates the process of adaptation in the

physiologic mode by means of the regulator subsystem. Behaviors can be operationalized as clinical indicators so that caregivers may evaluate them. Monitoring of behavioral output allows nurses to create interventions that promote adaptation and to compare the efficacy of different interventions. In the proposed study, the RAM provides the theoretical framework for the model of extubation success.

Purpose

Premature infants with RDS requiring prolonged ventilation are at increased risk for morbidity and mortality. Continuous positive airway pressure has been shown to promote extubation success. However, the most effective type of CPAP for promoting extubation success has not yet been shown. The purpose of this cohort study was to compare extubation success in premature infants with RDS treated with SiPAP versus those treated with NIPPV.

Hypotheses

The primary hypothesis was that premature infants with RDS extubated to SiPAP were more likely to remain extubated at 7 days than infants who were extubated to NIPPV. A secondary hypothesis was that infants treated with SiPAP would have a shorter duration of oxygen therapy than those treated with NIPPV.

Assumptions

Assumptions of the model of extubation success are:

1. Premature infants diagnosed with RDS require positive pressure ventilation.

2. Upon extubation from mechanical ventilation, infants will be treated with either SiPAP or NIPPV.
3. Infants have adequate respiratory drive to be successfully extubated.
4. Infants who remain extubated for at least 7 days are unlikely to require reintubation, unless they experience complications such as sepsis, pneumonia, or patent ductus arteriosus.

Summary

Prolonged ventilation of premature infants with RDS increases their risk of complications such as chronic lung disease, pneumonia, and neurodevelopmental delay. Continuous positive airway pressure decreases extubation failure. Two types of CPAP, continuous flow and variable flow, have been used to support premature infants after extubation. The newest type of variable flow CPAP, SiPAP, adds a bilevel mode of support that holds promise in improving respiratory outcomes, such as extubation failure. Research is needed to support this claim.

CHAPTER 2

CRITICAL REVIEW OF RELEVANT LITERATURE

Introduction

Premature infants with respiratory distress syndrome (RDS) who require prolonged ventilation are at increased risk for morbidity and mortality (Martin et al., 2010). Those who need long courses of ventilatory support are susceptible to adverse outcomes such as pneumonia, chronic lung disease, retinopathy of prematurity, and neurodevelopmental impairment (Higgins et al., 1991; Walsh et al., 2005). Strategies known to contribute to extubation success include methylxanthine administration (Henderson-Smart & Davis, 2010) and the application of continuous positive airway pressure (CPAP) after extubation (Davis & Henderson-Smart, 2003). Insufficient evidence exists to support the effectiveness of one type of CPAP over another. All types of CPAP can be classified as either continuous or variable flow based on their delivery mechanism. Therefore, the purpose of this review is to compare studies of continuous flow CPAP and variable flow CPAP on the outcome of extubation success.

Review of Relevant Literature

Factors affecting extubation success include birthweight, gestation, post-extubation respiratory support, and methylxanthine therapy. Infants weighing less than 1250 grams (g) at birth are at highest risk for extubation failure (Kamlin et

al., 2006). Successful extubation is dependent upon the infant possessing adequate respiratory muscle strength and effective respiratory drive (Greenough & Prendergast, 2008). Low birthweight and short gestation are known contributors to extubation failure (Dimitriou, Greenough, Endo, Cherian, & Rafferty, 2002; Hermeto, Martins, Ramos, Bhering, & Sant'Anna, 2009). In a study of infants weighing less than 1000 g, Stefanescu et al. (2003) found that 40% of infants failed extubation. Apnea is often the cause of extubation failure (Dimitriou et al., 2002). Both continuous flow CPAP (Andreasson, Lindroth, Svenningsen, & Jonson, 1988) and methylxanthine therapy (Henderson-Smart & Davis, 2010) have been shown to be effective therapies to manage apnea post-extubation.

Caffeine to Promote Extubation Success

In a *Cochrane Review*, Henderson-Smart and Davis (2010) recommended the initiation of caffeine prior to extubation. In their meta-analysis, they found that infants who received methylxanthines were more likely to be successfully extubated at 7 days than infants who received no treatment or a placebo (*RR* 0.48, 95% CI [0.32, 0.71]). Their meta-analysis included six studies with an outcome of extubation success. Although their analysis included studies of aminophylline and theophylline as well as caffeine, they recommend caffeine based on its wider margin of safety. In the largest study of caffeine therapy to date (*N* = 954), Schmidt et al. (2006) found that infants who received caffeine weaned from mechanical ventilation and oxygen sooner than infants who did not receive caffeine.

Continuous Positive Airway Pressure to Promote Extubation Success

Nasal CPAP is a treatment strategy commonly used in preterm infants with RDS. As early as 1971, Gregory, Kitterman, Phibbs, Tooley, and Hamilton showed that infants with RDS could be successfully treated with CPAP. They documented improved oxygenation in their subjects as well as reduction in apnea and improved survival beyond that which was expected. They attributed the improved oxygenation to inflation of atelectatic alveoli in infants who received CPAP.

In addition to its use as a primary treatment for RDS, CPAP is also used to prevent extubation failure in the smallest babies. In 1991, Higgins, et al. demonstrated that nasal CPAP facilitated extubation in infants weighing less than 1 kilogram (kg). They randomized 58 infants to receive either CPAP or head box oxygen post-extubation. A head box is a hood used to provide warmed, humidified oxygen. Higgins et al. (1991) defined extubation success in their study as no additional support needed for five days post-extubation. Criteria for treatment failure included any one of the following: $FiO_2 \geq .60$, $PaCO_2 \geq 60$ mmHg, pH ≤ 7.23, or moderate to severe apnea. They characterized moderate to severe apnea as three or more episodes per hour or any that required vigorous stimulation or bag-mask ventilation.

