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NASAL CANNULA TREATMENT FOR APNEA OF PREMATURITY

by

Dolores Quinn, RN. MN

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of
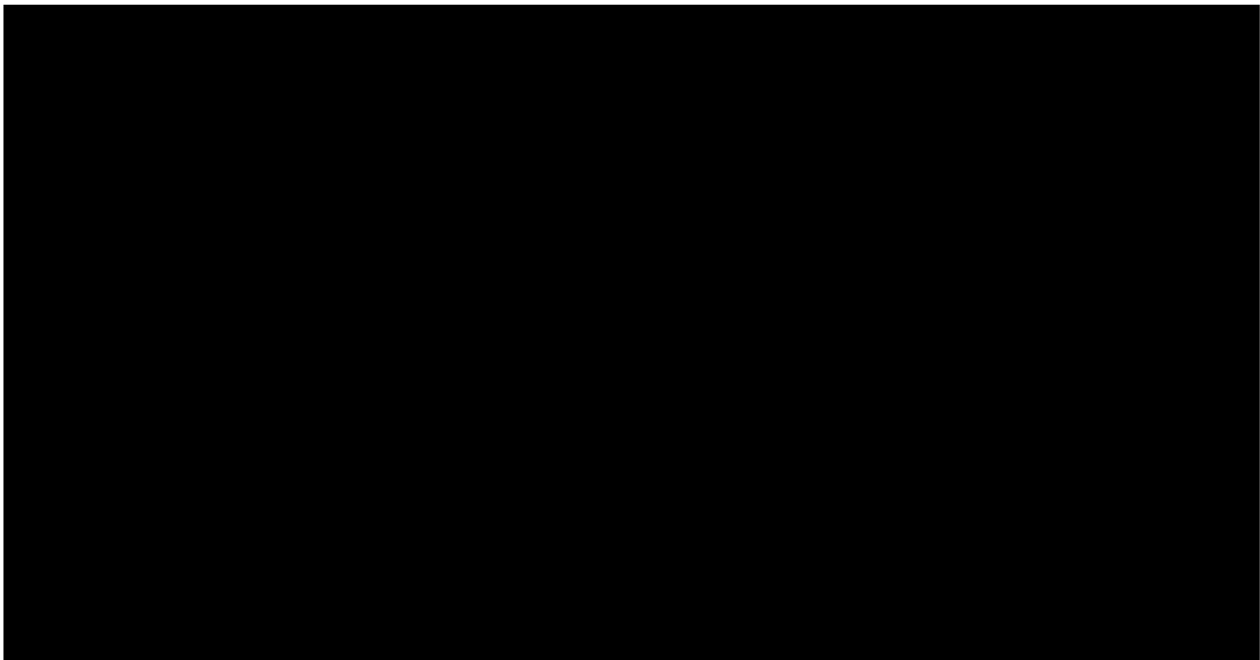
DOCTOR OF PHILOSOPHY

in

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in the

GRADUATE DIVISION

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NASAL CANNULA TREATMENT FOR APNEA OF PREMATURITY

DOLORES QUINN, RN MN

ABSTACT

Apnea of prematurity (AOP) affects approximately 80% of infants born before 37 weeks gestation. The primary cause of AOP is immaturity of the respiratory system. When an apnea episode occurs, prompt treatment is essential to prevent cellular damage especially to the brain cells. Current therapies range from tactile stimulation to mechanical ventilation, which have adverse effects.
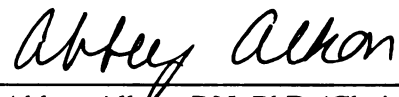
The purpose of the study was to evaluate the use of a nasal cannula 1 Liter/minute FiO_2 .21 as a new therapy to treat apnea episodes for premature infants with the diagnosis of AOP. A randomized interrupted time series clinical trial was conducted in the NICU at Children's Hospital UCSF Medical Center.

Once baseline data (heart rate, respiratory rate and O_2 saturation) were recorded, the infant was randomized to one of two orders. "Order 1" started with the nasal cannula on and "Order 2" started with the nasal cannula off. The duration of the study was six hours and the primary outcome was the frequency of apneic episodes.

Ten infants with a mean (SD) gestation of 30.4 (1.35) weeks and mean (SD) birthweight of 1504 (178.54) grams participated in the study. Five infants were randomized to Order 1 and five were randomized to Order 2. The mean (SD) frequency of apneic episodes for the group (N = 10) 24 hours before study treatment was 10.6 (4) and mean frequency during study was 3 (1.82) and 24 hours after the study was 6.1 (4.2). There was a statistically significant reduction in the frequency of apneic episodes ($t_{(9)}$ = 3.551, p = 0.006) from the 24 hours before to 24 hours after nasal cannula treatment.

During the six hours with alternating use of nasal cannula treatment, there was a statistically significant reduction in the frequency of apneic episodes ($F_{(5,45)}$, = 3.423, p = 0.011). None of the infants studied showed any adverse effects.

Nasal cannula 1Liter/minute FiO_2 .21 reduced the frequency of apneic episodes in a small sample of premature infants diagnosed with AOP. This treatment may be an alterative in the management of apneic episodes.

Abbey Alkon

Abbey Alkon, RN, PhD (Chair)

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CHAPTER 1

INTRODUCTION

Apnea of prematurity affects approximately 80% of infants born before 37 weeks gestation age (Henderson-Smart, 1981; Grisemer, 1990; Eichenwald & Stark, 1993). The definition of apnea of prematurity is a cessation of respiration for a period of >20 seconds. The primary cause of apnea of prematurity is central immaturity of the respiratory centers (Martin, Miller, & Carlo, 1986). When an apneic episode occurs, there is a decrease in heart rate, blood pressure and oxygen saturation, which could result in damage of the cells of the body, especially the brain (Poets, Samuels, & Southall, 1994). Therefore, prompt treatment of apnea is essential. Unfortunately, many of the current therapies ranging from tactile stimulation, medication and mechanical ventilation have unwanted side effects such as nasal trauma (Duxbury, 1987), gastric distention, and feeding intolerance (Hodgeman, 1978), and barotraumas (deLemos & Coalson, 1992; Spitzer, Shaffer & Fox, 1992). It has been suggested that a novel treatment for apnea of prematurity may be the nasal cannula, a soft two-prong system that delivers gentle airflow, could be used to treat apnea since it may not have the adverse effects of other forms of therapy.

Significance

Apnea of prematurity, a problem affecting infants born before 35 weeks gestation, has been shown to be inversely proportionate to gestational age; as the gestational age increases the incidence of apnea decreases (Henderson-Smart, 1981). Clinically significant apnea requiring intervention, either tactile stimulation or medication, occurs in approximately 25% of premature infants who are <2500 grams at birth and 80% of

premature infants <1000 grams at birth (Grisemer, 1990). Apneic episodes have been observed as early as the first week post conceptional age and as late as 44 weeks post conceptional age (PCA) (Grisemer, 1990)

Definition: The definition of apnea has evolved over time. The American Academy of Pediatrics Task Force on Apnea, in 1978, modified the definition as a cessation of airflow for greater than or equal to 20 seconds in duration (Nelson, 1978). This is the definition currently used by neonatal clinicians (Barrington & Finer, 1991). Although bradycardia (heart rate < 100 beats per minute) or oxygen desaturation (SaO_2 < 95%) are associated with apneic episodes, they are not included in the definition (Nelson, 1978).