In a *Cochrane Review*, Davis and Henderson-Smart (2003) reported that prophylactic use of nasal CPAP reduces adverse events that lead to reintubation. Their meta-analysis included nine studies of premature infants with RDS who were randomized to receive either CPAP or head box oxygen after a period of mechanical ventilation. The definition of extubation success varied among the

nine studies (48 hours in two of the studies, 72 hours in two, five days in one, seven days in three, and one did not specify duration). Criteria for extubation failure were more consistent, with all studies including parameters for respiratory acidosis, increased FiO_2 need, and apnea. The meta-analysis showed a statistically significant ($p < .00001$) reduction in extubation failure in the subjects treated with CPAP (*RR* 0.62, 95% CI [0.49, 0.79]).

A variation of CPAP is the addition of intermittent positive pressure breaths to the baseline CPAP. In a *Cochrane Review*, Davis et al. (2001) reported that the addition of intermittent positive pressure breaths to continuous flow nasal CPAP improves extubation success. Their meta-analysis included three small studies that compared extubation success in infants who received nasal intermittent positive pressure ventilation (NIPPV) versus CPAP alone. Infants who received NIPPV were less likely to require reintubation than those treated with continuous flow CPAP alone (*RR* 0.39, 95% CI [0.16, 0.97]). Recently, a bilevel mode has been added to variable flow CPAP (product name SiPAP). This bilevel mode cycles between two levels of positive pressure. In the bilevel variable flow mode intermittent breaths are delivered at lower peak pressures than with NIPPV and usually with longer inspiratory times (Courtney & Barrington, 2007). No studies were retrieved comparing NIPPV to bilevel variable flow CPAP.

Variable Flow versus Continuous Flow CPAP

Although continuous flow CPAP was the leading type of CPAP used in the 1970s to 1980s, variable flow CPAP has gained in popularity since it became available in the United States in 1995 (Wiswell & Srinivasan, 2003). Several studies have shown advantages of variable flow CPAP such as reducing work of breathing and oxygen need. In a lung model designed to simulate a newborn lung, Moa, Nilsson, Zetterström, and Jonsson (1988) compared variable flow CPAP to continuous flow CPAP. They found that variable flow CPAP created a more stable mean airway pressure with less resistance to flow than continuous flow CPAP. In a randomized controlled trial, Mazzella et al. (2001) found that preterm infants receiving variable flow CPAP had lower respiratory rates and oxygen requirements than infants receiving continuous flow CPAP. Boumecid et al. (2007) compared preterm infants' breathing patterns while receiving continuous and then variable flow CPAP. They found that variable flow CPAP increased tidal volume more than continuous flow CPAP. They attributed the increase in tidal volume to improved thoraco-abdominal breathing synchrony during variable flow CPAP.

In a MEDLINE search of the combined terms, "continuous positive airway pressure" and "newborn" and "extubation," three studies comparing variable flow CPAP to continuous flow CPAP with an outcome of extubation success were identified. Results of these trials were conflicting. In the largest of the studies, Stefanescu et al. (2003) recruited 162 infants with birthweights ≤ 1000 g and randomized them to receive either variable flow CPAP (*n* = 78) or continuous

flow CPAP (*n* = 84). There were no statistical differences between the two groups on maternal or infant characteristics. Infants in the continuous flow group had a mean birthweight of 755 g (*SD* = 155) and a mean gestation of 25.7 weeks (*SD* = 2). Infants who received variable flow CPAP had a mean birthweight of 744 g (*SD* = 123) with a mean gestation of 25.9 weeks (*SD* = 1.5). Stefanescu et al. (2003) defined extubation success as avoiding reintubation for 168 hours (7 days). Criteria for reintubation included $FiO_2 \geq .50$, $PaCO_2 \geq 65$ mmHg with pH < 7.25, or recurrent or significant apnea or bradycardia. They found no significant differences in extubation success rates between the two groups (61.5% of variable flow group, 61.9% of continuous flow group). Their study did show secondary benefits of variable flow CPAP with the variable flow group having fewer total days on oxygen (*p* = 0.03) and shorter lengths of stay (*p* = 0.017).

Conversely, two groups of researchers showed better extubation success in infants receiving variable flow CPAP compared to continuous flow CPAP. Roukema, O'Brien, Nesbitt, and Zaw (1999) randomized 93 infants weighing ≤ 1250 g at birth to receive either variable or continuous flow CPAP. The mean birthweight of their entire sample was 852 g with a mean gestation of 26.2 weeks. They defined extubation success as ≤ 7 days. Extubation failure criteria were not provided. They found that infants in the variable flow group were 2.5 times more likely to be successfully extubated at 7 days of age than were the infants in the continuous flow group (*OR* 2.5, 95% CI [1.1, 5.8]). Extubation rates were not provided.

Sun and Tien (1999) randomized 73 patients weighing ≤ 1250 g to receive either variable flow CPAP (*n* = 38) or continuous flow CPAP (*n* = 35). The infants in the continuous flow CPAP group had a mean birthweight of 857 grams (*SD* = 200) and a mean gestation of 26.3 weeks (*SD* = 1.8). Infants randomized to variable flow CPAP had a mean birthweight of 800 grams (*SD* = 193) and a mean gestation of 26.3 weeks (*SD* = 2). There were no significant differences in birthweight or gestation between the two groups. Sun and Tien (1999) measured extubation failure at both ≤ 24 hours and ≤ 7 days. Criteria for extubation failure were not given. They found that infants in the variable flow group were less likely to fail extubation at ≤ 24 hours ($p < 0.001$) and ≤ 7 days ($p < 0.001$). Extubation success rates at ≤ 7 days were 84% for the variable flow group and 46% for the continuous flow group. The improved extubation success rates seen by Roukema et al. (1999) and Sun and Tien (1999) may have been due, in part, to the larger mean birthweight of their subjects compared to those of Stefanescu et al. (2003).

Bilevel Variable Flow CPAP

In a MEDLINE search combining the terms, “continuous positive airway pressure” and “bilevel or bi-level” and “newborn,” two relevant studies were retrieved. Both were studies comparing variable flow CPAP to bilevel variable flow CPAP. No studies comparing bilevel variable flow CPAP to continuous flow CPAP or NIPPV were found. Both of the studies that compared variable flow to bilevel variable flow CPAP showed that bilevel variable flow CPAP improved respiratory outcomes more than variable flow CPAP alone. In a crossover study,

Migliori, Motta, Angeli, and Chirico (2005) compared the effects of variable flow CPAP and bilevel variable flow CPAP. They recruited 20 infants born at ≤ 32 weeks gestation. Their sample had a mean postconceptual age of 29.6 weeks and a mean weight at time of study of 1033 g. They studied all infants over four one-hour time periods of alternating variable flow and bilevel variable flow CPAP. During periods of bilevel variable flow CPAP infants had higher transcutaneous oxygen levels ($p < 0.001$), lower transcutaneous carbon dioxide levels ($p < 0.001$), and reduced respiratory rates ($p < 0.001$).

Lista et al. (2010) recruited 40 infants born at < 35 weeks and randomized them to receive either variable flow CPAP ($n = 20$) or bilevel variable flow CPAP ($n = 20$) after extubation. Infants in the variable flow CPAP group had a mean birthweight of 1429 g ($SD = 545$) and mean gestation of 30.3 weeks ($SD = 2$). Infants who received bilevel variable flow CPAP had a mean birthweight of 1411 g ($SD = 560$) and a mean gestation of 30.2 weeks ($SD = 2$). There were no significant differences between the groups on birthweight or gestation. They found that infants in the bilevel variable flow CPAP group had fewer days on respiratory support with the bilevel variable flow CPAP group having a mean duration of 3 days ($SD = 1$) and the variable flow CPAP group a mean of 6.2 days ($SD = 2$). The difference in days on respiratory support was significant ($p = 0.025$). Infants in the bilevel variable flow CPAP group also had fewer total days on oxygen ($p = 0.027$) and were discharged sooner ($p = 0.02$). The researchers hypothesized that the reduced need for respiratory support and oxygen in the

bilevel variable flow CPAP group may have been due to improved stabilization of airways and maintenance of optimal functional residual capacity.

Summary

Neonatal healthcare providers are eager to identify strategies to minimize the time their premature patients spend on the ventilator. Infants who require intubation and mechanical ventilation are at increased risk for morbidities such as infection, chronic lung disease, and developmental delay. Reducing days on the ventilator can reduce these complications and decrease hospital lengths of stay. Nasal CPAP is a strategy that has been shown to facilitate successful extubation. Most of the nasal CPAP research has been done on continuous flow CPAP. The newer variable flow CPAP holds promise in improving oxygenation, reducing work of breathing, and facilitating successful extubation. Three studies were retrieved that compared continuous flow CPAP to variable flow CPAP on the outcome of extubation success. Those three studies had conflicting results. Perhaps Stefanescu et al. (2003) were unable to demonstrate improved extubation success rates in their variable flow CPAP group because their babies were smaller and born at shorter gestations than the babies studied by Roukema et al. (1999) and Sun and Tien (1999).

The most recent technological advance in CPAP adds a second, higher level of support to the baseline CPAP provided by the variable flow CPAP device. Two small studies have compared this bilevel mode of variable flow CPAP to variable flow CPAP alone. Both found improved respiratory outcomes in the bilevel variable flow groups. No published studies comparing continuous flow

CPAP or NIPPV to bilevel variable flow CPAP were found. Research is needed to evaluate extubation success rates in infants receiving bilevel variable flow CPAP.

CHAPTER 3

METHODS AND PROCEDURES

Introduction

This retrospective study compared two methods of continuous positive airway pressure (CPAP) delivery on extubation success in premature infants with RDS. This chapter will begin with a description of research design, sample, and setting. Measurement method, procedure, and ethical considerations will be discussed. The chapter will conclude with data analyses and delimitations.

Research Design

A retrospective cohort study design compared extubation success in premature infants treated with two different types of CPAP. Although the strongest support for causation is provided by findings from randomized controlled trials (RCT), experiments in the clinical setting are not always feasible (Cummings, Newman, & Hulley, 2007). Cohort studies are useful when evidence exists to support an association between the outcome of interest and the predictors in the study (Gordis, 2009). Cohort studies can explore the differences between two groups when one has received a treatment and the other has not received that treatment, and only minor differences exist between the groups (Shadish, Cook, & Campbell, 2002). Because a cohort study begins with a defined population, it is useful in exploring the roles of multiple predictors on the outcome of interest (Gordis, 2009).

Types of Cohort Studies

In a cohort study, the cohorts may be prospective, retrospective, or both (Gordis, 2009). In a prospective cohort, participants are recruited based on characteristics they possess that may predict a certain outcome. The subjects are then followed until the outcome of interest occurs (Gordis, 2009). A retrospective cohort is constructed from historical data, which enables the researcher to obtain results on the outcome of interest immediately (Shadish et al., 2002). Exposure and disease status can be simultaneously assessed in a population and provide information about the disease's characteristics and frequency, and relative risk of disease can be calculated (Gordis, 2009). Although a retrospective cohort design is both time and cost-efficient, the researcher must depend upon existing data that may be incomplete, inaccurate, or lacking the variable of interest (Cummings et al., 2007).

Cohort Studies to Support Causal Inference

A retrospective cohort design was chosen to explore extubation success in infants treated with two types of CPAP. Limited data exist on the effectiveness of different types of CPAP used post-extubation. SiPAP became available at the study site in 2008. As SiPAP gained acceptance, traditional continuous flow CPAP was no longer used in this unit. Therefore, the independent variable, type of CPAP, could not have been manipulated as required in a RCT design. The inability to manipulate a variable is a common reason that researchers choose designs other than experiments (Shadish et al., 2002). The retrospective cohort consisted of two groups of patients, one group treated with nasal intermittent

positive pressure ventilation (NIPPV) in 2006-2007 and the other with SiPAP in 2010, from the same hospital from two different time periods. Selection differences are smaller between cohorts drawn from the same population than if non-cohort comparison groups are chosen (Shadish et al., 2002). Therefore, the sample was selected from the same setting at two different time periods instead of choosing a group of patients receiving NIPPV at another institution for comparison.