Classification: The premature infant may exhibit apnea as a presenting symptom of a pathologic disorder. Martin et al (1986) have classified apnea as central apnea, obstructive apnea, and mixed apnea. These classifications are based on the presence or absence of airflow in the upper airway. The treatment is non-specific to the type of apnea that is clinically not distinguished.

Physiologic effects: The physiologic response to apnea includes bradycardia, initially hypertension followed by hypotension and arterial oxygen (SaO_2) desaturation leading to hypoxia (Martin, Miller, & Carlo, 1986). The full term infant and adult respond to this hypoxia with an increase in respiratory rate in contrast to the premature infant who has bradycardia with an apneic episode. This drop in heart rate may start within 1.5 to 2 seconds after the commencement of the apneic episode (Henderson-Smart, Pettigrew & Campbell, 1983; Poets, Samuels & Southall, 1994).

When the premature infant has episodes of apnea associated with bradycardia and cyanosis, the resultant hypoxia and hypercapnia have significant consequences for the

infant's cardiorespiratory stability. Kitchen (1983) reported a correlation between apnea requiring therapy (theophylline) and later developmental delays (n= 252) suggesting a relationship between apnea and diffuse hypoxic-ischemic injury. Their findings were related to the extremely premature (<27 weeks gestation) infants who had severe and persistent apneic episodes with significant cardiovascular and respiratory consequences.

Management: Various therapies have been used to treat apnea, ranging from supportive care, including tactile stimulation, to intensive therapy, such as mechanical ventilation. Tactile stimulation consists of simply touching the infant to resume breathing. Kattwinkel et al (1975) evaluated the use of cutaneous stimulation of the premature infants by the neonatal nurse. They proposed that tactile stimulation reduce apneic episodes. The nurse stimulated the infant by touching the infant's foot for 5 minutes every 15 minutes. This intervention resulted in a decrease in apneic episodes. However, this technique was labor intensive and therefore costly.

Korner et al (1975) studied the effects of an oscillating bed on the frequency of apneic episodes with a sample of premature infants <34 weeks gestation with clinically significant apneic episodes requiring intervention. The infants were placed on a bed oscillating 12-14 regular cycles per minute. A decrease in the frequency of apneic events was noted after the intervention was completed. Other researchers also investigated the efficacy of the oscillating bed as treatment for apnea. Jirapaet (1993) used a crossover design to investigate the hypothesis that vestibular-proprioceptive stimulation (VPS), using an oscillating mattress, would decrease the frequency of apneic episodes and would require minimal intervention by the nurses. Premature infants 29 to 34 week gestation received regular cycles of vertical pulsating stimulation (VPS) 16±4 times per minute.

VPS produced wave motion of 1 cm. The findings supported the hypothesis that the oscillator bed would decrease the frequency of apneic episodes. This study was conducted over a short period of time, 6 hours. In contrast to this study, other researchers reported no effect from cutaneous stimulation by using an oscillating bed to treat apnea of prematurity (Jones, 1981; Saigal, Watts & Campbell, 1986; Monin, 1994). A comparison of the studies reporting a significant reduction in the frequency of apnea (Korner et al, 1975) and those reporting no effect of the oscillating bed (Jones, 1981), reveal the primary difference to be duration of the intervention, 24-hours versus 7-25 days. Results suggest only short-term benefits from the oscillating bed.

The therapy that has been shown to be most effective in treating apnea is the administration of stimulants such as theophylline, caffeine, and doxapram (Aranda, Chemtob, Laudignon & Sasyniuk, 1986; Muttitt, Tierney & Finer, 1988). Caffeine stimulates the respiratory center by blocking adenosine receptors, which is a neurotransmitter that inhibits inspiration. Researchers have evaluated the efficacy of theophylline compared to caffeine in reducing apneic episodes (Davis, Spitzer, Stefano, Bhutani & Fox, 1987). In all these studies both the drugs were effective in reducing apneic episodes. However there has been reports of side effects associated with the use of caffeine and theophylline which include: cardiac arrhythmia (i.e. tachycardia), diuretic effect, arousal, relaxation of the esophageal sphincter tone, gastrointestinal intolerance, failure to gain weight, irritability, jitteriness, sleeplessness, hyper-reflexes, seizures, increase metabolic rate, and decrease weight gain (Kriter, & Blanchard, 1989). Doxapram was first described as a potent stimulant of the respiratory center in treating adult central hypoventilation syndrome. Researchers found doxapram useful in the

treatment of apnea that is refractory to caffeine and theophylline (Eyal, Alpan, Sagi,

Glick, Peleg, Dgani & Arad, 1985). Doxapram stimulates the respiratory drive through

the action of the peripheral chemoreceptors and the medullary neurons. In a double-

blinded clinical trial (n = 16), Eyal et al (1985) compared the effects of theophylline and

doxapram on reducing the frequency of apnea. Doxapram decreased apneic episodes.

However, doxapram was given in combination with theophylline. Therefore, its sole

effect was not tested. Jamali et al (1991) found that doxapram was effective in treating

premature infants with apnea unresponsive to theophylline. But again in this study,

doxapram was given in combination. Clinically, doxapram has limited use since it must

be given by a continuous intravenous route due to its short half-life, and the dose needs to

be increased over time because of habituation (Jamali, Couts, Malek, Finer & Peliowski,

1991).

Occasionally, apneic episodes are not controlled with medication alone and

infants require ventilatory support— either continuous airway positive pressure (CPAP)

or mechanical ventilation. CPAP is delivered through nasal prongs inserted into the nares

secured to the face via a strap surrounding the head. Nasal CPAP (nCPAP) supports the

nasopharyngeal structures and increases the functional residual capacity (FRC).

Kattwinkel et al (19975) first described nCPAP as an effective method of decreasing

obstructive apneic episodes in 18 premature infants. Other researchers have confirmed

this finding and it is now widely used (Sullivan, Issa, Berthon-Jones & Eves, 1981).

Ryan et al (1989) demonstrated that nCPAP is also effective in treating central apnea.

Even though nCPAP and mechanical ventilation are two effective methods in treating and

preventing apnea, they can have significant side effects. Nasal trauma has been reported

as a result of nCPAP. The pressure on the nares and nasal septum causes tissue damage that may require surgical repair. Barotrauma and resultant chronic lung disease are documented side effects of mechanical ventilation (Monin & Vert 1987). These adverse effects have prompted investigators to explore alternative methods to treat apnea of prematurity.

Neonatal clinicians have often observed an improvement in the respiratory status after starting nasal cannula therapy (Locke, Wolfson, Shaffer, Rubenstein & Greenspan, 1993). Locke et al (1993) hypothesized that the improvement that was observed with nasal cannula therapy may be related to delivering end-distending pressure. To test this hypothesis, a randomized clinical trial was conducted whereby 13 premature infants were assigned to either size nasal cannula, 0.2-cm or 0.3-cm, that was given various oxygen flow rates, 0.5, 1 and 2 L/m. The investigators found that, in addition to delivering supplemental oxygen via the nasal cannula, the premature infants received uncontrolled amounts of end-distending pressure when the 0.3-cm size nasal cannula was used. Therefore, prescribing the use of the 0.3-cm nasal cannula at high oxygen flow rates to the premature infant should be done cautiously.

Sreenan et al (2001) conducted a crossover study to evaluate the possibility that the nasal cannula with oxygen could be used in the treatment of apneic episodes. If effective, the nasal cannula could be used as an alternative therapy to nCPAP with oxygen thus avoiding adverse effects such as nasal trauma. Forty premature infants initially received nCPAP with oxygen. After 6 hours they were switched to nasal cannula at various oxygen flow rates, 0.5, 1 and 2 L/m. The investigators reported that the nasal cannula delivered positive airway pressure ranging from 1.4 to 9.8 cm at the various flow

rates, 0.5, 1 and 2 L/m, concluding that the nasal cannula with oxygen was as effective as nCPAP in treating apnea.

In both of these studies, the nasal cannula at flow rates of 0.5, 1 and 2 L/m was shown to reduce apneic episodes with 1 L/m delivering approximately 4-5 cm positive airway pressure (Locke, Wolfson, Shaffer, Rubenstein & Greenspan, 1993; Sreenan, Lemke, Hudson-Mason & Osiovich, 2001). It has been shown that nCPAP of 4-5 cm positive airway pressure is therapeutic in reducing apneic episodes (Sullivan, et al 1981). Therefore, it is proposed in this study that administration of airflow (FiO_2 21%) via the nasal cannula therapy at flow rate of 1 L/m would effectively decrease apneic episodes by providing stimulation to the nasopharyngeal area. It is also proposed that the nasal cannula therapy would be non-intrusive and comfortable for the premature infant.

Apnea of prematurity caused by immaturity of the respiratory and neurologic systems is a time-limited disorder. The treatment strategies should be directed toward supporting the premature infant as he/she grows and matures. Use of airflow (FiO_2 21%) applied via a nasal cannula at 1 Liter per minute (1L/m) is proposed as an alternative therapeutic modality that will still avoid the adverse effects associated with the conventional therapies by preventing collapse of the airway.

Purpose of the Study

The purpose of the study was to evaluate the feasibility and effect of airflow (FiO_2 21%) via the nasal cannula a 1L/minute as a treatment for premature infants with the diagnosis of apnea of prematurity to reduce the frequency, duration, and severity (change in oxygen saturation) of apneic episodes.

Hypotheses

The null hypotheses tested in this study were:

1) There will be no change in the frequency of apneic episodes when the preterm infant receives one-liter airflow (FiO_2 21%) by nasal cannula.

2) There will be no change in the duration of apneic episodes when the preterm infant receives one-liter airflow (FiO_2 21%) by nasal cannula.

3) There will be no change in the severity (oxygen desaturation) of apneic episodes when the preterm infant receives one-liter airflow (FiO_2 21%) by nasal cannula.

Assumptions

The clinical assumptions underlying this study were as follows:

1. Premature infants will have episodes of apnea associated with bradycardia and oxygen desaturation.

2. Apneic episodes require treatment.

3. If apneic episodes are not treated promptly, damage to organs especially brain, may occur.

4. The standard of care for treating apneic episodes is the use of tactile stimulation, medication, CPAP and mechanical ventilation.

5. These methods of treatment have unwanted adverse effects.

6. The Nasal Cannula is a noninvasive method of delivering air to premature infants through the nares.

Definitions of Terms

Apnea is defined as a pause in breathing for >20 seconds and may be associated with bradycardia and or desaturation.

Apnea duration is defined as the time of an apneic episode in seconds that includes the initial 20 seconds before the alarm signals an apneic episode.

Bradycardia is a heart rate that is <100 beats per minute.

Desaturation is an oxygen saturation level <85%.

Birthweight will describe the infant's weight at time of delivery.

Gestational age will be the complete weeks of gestation as determined by maternal history.

Age at enrollment will be the infant's first day of life.

Primary diagnosis will be the diagnosis that was stated on the admission record in the infant's hospital chart.

Illness severity will be estimated by calculating the Score for Neonatal Acute Physiology (SNAP) (Richardson, Gray, McCormick, Workman & Goldman, 1993). The SNAP is a 26-item scoring system that is completed within 24 hours after birth. The 26 items included are: physiologic measures (heart rate, blood pressure, respiratory rate, and temperature), laboratory measures (complete blood count, electrolytes, glucose, blood gases, hematocrit, indirect bilirubin, and direct bilirubin), apnea (responsive to stimulation, unresponsive to stimulation or complete apnea), and seizure (single or multiple). The score may range from 5 to 70 points with the high score indicating higher illness.

Feeding will indicate if the infant is taking enteral nutrition by either gavage or nipple.

Urine output will be the measure of urine per kilogram (kg) per hour in a 24-hour period.

Caffeine dose will indicate the dose of caffeine citrate giving orally in mg/kg/day the infant is receiving.

Hematocrit will be the serum measurement of the percent of erythrocytes.

The Nasal Cannula that will be used is a soft 2-prong system, infant size (Salter Labs REF 1601), placed in the infant's nares.

CHAPTER 2

LITERATURE REVIEW

Introduction

This chapter reviews the relevant literature on Apnea of Prematurity. A review of the definition and classification of apnea, the physiologic effects of apnea and the current methods of treating apnea will be presented.

Definition and Classification of Apnea

Apnea of prematurity (AOP) affects approximately 80% of infants born before 37 weeks gestation. Researchers (Henderson-Smart, 1981; Eichenwald, Aina & Stark, 1997) have reported that the incidence of apnea of the premature infant is inversely proportionate to gestational age, as the gestational age increases the incidence of apnea decreases. In a study conducted by Henderson-Smart (1981) the influence of gestational age on the time course and recurrence of apnea was evaluated. In this retrospective cohort study, the medical records of infants born at King George V Memorial Hospital in London during a 6-year period (1974 through 1979) were reviewed. The investigators classified the infants as having recurrent apnea if three or more episodes lasting longer than twenty seconds were recorded on the heart rate monitor. Gestational age was estimated from either the last menstrual period or an ultrasound assessment. If the gestational age was questionable, a Dubowitz assessment, (a score based on physical and neuromuscular characteristics), was performed. The investigators discovered that 249 (1%) of the 25,154 live births during the 6-year period had recurrent apnea (apneic episodes that occurred more than 6 times in a 24 hour period). Eighteen of those infants were born at term (37-41 weeks gestation). During the earlier years, 1974 through 1977

the incidence of recurrent apnea was 38% of those at 26-27 weeks gestation, 48% of those at 28-29 weeks gestation, 54% of those at 30-31 weeks gestation, 15% of those at 32-33 weeks gestation, and 7% of those at 34-35 weeks gestation. During 1978 and 1979, the incidence of recurrent apnea increased to 78% of those at 26-27 weeks gestation and 75% of those at 28-29 weeks gestation and remained similar at 54% of those at 30-31 weeks gestation, 15% of those at 32-33 weeks gestation, and 7% of those at 34-35 weeks gestation.