Causal inferences from descriptive studies are challenging because of lack of control of treatment and lack of randomization to control for confounders (Shadish et al., 2002). However, few phenomena can be clearly reduced to a single causal factor. Multicausal phenomena require that all causal factors be explored and this produces a clearer understanding of the phenomena of interest. One way that a cohort study design can support causal inference is by demonstrating temporal ordering (Newman, Browner, & Hulley, 2007). In this study, premature patients were chosen based on their diagnosis of RDS, which occurred prior to the outcome of interest, extubation. The internal validity of a cohort study is supported when the foundation of the research question is based on a known relationship (Shadish et al., 2002). For example, there is evidence that post-extubation CPAP improves extubation success (Davis & Henderson-Smart, 2003). Statistical conclusion validity, another type of internal validity, was supported by assuring adequate statistical power and measuring effect sizes.

Descriptive studies lack the control of confounders from randomization in a RCT. Confounders need to be identified and controlled in either the design or

the analysis phase of a cohort study (Shadish et al., 2002). In the design phase of a cohort study, confounders can be controlled by matching subjects on known confounders. Several disadvantages to matching exist. A common disadvantage is over-matching, which occurs when the selected variable is not closely associated with the outcome of interest (Newman et al., 2007). If a variable used for matching is not truly a confounder, the power of the study may be reduced (Newman et al., 2007). Matching can be difficult when there are multiple confounders (Shadish et al., 2002). If matching is chosen as a strategy to control for confounders in the design phase, the researcher cannot decide later to control for variables in the analysis phase (Newman et al., 2007). Alternately, matching can be performed in the analysis phase using propensity score methods (Newman et al., 2007). Although propensity score methods have theoretical advantages over traditional regression, they yield similar results of significance and strength of associations (Shah, Laupacis, Hux, & Austin, 2005). Because there were multiple known contributors to extubation success, confounders of gender, gestation, maternal race, and caffeine administration were incorporated in the analysis phase using logistic regression.

Another threat to the internal validity of cohort studies is that of history (Shadish et al., 2002). The threat of history is an event that affected all of the subjects in one group, but not the other, which affected the outcome of interest. No novel therapies, other than SiPAP, became available between 2006 and 2010 that have changed practice patterns in the population sampled that would affect extubation success. To support the external validity of the study, a sample was

selected that was as representative of the population of premature infants with RDS as possible. This was achieved by selecting patients from a large, urban Level III neonatal intensive care unit (NICU) with a diverse patient population.

Studies Using Cohort Design

One of the most well-known cohort studies is that of Doll and Hill (1954). They studied a cohort of British physicians and divided them into groups by smoking history. They followed the physicians over 29 months and documented the incidence of lung cancer in those who died during that period. Their study results provided evidence for the causal relationship between smoking and lung cancer.

Cohort studies have also been used to explore clinical problems in the neonate. In a retrospective cohort study of infants with central venous lines and bacteremia, Benjamin et al. (2001) found that patients whose catheters were discontinued immediately upon a positive blood culture result had better outcomes than those whose catheters were removed after 24 hours. The outcomes they evaluated were end organ damage and death. Cauchi, Parikh, Samuel, and Gornall (2006) used an ambispective cohort design to study outcomes of newborns with gastroschisis who received two different treatment strategies. Infants in the retrospective group had conventional reduction under general anesthesia, while those in the prospective group had bedside reduction without general anesthesia. They found no significant differences between the two groups in morbidity or mortality, supporting the newer procedure as a viable, less costly alternative.

Sample

Data for this study were abstracted from the BabySteps® database for a large, metropolitan, 93-bed, NICU with over 700 admissions per year. The sample included inborn premature infants (born at less than 37 weeks gestation) with a diagnosis of RDS at birth.

All consecutively born premature infants in 2006-2007 with a diagnosis of RDS extubated to NIPPV were selected for Group 1. Infants in Group 2 were born in 2010 and extubated to SiPAP. Choosing consecutively born subjects minimizes selection bias (Hulley, Newman, & Cummings, 2007). The years 2006-2007 were chosen for the NIPPV group, as the two years prior to the acquisition of the SiPAP device and to provide a distinct time separation for the two groups. The year 2010 was chosen because it was the most recent data available. In addition, by 2010, the medical and nursing staff had developed expertise in the care of infants receiving SiPAP.

Selecting patients for both groups from the same NICU population ensured consistency with medical and nursing care. No novel therapies affecting extubation success, other than SiPAP, were initiated in this unit between 2006 and 2010, nor were there significant strides in the medical care of premature infants with RDS during that period. The majority of infants (100% of those in the SiPAP group and 96% of those in NIPPV group) received bovine surfactant, either Infasurf or Survanta. Bovine surfactants are animal-derived surfactants which have been shown to be effective in the treatment of RDS (Seger & Soll, 2009). Most infants received caffeine as well (87% in SiPAP group and 76% of

those in NIPPV group, with no significant difference between the two groups, $\chi^2(1) = 3.42$, $p = .064$).

Study inclusion criteria were premature infants (less than 37 weeks gestation) with a diagnosis of RDS who required mechanical ventilation on the first day of life. Exclusion criteria were those things that could inhibit successful extubation. The exclusion criteria reported by Stefanescu et al. (2003) were adopted for this study. Infants with any of the following conditions were excluded: airway anomalies, neuromuscular disease, major chromosomal and/or congenital anomalies. In addition, infants who were transported in were excluded as they may have been inherently different than inborn infants. Infants who were transported out or died prior to extubation were excluded as well. Inclusion and exclusion criteria were the same for both groups.

Power analysis was performed using G*Power (3.1.0) for a two-tailed Fisher's exact test. An alpha level of .05, power of .80, and medium effect size were used to calculate a priori sample size. With a prediction of a .50 extubation success rate in Group 1 (NIPPV), .75 in Group 2 (SiPAP), and a 1:1 allocation ratio, 64 infants needed to be recruited for each group. A convenience sample of 194 consecutively born infants was recruited with 70 in the SiPAP group and 124 in the NIPPV group.

Setting

The setting for the study was a large, urban Level III NICU in Dallas, Texas. The 93-bed NICU is part of a 998-bed, not-for-profit hospital. The majority

of the infants in the NICU are inborn, but the unit offers transport services to outlying hospitals.

Measurement Methods

The method of data collection was a review of existing electronic medical records. Data were abstracted from the BabySteps® database. The BabySteps® software program and database is owned by Pediatrix Medical Group. The dependent variable of extubation success was defined as avoiding reintubation for 7 days after initial extubation from mechanical ventilation. This definition of extubation success (7 days) was chosen because it was the most commonly used definition in the literature review. Data were also collected on the independent variables of type of CPAP at extubation, gestation, gender, maternal race, and caffeine administration. Low birthweight, short gestation, and male gender are predictors of RDS mortality (Thomas, 2011). These factors may negatively affect extubation success and, therefore, were controlled for in the analysis. The total duration of oxygen therapy (in days) was documented to answer the secondary research question.

Procedure

Following institutional review board (IRB) approval from the hospital and the University of Texas at Arlington, a retrospective cohort of premature infants with RDS was constructed from the BabySteps® database. The retrospective cohort was comprised of two groups of patients, those having received NIPPV post-extubation in 2006-2007 for Group 1, and those having received SiPAP post-extubation in 2010 for Group 2. By obtaining data for both groups from the

same database, the comparability of the data for both groups was ensured. The database requires the entry of gender, gestation, and birthweight for an admission note to be produced. Therefore, all patient records have data entered for those variables. BabySteps® alerts the user if a value is entered for gestation or birthweight that is out of a reasonable range. In this way, the accuracy of the data is improved. The program also requires a daily entry of type of respiratory support, which the provider selects from a drop down menu. The variable of caffeine administration was dependent upon the provider having entered caffeine into the medication list.

To ensure the accuracy of data collection and entry, a random selection of 10% of the records were audited for data collection, and 20% for data entry. All entries were correct for the study variables. There were no missing data for the study variables for any of the subjects in the database. A copy of the data collection tool is provided in Appendix A.

Ethical Considerations

Because the study was a review of existing information in a database, the only risk to participants was loss of confidentiality. To protect the confidentiality of subjects in the study, the only protected health information collected was the medical record number which was de-identified. Patients were assigned a unique study identifier. A list of medical record numbers associated with the study identifiers was kept in a separate file from the study data. The flash drive and a hard copy of the record were stored in a locked file cabinet. Infant birthdates were not used. Instead, their day of life was recorded with day of life 1 as their

day of birth (as in the BabySteps® database). A waiver of consent was approved from both IRBs.

Data Analyses

SPSS Statistics (17.0) was used to analyze the study data. Descriptive statistics were computed for each group on the categories of birthweight, gestation, gender, and maternal race. To test the primary hypothesis, proportions of infants successfully extubated to SiPAP versus NIPPV were compared using a two-tailed Fisher's exact test. Nonparametric tests were computed to compare duration of oxygen therapy and day of life extubated because the distribution of those variables was significantly skewed. A logistic regression model was created to evaluate the contributions of the independent variables (gestation, gender, type of CPAP, maternal race, and caffeine administration) on the dependent variable of extubation success.

Although data were collected on both birthweight and gestation with descriptives reported for both variables, only gestation was used in the logistic regression analysis. Birthweight and gestation are highly correlated (Blair, 1996). When two variables are highly correlated, there is a risk of multicollinearity in regression analysis (Schroeder, Lander, & Levine-Silverman, 1990). Gestation is recognized as the marker of maturity. Birthweight reflects growth and varies between individuals and can be affected by maternal and fetal conditions (Blair, 1996). Therefore, gestation represented the variable of maturity in the logistic regression model. The adjusted odds ratio represented the effect size.

Delimitations

Only premature infants born at less than 37 weeks gestation were recruited for the study, as they were most likely to be affected by RDS and require intubation. Because data were obtained from a convenience sample of infants born in one hospital, the generalizability of the study results is limited.

Summary

A retrospective cohort study design was chosen to compare extubation success in infants treated with two types of CPAP. Cohort studies can provide support for causal inference and have been used by other researchers to study clinical problems in neonates. Cohort studies lack the control of confounders as in a RCT design. Therefore, confounders were controlled in the analysis phase.

CHAPTER 4

FINDINGS

Introduction

The findings of this retrospective cohort study which compared extubation success in premature infants with respiratory distress syndrome (RDS) treated with two different types of continuous positive airway pressure (CPAP) are presented in this chapter. The results of the analyses will be presented for each of the research hypotheses. The chapter will conclude with additional results gleaned from the analyses.

Results

Sample Demographics

The sample included 194 premature infants born at a large, metropolitan, 93-bed, Level III neonatal intensive care unit (NICU). There were 124 infants in the nasal intermittent positive pressure (NIPPV) group, and 70 in the bilevel variable flow CPAP (SiPAP) group. The groups included all infants who met the criteria for the study during the selected time periods. The sample was racially diverse and had approximately equal numbers of males and females. The proportions of infants by gender and maternal race are presented in Table 1.

Table 1 Demographic characteristics of infants (N=194)

		NIPPV group n (%)	SiPAP group n (%)	*p*
Gender	Male	61 (49.2%)	33 (47.1%)	*ns*
	Female	63 (50.8%)	37 (52.9%)	
Maternal race	White	55 (44.4%)	20 (28.6%)	*ns*
	Black	45 (36.3%)	37 (52.9%)	
	Hispanic	18 (14.5%)	9 (12.9%)	
	Other	6 (4.8%)	4 (5.7%)	
Maternal race (collapsed)	White	55 (44.4%)	20 (28.6%)	.03
	Other	69 (55.6%)	50 (71.4%)	

There was no difference in gender between the SiPAP and NIPPV groups, $\chi^2(1) = .08$, $p = .784$. There was no difference in maternal race between the two groups when race was categorized as White, Black, Hispanic, and Other, $\chi^2(1) = 5.94$, $p = .114$. However, when the maternal race variable was collapsed into two categories (White and ethnic minority), there were significantly more minority infants in the SiPAP group than the NIPPV group, $\chi^2(1) = 4.70$, $p = .03$.