In this study, the increase in incidence rate for 26 – 29 weeks gestation infants between the two time periods has been attributed to the increased survival rate at younger ages. The researchers also found that the first episode of apnea was observed on either day 1 or day 2 of life; if apnea had not occurred within the first 7 days of life, it was unlikely that apnea would occur at all. Henderson-Smart (1981) concluded that there is a negative linear relationship between gestational age and the incidence of recurrent apnea. The reason for this link is multifactorial and includes conditions such as infection, metabolic disturbances, intraventricular hemorrhage and heart failure, but is predominantly related to immaturity of the central respiratory control center.

To study the effect of time on the incidence of recurrent apnea, Eichenwald et al (1997) conducted a prospective cohort study to document the natural history of recurrent apnea. The sample included 226 preterm infants between 24 and 28 weeks' gestation at Brigham and Women's Hospital Neonatal Intensive Care Unit (NICU) during the time period of January 1989 to March 1994. The documentation of apnea episode was based on the nursing observation of cardiac and respiratory impedance monitor alarms and clinical assessment of the infant's condition at the time of the alarm. The alarm settings

were 20 seconds for apnea and <100 beats per minute for heart rate. Documentation included information such as apnea alone, bradycardia alone, or both apnea and bradycardia. Any change in skin color (oxygenation documentation) and the type of intervention (tactile stimulation, supplemental oxygen or bag and mask ventilation), required to resolve the incident was recorded. To evaluate the effect of recurrent apnea on the length of the hospital stay, variables that influenced the decision to discharge an infant home, such as temperature control in an open crib, time to full nipple feeding, use of methylxanthines and need for home cardiorespiratory monitor, were recorded. Other variables that may influence the incidence of recurrent apnea, such as diagnosis of chronic lung disease (CLD), and severe abnormalities noted on cranial ultrasound were also recorded. Clinical guidelines for the treatment of apnea, including the use of methylxanthines, were followed. Infants were required to be "spell free" for five days once off methylxanthines therapy before being discharged home.

During the 5-year study period, 788 infants who met the inclusion criteria of AOP between 24 and 28 weeks gestational age were admitted to the Brigham and Women's Hospital NICU. However, only 226 infants with AOP were included in the study sample. The reasons for excluding the remaining infants included transfer to community nurseries before discharge and death immediately after birth. All of the infants included in the sample received methylxanthine therapy. The postconceptional age (PCA) when methylxanthine therapy was discontinued ranged from 34.4 to 35.6 weeks. The PCA was slightly higher in the 24 to 27 week gestational age infant compared to the 28-week gestational age infant ($p < .05$). Recurrent apnea episodes occurred more frequently in the younger gestational age infants ($p < .01$) and persisted beyond 36 weeks PCA in those

infants who were born between 24 and 27 weeks gestation (p < .05). If the infant was born between 24 and 26 weeks gestation, the incidence of recurrent apnea beyond 38 weeks PCA was significantly higher (p < .05). The findings showed that the infants who born at 24 weeks gestation had recurrent apnea episodes beyond 40 weeks PCA (p < .05).

A diagnosis of CLD predicted the recurrent apnea regardless of gestational age (p < .05). There was also a strong trend shown with the infants with 24 weeks gestation to have recurrent apnea at a later PCA, even when the diagnosis of CLD was controlled in the analysis (p = .06). There was no statistically significant correlation between severe cranial ultrasound abnormalities and recurrent apnea. However, only 10% (21/226) of the infants had severe cranial ultrasound abnormalities so there may have been a lack of statistical power to detect a significant relationship.

The pattern of recurrent apnea resolution initially included nursing interventions to resolve the episodes, followed by self-resolved episodes (observed but no intervention needed). The self-resolved episodes that occurred but were not observed persisted $7.4 \pm$ 1.5 days after the last observed episode according to nursing documentation of monitor alarms. The postnatal age when the infant achieved full nipple feeding and ability to maintain adequate skin temperature in an open crib was correlated with the last documented apnea episodes (p < .001). Approximately 15% of the sample (n = 35) was discharged home with a cardiorespiratory monitor. The remainder of the study sample (n = 191) had no further problems. The PCA of the infants sent home on a cardio-respiratory monitor was significantly higher (41 ± 2.6 weeks) compared to those without a monitor (38 ± 2.6 weeks). Only 10 of these 35 infants were discharged home still receiving methylxanthine therapy.

The investigators concluded that the duration of recurrent apnea was longer for younger gestational age infants compared with older gestational age infants. They also suggested that the pathogenesis of recurrent apnea is multifactorial, with the primary etiology as the immaturity of central respiratory control center. Their research findings are consistent with the results reported by Henderson-Smart (1981) that the incidence and duration of apnea are inversely proportionate to gestational age.

Physiologic Effects of Apneic Events

The events that occur after an apneic episode include bradycardia, hypertension and arterial desaturation (Miller & Martin, 1986; Martin, Miller & Carlo, 1986; Brooks, 1996). The infant's physiologic response to hypoxia is an increase in respiratory rate. The premature infant will have bradycardia with the apneic episode. This drop in heart rate (bradycardia) may start within 1.5 to 2 seconds after the commencement of the apneic episode (Miller & Martin, 1992). It has been suggested the bradycardia is a result of hypoxia during the episode of apnea (Henderson-Smart, Butcher-Puech & Edwards, 1986; Girling, 1972). Whereas other investigators postulated that the bradycardia occurs too early in the apnea episode to be related to the decline in oxygen level and the drop in heart rate could be attributed to airway closure (Vyas, Milner & Hopkin, 1981; Upton, Milner & Stokes, 1992; Gabriel & Albani, 1976). It was not until the advent of valid and reliable measures for continuous oxygen saturation that these speculations were challenged.

In a prospective cohort study conducted by Henderson-Smart et al (1986), the oxygen saturation (SaO_2) levels were documented during an apneic episode. The purpose of the study was to investigate the relationship between bradycardia, apnea and

hypoxemia. The SaO_2 level was measured during apneic episodes of 28 preterm infants of gestational age ranging from 27 to 34 weeks. The recording time ranged from 2.8 to 20.5 hours for each infant. The physiologic recordings were of the heart rate measured from ECG leads, nasal airflow from a thermistor in the upper nostril and breathing efforts from a mercury-filed gauge around the abdomen at the level of the umbilicus. In five of the 28 infants, oxygen saturation was also measured. Supplemental oxygen via a plastic head box was administered to 15 infants and theophylline was prescribed for 10 infants. Bradycardia was defined as a drop in heart rate >30% below the baseline. The duration of the apnea episode of >10 seconds was determined from the nasal airflow tracing. The type of apnea was described as central if both abdominal movements and airflow stopped, obstructive if breathing movements continued but airflow stopped, and mixed if a combination of central and obstructive apnea was observed.

In this study, 1520 apneic episodes >16 seconds in duration were recorded during 243 hours period of recording in 28 premature infants. Of these 1520 episodes, 1055 were central, 205 were mixed, and 100 were obstructive. Bradycardia was associated with 363 apnea episodes. The incidence of bradycardia was greater when the duration of apnea increased >20 seconds (p < .001). In addition, the incidence of bradycardia was higher (p < .001) in the 10 infants receiving theophylline (34%) compare to 18 infants without theophylline (20%). However, the duration of the apneic episode was shorter for the infants receiving theophylline 1(0 to 14 seconds) (p < .001). Of the five infants who had continuous SaO_2 measured, 133 apnea episodes were recorded. There was an association between the fall in SaO_2 readings and the onset of bradycardia. The mean time of the drop in SaO_2 was 6.9 ($\pm$3.4) seconds and the mean time for bradycardia was

9.3 (+4.3) seconds. There was a significant linear relationship between these two

variables, mean time of the drop in SaO_2 and mean time for bradycardia ($r = 0.67$, $p <$

.001). The linear regression analysis was also significant between fall in SaO_2 and

bradycardia, controlling for different the apnea duration (apnea 10-14 seconds $r = 0.51$,

apnea 15-20 seconds $r = 0.62$, and apnea > 20 seconds $r = 0.69$). These research findings

suggested that bradycardia occurs as a result of the drop in SaO_2 level. The investigators

postulated that the cause of this phenomenon could be a peripheral chemoreceptors reflex

response, which occurs when breathing either stops or is ineffective.

To further study the relationship between apnea, bradycardia and hypoxia, Poets

et al (1993) conducted a prospective cohort study. The purpose of this study was to

evaluate the relationship between apnea, bradycardia and drop in SaO_2 level and the

sequence of these events.

The study sample consisted of 80 preterm infants (46 male and 34 female), in a

northern England hospital. Twenty-one infants were born between 26 and 31 weeks

gestation, 24 infants were born between 32 and 33 weeks and 35 infants were born

between 34 and 36 weeks. The mean birthweight was 1892 grams ($\pm$547 grams) and the

mean weight at enrollment in the study was 2236 grams ($\pm$330 grams). Forty-two infants

had been diagnosed with respiratory distress syndrome and 25 infants required positive-

pressure ventilation. Twenty-five infants had a history of recurrent apnea as defined as a

cessation of breathing movement and/or airflow for $\geq$4 seconds associated with a fall in

heart rate of $\geq$33% from baseline and a fall in SaO_2 level to $\leq$80%. None of the infants in

the sample were receiving supplemental oxygen, theophylline or cardiotropic

medications. Approximately 12-hour recordings of SaO_2, heart rate, breathing

movements, and nasal airflow were obtained from each infant. Three practicing neonatologist blinded to the infant's clinical history, analyzed a graphic printout of the data. The bradycardia episodes were classified according to the association with a desaturation event and an apnea episode of >4 seconds. Each neonatologist was given instructions on the scoring procedure. Inter-rater reliability was not discussed.

The investigators recorded 193 episodes of bradycardia in 46 of 80 infants. The mean gestational age of the 46 infants was 31.8 weeks compared to 33.4 weeks for the 34 infants who had no bradycardia episodes. Of the 193-bradycardia episodes only 166 had an interpretable SaO_2 signal and 172 had interpretable airflow and breathing patterns. There was a strong association between episodes of apnea and desaturation: 143 (86%) of the 166 episodes and 143 (83%) of 172 airflow and breathing patterns were apneic episodes. Cessation in airflow and breathing movement was detected in 129 (90%) of 172 episodes.

The investigators observed that bradycardia occurred after the apneic episode and after the SaO_2 began to decline. The median time interval between the episode of apnea and desaturation was 0.8 seconds and a median time interval of 4.8 seconds between the apnea and bradycardia. These data suggested a relationship between apnea, bradycardia and desaturation that supports the findings of previous investigations.

In contrast, researchers have challenged the hypothesis that there is a relationship between apnea, bradycardia, and hypoxia (Vyas, Milner & Hopkin, 1981; Upton, Milner & Stokes, 1992). In an effort to show a relationship between apnea, bradycardia and hypoxia, as well as identify the factors responsible for recurrent bradycardia and the different types of apnea, Vyas et al (1981) conducted a prospective cohort study. The

study sample consisted of seven infants who were between the gestational age of 29 and 36 weeks and had a birthweight between 1080 and 2160 grams. All of the infants had recurrent episodes of apnea that were defined as cessation of breathing > 5 seconds and bradycardia that was defined as heart rate < 100 beats per minute but none required any form of respiratory support, i.e. oxygen therapy, nasal continuous positive pressure (CPAP), or mechanical ventilation. The infant's heart rate was monitored with ECG from chest leads, nasal airflow and tidal volume were measured with a face mask pneumotachograph, and intrathoracic pressure changes were monitored with an esophageal catheter that had a soft latex balloon (3 cm x 0.8 cm) mounted on a nasogastric tube. The recordings were obtained for a time period of 30 to 45 minutes.

In this study 172 episodes of apnea (cessation of breathing for > 5 seconds) were recorded in seven infants. Of these episodes of apnea, 44 were associated with bradycardia (heart rate <100 beat per minute). The investigators were able to identify three types of apnea. Obstructive apnea was described as absence of any heart rate signal and breathing effort (n = 86), central apnea was characterized by heart rate impulse on the flow signals (n = 48) and mixed apnea was a combination of both obstructive and central (n = 38). The mean duration of the apnea differed according to the type of apnea, obstructive was 9.93 seconds, central was 8.3 seconds, and mixed was 10.9 seconds. There were 44 apneic episodes associated with bradycardia, 31% were obstructive apnea, 23% were mixed apnea and 16.6% were central apnea. The mean duration of the bradycardia was greatest in the obstructive apnea episode compared to central and mixed apnea (15 seconds vs 10.2 seconds vs 14.2 seconds). The researchers documented that the heart rate in obstructive apnea dropped following attempts to reestablish respiratory

effort as compared to the heat rate in central apnea that dropped quickly and returned to baseline quickly once breathing had commenced.

The investigators concluded that the change in heart rate associated with apnea occurs too rapidly to be caused by a decline in SaO_2 level. They speculated that there is a peripheral mechanism (vagus nerve stimulation) responsible for the bradycardia when an episode of apnea occurs and not when hypoxia occurs. In addition, the researchers also suggested that bradycardia associated with obstructive apnea was related to respiratory effort made against a closed glottis. Unfortunately, they commented about the response in oxygen saturation during an apnea and bradycardia episode without measuring the SaO_2 level. Therefore, Upton et al (1992) designed a study that would address the importance of apnea, bradycardia and SaO_2 level. They monitored the SaO_2, ECG, thoracic impedance and abdominal respiratory pattern in 27 preterm infants. The median gestational age was 29 weeks (range 25 to 32 weeks), median birthweight was 1140 grams (range 710 to 1700 grams), and median study day was 15 (range 1 to 55 days). Bradycardia was defined as a heart rate < 90 beats per minute. Airflow was measured via facemask applied over the nose and mouth.

During the total of 353 hours (median study time was 3.96 hours, range 2.19 to 5.29 hours) of recording, 605 episodes of bradycardia were detected in 27 infants. There was a positive linear relationship between the duration of bradycardia and the duration of apnea ($r = .49$, $p < .0001$). There was also a positive linear relationship between the apnea duration and time of onset of bradycardia ($r = .55$, $p < .0001$). Forty-one bradycardia episodes were associated with a closed airway obstructive apnea. The median duration of the apnea was 14 seconds (range 2 to 51 seconds) and the median

onset of bradycardia was after 11 seconds of apnea (range 1 to 34 seconds). There was a strong positive linear relationship between onset of bradycardia and obstructive apnea (r = .73, p < .0001). Upper airway closure occurred more frequently with bradycardia (p = .005).