Both birthweight and gestation were comparable between the two groups. Infants in the SiPAP group had a mean birthweight of 931 g (*SD* = 351) compared to infants in the NIPPV group with a mean birthweight of 894 g (*SD* = 304). An independent samples *t*-test showed no significant difference between the two groups on birthweight ($p = .439$). The SiPAP group had a median gestation of 26 weeks (range 23-32) and the NIPPV group 27 weeks (range 23-

32). An independent samples *t*-test comparing mean gestational age showed no significant difference between the two groups on gestation (*p* =. 409).

Extubation Success

Comparison of SiPAP and NIPPV groups

The primary hypothesis of the study was that premature infants with RDS extubated to SiPAP were more likely to remain extubated at 7 days than infants who were extubated to NIPPV. There was no difference in extubation success between the NIPPV group and the SiPAP group (*p* = .856, two-tailed Fisher's exact test). Both groups had high extubation success rates which are presented in Table 2.

Table 2 Extubation success rates by type of CPAP

	NIPPV n (%)	SiPAP n (%)
Successfully extubated	98 (79%)	54 (77.1%)
Not successfully extubated	26 (21%)	16 (22.9%)
Total	124 (100%)	70 (100%)

Logistic Regression Model of Extubation Success

Logistic regression analysis with extubation success as the dependent variable and gender, maternal race, gestation, caffeine administration, and type of CPAP as predictors indicated that extubation success increased with increasing gestation, $\chi^2(5) = 13.10$, $p = .022$. The odds ratio for gestation was 1.37, 95% CI [1.14, 1.65] indicating that for every additional week of gestation, the infants were 1.3 times more likely to be successfully extubated. Results of the

analysis with all of the model predictors are provided in Table 3. The model explained 10% of the variance in extubation success.

Table 3 Results of logistic regression model of extubation success

	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Gender (female)	1.08 (.55 - 2.14)	.821	1.08 (.53 - 2.19)	.841
Maternal race (ethnic minority)	1.10 (.55 - 2.21)	.785	1.64 (.75 - 3.56)	.214
Caffeine (yes)	1.33 (.59 - 3.00)	.499	1.63 (.68 - 3.91)	.277
Type CPAP (SiPAP)	0.90 (.44 - 1.81)	.759	0.80 (.38 - 1.71)	.572
Gestation (in weeks)	1.31 (1.10 - 1.57)	.002	1.37 (1.14 -1.65)	.001

Duration of Oxygen Therapy

A secondary hypothesis was that infants treated with SiPAP would have a shorter duration of oxygen therapy. The distribution of the variable days on oxygen was significantly skewed; therefore, nonparametric tests were chosen. The Mann-Whitney U test on total days on oxygen revealed no significant difference between the NIPPV and SiPAP groups, U = 4121, z = -.58, $p = .561$. A Kaplan-Meier survival analysis was performed to analyze time to wean from oxygen for the SiPAP and NIPPV groups. The number of days to wean from oxygen was similar for both groups, with the SiPAP group having a median duration of 71 days and the NIPPV group 67 days, (log rank test $\chi^2(1) = .12$, $p = .734$).

Day of Life Extubated

During data analysis, an additional finding related to extubation was found. Infants who were extubated to SiPAP were extubated sooner than those extubated to NIPPV. The distribution of the variable day of life extubated was significantly skewed, so nonparametric tests were used. A Mann-Whitney U test on day of life extubated revealed that infants in the SiPAP group were extubated significantly sooner than infants in the NIPPV group, U = 3373, z = -2.58; p = .01. A Kaplan-Meier survival analysis was subsequently performed to analyze time to extubation for the SiPAP and NIPPV groups. The median days to extubation for the SiPAP group were 7, compared to 23 days for the NIPPV group. The log rank test approached significance $\chi^2(1) = 3.65$, p = .056, with a significant Breslow test $\chi^2(1) = 7.04$, p = .008, and Tarone-Ware test $\chi^2(1) = 5.59$, p = .018, indicating that infants treated with SiPAP were extubated significantly sooner than those in the NIPPV group.

Summary

Analyses revealed that the proportion of males and females in the SiPAP and NIPPV groups were similar. Infants in the SiPAP group were more likely to be born to mothers of ethnic minorities than to White mothers. The two groups did not differ significantly on birthweight or gestation. Extubation success rates were equally high for both groups. Infants in the SiPAP group were extubated sooner than those in the NIPPV group, but did not significantly differ on duration of oxygen therapy. A logistic regression model demonstrated that extubation success significantly increased with advancing gestational age.

CHAPTER 5

DISCUSSION

Infants born prematurely are at high risk for morbidity and mortality. Those who require prolonged mechanical ventilation often experience complications such as ventilator-associated pneumonia, bronchopulmonary dysplasia (BPD), and retinopathy of prematurity. Strategies are needed to reduce infants' time on the ventilator. Therefore, the purpose of this study was to compare extubation success in premature infants with respiratory distress syndrome (RDS) treated with two different types of continuous positive airway pressure (CPAP).

The pathophysiology of respiratory distress syndrome was reviewed in the first chapter. Two types of CPAP, continuous flow and variable flow, have been used to support premature infants after extubation. The newest type of CPAP, SiPAP, combines variable flow technology with a bilevel mode of support. The mechanism of action of each type of CPAP was described in chapter one, as well as the role of CPAP in facilitating extubation success. A model of extubation success was proposed as a framework for the research. The Roy Adaptation Model provided the theoretical basis for the model and Gibb's framework of theory construction facilitated the creation of clinical indicators from theoretical constructs.

In chapter two, the relevant literature on strategies shown to promote extubation success was presented. Previous research on continuous flow and

variable flow CPAP on the outcome variable of extubation success was synthesized. No published studies compared nasal intermittent positive pressure ventilation (NIPPV) to bilevel variable flow CPAP (SiPAP). Although nasal CPAP is a strategy that has been shown to facilitate successful extubation, most of the research has been done on continuous flow CPAP. The newer variable flow CPAP holds promise in improving oxygenation, reducing work of breathing, and facilitating successful extubation. Three studies were retrieved that compared continuous flow CPAP to variable flow CPAP on the outcome of extubation success. Those three studies had conflicting results. The most recent technological advance in CPAP adds a second, higher level of support to the baseline CPAP provided by the variable flow CPAP device. Two studies documented improved respiratory outcomes in infants treated with bilevel variable flow CPAP compared to variable flow CPAP alone.