The researchers confirmed the findings of Vyas et al (1981) that airway closure is more common during apnea associated with bradycardia. They suggested that the episode of bradycardia may be related to the reestablishment of respiratory effort against a closed glottis and the reflex bradycardia may be potentiated by the presence of relative hypoxemia. The researchers recommend that clinicians consider techniques that would splint open the airway when treating preterm infants who are having episodes of apnea associated with bradycardia.

To further evaluate the physiologic response of the preterm infants to the different types of apnea, Finer et al (1992) conducted a secondary analysis of two previous prospective cohort studies. The initial clinical trial evaluated apnea in preterm infants who were receiving theophylline compared to no therapy and the subsequent study was a randomized, placebo controlled clinical trial to evaluate doxapram and theophylline. The study sample included 47 infants between 27 and 34 weeks gestational age and birthweight between 920 and 2470 grams. The mean age at the time of study was 4.5 days (range 1 to 21 days). Infants were included in the study if apnea episodes occurred > 0.3 times per hour (8 episodes in 24 hours) lasting ≥ 15 seconds and either a 5% drop in SaO_2 level or 20% decrease in heart rate or both. The parameters used to measure the apnea episodes included heart rate, impedance respiration, SaO_2 level via pulse oximeter, and end-tidal CO_2 level. Central apnea was defined as no respiratory effort as indicated

by the absence of chest movement and no end-tidal CO_2 recording. An obstructive apnea episode was defined as recording chest impedance without detecting end-tidal CO_2 level. A mixed apnea episode was defined as evidence of a combination of central apnea and obstructive apnea lasting at least 3 seconds.

There were 2750 episodes of apnea (1500 central apnea, 1032 mixed apnea, and 218 obstructive apnea) recorded from the study sample. However, only 2082 episodes were included in the data analysis. There were 1204 episodes that occurred in infants treated with either aminophylline or theophylline, 251 episodes from infants receiving doxapram, 42 infants required both theophylline and doxapram, and 585 episodes from infants not receiving medication for apnea. There was a correlation between the duration of apnea episode and fall in SaO_2 level ($r = .26$, $p = .0001$). The fall in heart rate (<100 beats per minute), was more frequently associated ($\chi^2 = 87.5$, $p < .0001$) with central apnea (83.5%) compared to mixed apnea (66.7%) or obstructive apnea (60.5%). There was a significant decrease in heart rate with prolonged (>50 seconds) central and obstructive apnea ($p < .001$). The infants who were not receiving medication had a significantly greater decrease in heart rate during all types of apnea compared to those receiving medication ($p < .0001$). The investigators concluded that there are different heart rate responses to apnea depending on the treatment plan (medication versus no medication). Obstructive (closed glottis) apneic episodes are associated with more substantial falls in heart rate.

Another physiologic parameter that may be affected by apnea is cerebral blood flow. Rehan et al (1995) obtained cerebral blood flow (CBF) measurements by transcranial Doppler technique in 17 infants who were 37 to 41 weeks gestational age and

had a mean birthweight of 3610 grams (±490). The Doppler probe was positioned to measure Cerebral Blood Flow Velocity (CBFV) from the middle cerebral artery. In addition, ECG, chest impedance, airflow and SaO_2 were monitored. Isolated central apnea episodes were the focus of this study. The investigators defined central apnea as cessation of airflow for >5 seconds without other types of apnea, bradycardia, hypoxemia or other events within one minute before and after this cessation.

Each infant was monitored for a mean duration of 194 minutes (±8.2). During this time period, 267 episodes of central apnea were recorded. However, only 96 episodes were classified as isolated central apnea according to the inclusion criteria. The duration of the majority (94%) of the apnea episodes lasted 5 to 10 seconds. The researchers found no significant differences in the CBFV during apnea. They concluded that the CBF did not change during episodes of apnea. They suggested that perhaps the resultant hypoxia and hypercarbia occurring during apnea directly compensates for CBF and not the apnea event.

When the premature infant has episodes of apnea associated with bradycardia and desaturation (decrease in SaO_2), the resultant hypoxia and hypercapnia has significant consequences on cardiorespiratory stability. Kitchen et al (1983) conducted a study to evaluate the infants at risk for unfavorable outcomes (cerebral palsy and developmental delays). The sample included a total of 252 infants born between 1977 and 1978. The birthweight range was 500 to 1500 grams. An assessment was completed at 2 years of age to evaluate for evidence of major handicaps, cerebral palsy, mental developmental index (MDI) <69 on the Bayley scales, epilepsy, deafness or blindness. The risk factor of interest was exposure to theophylline. Fifty-nine (23%) infants were exposed to

theophylline during their neonatal hospitalization. Nineteen (32%) of the 59 infants were diagnosed with cerebral palsy and none had abnormal MDI scores. The researchers reported an association between apnea and exposure to theophylline ($\chi^2 = 4.59$, p = .03).

The investigators suggested a relationship between apnea and diffuse hypoxic-ischemic injury as a result of apneic episodes requiring theophylline therapy. Their findings were related to the extremely premature infants who had severe and persistent apneic episodes with significant cardiovascular and respiratory consequences.

These studies have shown that the infant responds to an apneic episode with reflex bradycardia and desaturation. In addition, the duration and type of apnea often potentiates this physiologic response. Therefore, identification and treatment of apnea is important in preventing hypoxic-ischemic injury.

Management of Apnea of Prematurity

Tactile Stimulation

In order to prevent cardiovascular decompensation, prompt identification of the cause of apnea is of paramount importance. Various therapies have been used to treat apnea. Treatment ranges from supportive care (including tactile stimulation) to intensive therapy (such as mechanical ventilation). Tactile stimulation consists of simply touching the infant to resume breathing.

In order to evaluate the feasibility of tactile stimulation as a method of treating apnea, Kattwinkel et al (1975) conducted a small prospective clinical trial to compare the use of prophylactic cutaneous stimulation of the premature infants by the neonatal nurse and continuous positive airway pressure (CPAP). The researchers hypothesized that there

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would be a reduction in apnea episodes by increasing afferent sensory input through tactile stimulation and an increase in lung volume by using CPAP.

The study sample was 18 preterm infants ranging in 26 to 31 weeks gestation, 620 to 1600 grams birthweight, and 2 to 35 days of age at entry into the study. Infants were considered eligible for the study if apnea episodes, defined as a cessation of respiratory effort for >15 seconds were associated with cyanosis. There were two treatment groups, prophylactic cutaneous stimulation group and CPAP group. Six infants were assigned in the prophylactic cutaneous stimulation group and 12 infants to the CPAP group. Each group was evaluated at separate time periods (completion of tactile stimulation group before commencing the CPAP treatment group).

After 3 hours of recorded observation (control period), the tactile stimulation treatment started. The treatment consisted of the bedside neonatal nurse stimulating the infant by stroking the infant's foot for 5 minutes every 15 minutes. The duration of this treatment was 3 hours. After 12 hours of observation (control period), the CPAP treatment was started. The CPAP was regulated to remain between 2 and 5 cm H_2O pressure. The duration of this treatment was between 20 hours to 5 days. The criteria for CPAP treatment period depended on the frequency of apnea episodes. Each infant had monitoring of the heart rate by ECG and respiratory rate by impedance measurements that were recorded on a Beckman Dynograph recorder. All infants were given supplemental oxygen ranging 25% to 28% and the environmental temperature was slightly decreased. No changes were made with the oxygen therapy or environmental temperature during the study period.

There was a reduction in apnea in both treatment groups: 35% reduction in the prophylactic cutaneous stimulation group and 69% in the CPAP treatment group. Statistical analysis using Students' t test was performed comparing the data from the control observation and the treatment period. There was a statistically significant difference between the control observation and the prophylactic cutaneous stimulation period ($p< .01$). There was also a statistically significant difference between control observation and CPAP treatment ($p< .02$).

The researchers did report that both methods of treating apnea were effective. However, the feasibility of prophylactic cutaneous stimulation treatment is questionable. This treatment plan would be very costly since it requires extensive neonatal nursing time.

<u>Vestibular-proprioceptive Stimulation – Oscillating Bed</u>

Alternative methods were investigated to replace tactile stimulation for the treatment of AOP. Research was then directed toward the use of the oscillating bed as an effective method of reducing apnea episodes. Korner et al (1975) designed a randomized clinical trial to evaluate the feasibility and clinical response of preterm infants to compensatory vestibular-proprioceptive stimulation similar to the uterine environment. In addition, the investigators studied the effects of an oscillating bed on the neurologic and behavioral maturation of the preterm infant.

Twenty-one premature infants <34 weeks gestation and < 2000 grams who were receiving care in the Stanford Intensive Care Unit between January and November 1974 were enrolled in the study. After obtaining parental consent, the infants were randomly assigned to either the experimental or control group. Ten infants ranging in age from 28

to 34 weeks gestation and 1260 to 1920 grams were assigned to the experimental group and eleven infants ranging in age from 27 to 34 weeks gestation and 1050 to 1900 grams were assigned to the control group. The infants in the experimental group were placed on an oscillating waterbed for a total of nine days, two days baseline and seven days study treatment period. The oscillating waterbed delivered gentle passive head-to-toe motion. The control group was observed for two days at baseline and for an additional seven days.

The primary outcome of this study was the frequency of apnea. Other data collected included mean daily heart rate, mean daily respiratory rate, and mean daily temperature and temperature range, daily weight, incidence of emesis, and administration of supplemental oxygen. The bedside nurses recorded the episodes of apnea whenever the respiratory alarm would indicate a fall in respiratory rate <20 breaths per minute and bradycardia episode if the heart rate would drop <100 beats per minute. These data were collected from the nurses' notes and medical chart.

The mean frequency of apneic episodes during the study period was .58 $\pm$4 episodes for the infants in the experimental group and 9.27 $\pm$22.8 episodes for the infants in the control group ($t_{.05, 19} = 4.40$, $p < .01$). Since it appears that the frequency of apnea is not normally distributed, it would have been more meaningful statistics to report the median. The infants in the experimental group had a significant decrease in the frequency in apneic events compared to baseline and compared to the control group who had an increase in the frequency of apnea.

The researchers concluded that placing the infant on an oscillating waterbed was safe. They also found that the infants on an oscillating waterbed had fewer apneic

episodes compared to the infants not on the oscillating waterbed (p < .01). Unfortunately there were measurement limitations to this study including the procedure for recording the frequency of apnea, the primary outcome. This study was conducted over a short period and the investigators counted the number of apneic episodes that were recorded in the nursing notes by the bedside nurse and not by impedance pneumogram.

To further investigate the use of the oscillating bed in the management of apnea, Jirapaet (1993) designed a study to test the hypothesis that vestibular-propriocetive stimulation, using an oscillating mattress, would reduce the frequency of apnea episodes and would require minimal intervention by the nurses. In this crossover design study, the effectiveness of the vertical pulsating stimulation (VPS) was investigated for the prevention of apnea. A purposive sample of 29 premature infants was enrolled in the study. They were between 29 to 34 weeks gestation, >24 hours of life, had > 3 episodes of apnea within six hours prior to entry into the study, and were not receiving respiratory stimulant medication or ventilatory support. The study was conducted from June 1989 to December 1989 in a newborn nursery at Siriraj Hospital and Children's Hospital.

After enrollment, the infants were randomly assigned to receive one combination of VPS. Combination I of VPS was with stimulation, without stimulation, with stimulation, and without stimulation. Combination II VPS was without stimulation, with stimulation, without stimulation, and with stimulation. Each combination was completed within 24 hours and each segment was six hours in duration. The VPS was a blood pressure cuff connected to a Bird's Mark 8 ventilator that inflated and deflated at a rate of 16 ±4 times per minute with a vertical wave of motion of 1 cm. The parameters monitored and recorded on a multi-channel system during the study period were the heart

rate, respiratory rate, nasal airflow, SaO_2, chest wall impedance. Apnea was defined as cessation of breathing >15 seconds and bradycardia as a heart rate <100 beats per minute. Any episodes of apnea that occurred during the study were terminated by gentle tactile stimulation (specifically shaking of the infant's arm or leg).

The results of the study showed a reduction in the frequency of apnea while the infant was receiving the treatment, from 348 apnea episodes off VPS to 12 apnea episodes on VPS ($F_{1.28}$ = 60.87, p< .001). In addition to the frequency of apnea, the type of apnea (central, obstructive and mixed) was also recorded. Twenty-six infants experienced central apnea, 28 experienced obstructive apnea, and 11 infants experienced mixed apnea. There was a statistically significant reduction in the frequency of central apnea during the VPS treatment compared to the period of time off VPS (t_{25} = 6.05, p< .001). There was a statistically significant reduction in the frequency of mixed apneic episodes (t_{10} = -4.50, p= .001). There was no statistically significant reduction in the frequency of obstructive apnea (t_{27} = -0.49, p= .316). There was a statistically significant negative relationship between the postconceptual age and the frequency of apnea, older infant's had fewer episodes of apnea (on VPS r =-0.804, P < .000, off VPS r=-0.667, P = .000). The findings supported the hypothesis that the oscillating mattress would reduce mixed apneic episodes. This study was over a short 6-hour period of time with a large enough sample to show statistical significant effects of the intervention.

Tuck et al (1982) also published results supporting the use of the oscillating bed to provide tactile stimulation for the treatment of apnea. These researchers hypothesized that repeated sensory stimulation with an oscillating bed would prevent recurrent apnea and avoid the use of continuous positive pressure or methylxanthines. To test their

hypothesis, a randomized clinical trial was conducted. In this clinical trial, twelve premature infants ranging 26 to 32 weeks, birthweight from 800 to 1700 grams postnatal age 2 to 45 days were enrolled. In order to be eligible, the infant had at least 3 episodes of apnea with bradycardia in the preceding 24 hours or 2 episodes in the preceding 12 hours. Apnea episode was defined as cessation of respiration > 12 seconds and bradycardia as a heart rate < 100 beats per minute. Four infants received supplemental oxygen and one received theophylline.