A retrospective cohort design was chosen to evaluate extubation success in infants treated with SiPAP versus NIPPV. The merits of the design, as well as the limitations, were discussed in chapter three. Cohort studies can provide support for causal inference and have been used by other researchers to study clinical problems in neonates. Cohort studies lack the control of confounders as in a randomized controlled trial (RCT) design. Therefore, confounders were controlled in the analysis phase. A plan for data collection and analysis was presented. A retrospective review of electronic medical records was undertaken to explore the outcomes of extubation success and days on oxygen. A power analysis was performed to ensure that an adequate sample size was selected.

In chapter four, the results of data analyses were presented. The infants in the SiPAP and NIPPV groups were comparable on gender distribution, birthweight, and gestation. There were more infants born to mothers of ethnic minorities in the SiPAP group than the NIPPV group. Infants in the two groups had equally high rates of extubation success. Those in the SiPAP group were extubated sooner than those in the NIPPV group, but the groups had similar days on oxygen. A logistic regression model demonstrated that extubation success increased with advancing gestational age.

Interpretation of Findings

Extubation Success

The primary hypothesis that infants treated with SiPAP were more likely to remain extubated at 7 days compared to those treated with NIPPV was not supported by the data. Extubation success rates were equally high in both study groups. This is the first study to compare NIPPV via conventional ventilator to bilevel variable flow SiPAP. Because there are no studies that are directly comparable, the findings are compared to those of researchers who studied other forms of CPAP on the outcome of extubation success. Stefanescu et al. (2003) compared infants treated with variable flow CPAP to those treated with continuous flow CPAP. They found no significant difference in extubation success rates between the two groups. However, the extubation success rates reported by Stefanescu et al. (2003) were lower than those in the current study. In the study of Stefanescu et al. (2003), 61.5% of those treated with continuous flow CPAP and 61.9% of those treated with variable flow were successfully

extubated. Their extubation success rates are comparable to those reported by other researchers. In their study of premature infants with respiratory distress syndrome (RDS), Verlato et al. (2008) found that 59% of the infants were successfully extubated to CPAP. Szymankiewicz et al. (2005) reported a 60.8% success rate for their patients who were extubated to CPAP.

In the present study, the extubation success rates of 77% in the SiPAP group and 79% in the NIPPV group are higher than expected. This may be due to the addition of intermittent breaths to the baseline CPAP in both of the study groups. In a *Cochrane Review*, Davis et al. (2001) reported that NIPPV can reduce extubation failure more than CPAP alone. Both the SiPAP and NIPPV groups may have experienced the positive benefits of additional breaths added to the baseline CPAP on the outcome of extubation success. In addition, the majority of infants in both groups received caffeine, 87% of those in SiPAP group and 76% of those in NIPPV group. Caffeine has been shown to promote extubation success, as well (Henderson-Smart & Davis, 2010).

The inability to show a difference in extubation success between the two groups may have been due to a ceiling effect. A ceiling effect occurs when the values of the outcome variable are clustered near the top of the range (Shadish et al., 2002). When that occurs, it becomes difficult to elucidate a difference between two treatments. In this study both the SiPAP and NIPPV groups had high rates of extubation success.

Duration of Oxygen Therapy

The secondary hypothesis that infants treated with SiPAP would have a shorter duration of oxygen therapy than infants treated with NIPPV was not supported. This is in contrast to the findings of Stefanescu et al. (2003) who found that infants treated with variable flow versus continuous flow CPAP had significantly fewer days on supplemental oxygen. Their continuous flow CPAP group had a mean duration of oxygen therapy of 77.2 days compared with 65.7 days for the variable flow group.

Analysis also revealed that infants in the SiPAP group were extubated sooner than infants in the NIPPV group, a statistically significant finding. Infants who are able to be extubated sooner would be expected to have a shorter duration of oxygen therapy. Many respiratory therapies that hold promise in improving respiratory outcomes have failed to reduce long-term oxygen need. Examples of these therapies include NIPPV, synchronized mechanical ventilation, and high frequency ventilation. In a *Cochrane Review*, NIPPV was shown to aid in extubation success when compared to CPAP, but there were no significant differences in oxygen need at 28 days of life (Davis et al., 2001). Several studies have shown positive benefits of synchronized intermittent positive pressure ventilation (SIMV) without a reduction in days on oxygen. In a *Cochrane Review*, Greenough, Dimitriou, Prendergast, and Milner (2008) reviewed 14 studies of synchronized ventilation. They found that infants treated with SIMV had a shorter duration of mechanical ventilation, but no significant reduction in oxygen need at 28 days. Although high frequency oscillatory

ventilation is used to reduce the barotrauma associated with positive pressure ventilation, researchers have been unable to demonstrate a reduction in oxygen dependency when compared to conventional ventilation (Johnson et al., 2002).

Prolonged oxygen need is the defining characteristic of the chronic lung disease of prematurity, BPD. Evidence has shown that BPD is a multifactoral disease. Not only are there neonatal predictors of BPD such as low birthweight, short gestation, prolonged need for mechanical ventilation, and post-natal infection, but there are also maternal factors including antenatal steroid administration and antenatal infection (Van Marter et al., 2002). The contradictory finding of reduced duration of mechanical ventilation in the SiPAP group without a resulting decrease in duration of oxygen need may have been due to a confounder that was not identified in this study such as antenatal or postnatal infection.

Limitations

A retrospective cohort study design limits the variables for study to those that are available in the database. In the current study, no data were available on levels of CPAP nor the rate of positive pressure breaths administered. Additional comparisons of the SiPAP and NIPPV groups could have been made with stratification of levels of treatment which would have provided additional information regarding the contribution of NIPPV and SiPAP on extubation success and oxygen dependency.

Another limitation of the retrospective cohort design is lack of control over confounders that may have impacted the outcomes. There were no protocols or

guidelines for extubation readiness or extubation failure in this neonatal intensive care unit (NICU). In a RCT design, protocols could be established so that uniform criteria exist for both extubation and the need for re-intubation which would limit variability due to differences in provider practice patterns. Although the known confounders of gestation, gender, and caffeine were identified, other confounders may have affected extubation success that have yet to be determined.

Despite the potential limitations of a retrospective cohort design, the essential variables related to extubation success and oxygen dependency were available in the BabySteps® database. This database had daily prompts which ensured that the respiratory variables of type of support and oxygen were entered for every day of the patients' stay. Whereas RCTs are expensive and time consuming related to subject recruitment, retrospective studies allow for data to be collected on a large number of patients at once ensuring adequately powered studies. Retrospective studies often provide evidence to support relationships between variables that can be further studied using a RCT design.

The infants included in this retrospective cohort study were selected from a convenience sample of premature infants born in one hospital. Although the sample drawn from this NICU was diverse, it may not be representative of the larger population of premature infants with RDS. This limits the generalizability of the findings.

Conclusions

This study is the first to compare SiPAP and NIPPV on the outcome of extubation success. The study showed that high extubation success rates are

possible with the use of SiPAP and NIPPV post-extubation. Another promising finding was that infants treated with SiPAP were extubated sooner than those treated with NIPPV. Promoting early extubation and extubation success are vital strategies to reduce complications of mechanical ventilation that adversely affect premature infants with RDS.

Implications for Nursing

Healthcare professionals seek best practices to guide the care of their patients. The results of this study support the use of both NIPPV and SiPAP to promote extubation success in premature infants with RDS. The high extubation success rates in this study may be due, in part, to the high level of expertise and experience of the nursing staff in the Level III NICU from which the patients were selected.

This study highlights the importance of nursing research to validate the subjective experience in the clinical arena. This study of extubation success was undertaken after a positive subjective experience with a new type of CPAP that had been introduced in the NICU. When informally surveyed, the majority of nurse practitioners (70%) at the study site felt that infants treated with SiPAP were more likely to be successfully extubated than those treated with NIPPV. The study findings did not support SiPAP as being more effective the NIPPV. However, the data showed higher than expected extubation success rates for infants treated with both SiPAP and NIPPV. When new technologies become available, nurses should develop studies to evaluate their effectiveness.

Recommendations for Additional Research

Minimizing time on the ventilator is an important goal in the treatment of premature infants with RDS. Identifying strategies that promote extubation success can improve respiratory outcomes for the most vulnerable patients. The current study demonstrated high extubation success rates for two types of CPAP. Potential differences between the types CPAP may be elucidated from a RCT comparing SiPAP to NIPPV. In a RCT, the level of CPAP and number of breaths could be controlled and subgroup analyses performed. In addition, protocols for extubation readiness and failure could be developed ensuring that infants who are being compared met uniform criteria. A multi-center design could broaden the pool of subjects and improve the generalizability of the findings.

Additional research is needed to explore the variables that contribute to oxygen dependency in premature infants with RDS. In the current study, infants in the SiPAP group were extubated sooner than those in the NIPPV group. However, there were no differences in the duration of oxygen therapy between the two groups. This finding suggests that there are additional factors that affect long-term oxygen need. The contribution of gestation, gender, and caffeine administration on oxygen dependency has been shown previously. These known predictors were controlled for in the analysis phase. Factors that affect oxygen dependency and the resulting chronic lung disease of prematurity, BPD, require further study. Previous studies of promising therapies such as high frequency ventilation and synchronized mechanical ventilation have failed to demonstrate reduction in oxygen dependence and BPD. However, as providers develop

expertise in using these new ventilators and modes of ventilation, additional well designed studies may provide insight into strategies that may reduce oxygen dependence and BPD.

APPENDIX A

DATA COLLECTION TOOL

Data Collection Tool

Demographic Data

STUDY ID#	birthweight in grams	gestation in weeks	gender	maternal race
1				
2				
3				
4				
5				

Gender: boy=0, girl=1;
Maternal race: White=1, Black=2, Hispanic=3, All other=4

Study Variables

STUDY ID#	DOL extubated	extubated at 7 days*	Days on O2	caffeine at extubation*	NIPPV or SiPAP
1					
2					
3					
4					
5					

*Yes=1, No=0

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BIOGRAPHICAL INFORMATION

Patricia Thomas completed her undergraduate nursing education at the University of Memphis in 1988. After having found her passion, caring for critically ill neonates, she pursued advanced education as a neonatal nurse practitioner. She received her M.S.N. degree from Vanderbilt University in 1991. Over the next 17 years, she devoted her time and energy to delivering care to her patients while participating in nursing education as a preceptor and lecturer and authoring several articles. She is a contributing member to both the Academy of Neonatal Nursing as well as the National Association of Neonatal Nurses.

In 2008, Patricia began her doctoral studies at the University of Texas at Arlington. While pursuing her doctorate, she received an Academic Scholarship Award from the Academy of Neonatal Nursing, the Graduate Dean Fellowship, and the Elizabeth Callahan-DeBruin Endowed Scholarship. In 2010 she was recognized as a University Scholar and received the M.L. Bond Endowed Fellowship to support her dissertation research. Patricia is a member of the international nursing honor society, Sigma Theta Tau, and was recently honored with membership into the Honor Society of Phi Kappa Phi.

After graduation, Patricia plans to pursue opportunities to teach graduate nursing students while maintaining her clinical practice as a neonatal nurse practitioner. She plans to extend her research into additional strategies which

may improve respiratory outcomes in premature patients with respiratory distress syndrome.

Patricia has been married to her husband, Gerard Bermel, for 25 years. They have one daughter, Rhea, who is a college senior. Patricia and her constant companion Becka, a Belgian Tervuren, compete in dog agility. Patricia is the vice-president and webmaster for the regional Belgian Tervuren club.