The study intervention (rocking bed) was a regular rocking movement of alternating inflation and deflation in 10 to 20 cycles per minute. There were two consecutive study periods, on rocking bed and off rocking bed, each lasting eight hours. Each infant was randomly assigned to a treatment sequence, on-off or off-on. The time off the rocking bed was considered the control period. During the study period the heart rate and impedance pneumogram were recorded via a Hewlett-Packard monitor. The primary outcome of this study was the frequency of apnea episodes.

The frequency of apnea during the control period was 119 and during the treatment period was 69. There was a statistically significant difference between the two conditions ($p < .001$). There was also a statistically significant difference between the frequency of apnea with bradycardia during the two study periods ($p < .01$). The investigators concluded that the rocking bed is useful in reducing the frequency of apnea.

Other researchers have challenged the effectiveness of the oscillating bed as a treatment for apnea (Jones, 1981; Saigal, Campbell, Ferguson & Duffy, 1986; Saigal, Watts & Campbell, 1986). Jones (1981) conducted a clinical trial to evaluate the benefit of the oscillating bed in preventing apnea. This study included 14 premature infants

admitted to the NICU at Hammersmith Hospital in London from September 1979 to June

1980. Infants who had recurrent apnea with bradycardia or cyanosis were eligible for the

study. Apnea was defined as cessation in respirations ≥ 10 seconds occurring at least 3

times in 24 hours and bradycardia was defined as heart rate ≤ 100 beats per minute. They

ranged from 27 to 32.6 weeks gestational age, birthweight was between 930 and1470

grams, and postnatal age was 1 to 32 days. Each infant was treated with theophylline

before starting the study treatment of regularly oscillating waterbed that was inflated 12

to 14 times per minute of 1 to 2 mm amplitude. The infant was placed on the waterbed

for a mean of 23 hours that was divided into 4-hour periods. The 4-hour periods, with

oscillation and without oscillation, were in random order. The heart rate and impedance

pneumogram were continuously recorded on a Healthdyne Infant Monitor. The primary

outcome for this study was frequency of apnea. There was no difference in the frequency

of apnea of > 10 seconds between the period without oscillation and with oscillation.

Forty-three percent of the infants (n=6) had apnea episodes ≥ 10 seconds and 36% (n=5)

had an increase in apnea with waterbed oscillation. These findings suggested that the

regularly oscillating waterbed had no effect on reducing the frequency of apnea.

However, the results may be confounded by the use of theophylline prior to starting the

oscillating bed intervention.

Saigal et al (1986) investigated the efficacy of the oscillating bed on the

prevention of apnea in a randomized clinical trial. The aim of the study was to determine

whether the oscillating air mattress (OAM) would prevent apnea, improve weight gain,

produce sleep and behavioral state difference in the early weeks of life, and accelerate

development in the first year of life. Infants between 750 to 1750 grams at birth and < 5

days of age were eligible for the study. After obtaining parental consent, the infants were randomly assigned to either the experimental group (OAM) or the control group using a random numbers table in blocks of two. The OAM was maintained at approximately 14 to 16 regular oscillating movements per minute. The control group was placed on a conventional mattress. Theophylline was prescribed for any infant (either experimental or control group) who had $\geq$10 apneic episodes in a 24-hour period. The duration of the study for both groups was a minimum of seven days or until discharge. The heart rate and respiratory rate, daily weight, and daily intake were monitored throughout the study. In the nursing record, documentation was made of apnea and bradycardia episodes as well cyanosis and need for tactile stimulation or bag mask ventilation. Apnea was defined as a respiratory pause of $\geq$15 seconds and bradycardia was a heart rate $\leq$100 beats per minute. A comparison of the apneic episodes recorded in the nursing notes and a 6-hour cardiorespiratory recording was made periodically throughout the study. A 90-minute sleep and behavioral assessment was completed before and 24 hours after weaning from the OAM. The sleep and behavioral assessment was completed on the infants in the control group at a corresponding time. The Albert Einstein Neonatal Neurobehavioral Scale and the Bayley Scales of Infant Development were administered during the follow-up visits at 6 and 12 months corrected age.

During a 16-month period, 112 infants were enrolled in this study, with 59 in the OAM group and 63 in the control group. The study duration ranged from 7-68 days. Approximately 31% of the infants in the OAM group and 35% in the control group required theophylline for apnea. There was no significant difference in the frequency of apnea between the two groups. There was a decrease in number of apneic episodes with

increasing age and birthweight. There was no significant difference between the groups in weight gain or in sleep and neurobehavioral assessment obtained at the beginning and end of the study. There was also no significant difference in the follow-up examination at 6 and 12 months corrected age.

The results of the study revealed that the oscillating air mattress provides no benefit in reducing the frequency of apnea. In addition, the OAM failed to improve growth or enhance growth and development.

To conclude, some of the studies reported a reduction in apneic episodes with the oscillating bed, whereas others reported no difference in the frequency of apneic episodes. The primary difference between these studies was the duration of the intervention, 24-hours to 7-25 days, suggesting that the oscillating bed had only short-term benefits in the treatment of apnea.

Several investigators defined apnea as a cessation of respiration between 10 and 20 seconds despite the AAP recommendation to define apnea as a cessation of respiration >20 seconds. Using this definition, events were identified that normally would not be detected. In addition, fewer apneic episodes may have been a result of treatment with theophylline and not as a result of the study intervention (OAM).

<div align="center">Medication</div>

<div align="center">Theophylline and Caffeine</div>

Still searching for effective long-term management of apnea researchers turned to medication—the methylxanthines. To test the effectiveness of theophylline in the treatment of apnea, Sims et al (1985) conducted a randomized clinical trial. Premature infants born at Los Angeles County – University of Southern California with a

birthweight <2250 grams, < 37 weeks gestational age, and > 6 hours of life were eligible

for this study. In addition, the infants experienced a minimum of two apnea episodes in

an eight-hour period or three episodes during a 24-hour period. Apnea was defined as

cessation of respiration for $\geq$20 seconds with or without heart rate deceleration.

Once informed parental consent was obtained the infant was randomly assigned to

either the control group (n = 22) or the treatment group (n = 18). The infants in the

control group did not receive theophylline. The treatment group received an intravenous

loading dose of theophylline of 6.8 mg/kg followed by a maintenance dose of 1.4 mg/kg

every eight hours. Serum levels of theophylline and caffeine were measured 24 hours

after theophylline was started then the serum levels were repeated every 48 hours. Since

caffeine is the metabolite of theophylline, serum caffeine levels were monitored along

with theophylline levels. If the theophylline level was sub-therapeutic (therapeutic levels

9 – 13.2 mg/dL), the dose of theophylline was increased to 1.4 mg/kg every six hours.

Theophylline was given for seven days. If the infant developed respiratory failure,

theophylline was discontinued and appropriate therapy instituted. For the infants who did

not have a 50% reduction in apnea from baseline, theophylline was continued until a 50%

reduction was reached.

Throughout the study, heart rate and chest wall impedance was monitored to

detect central apnea. If infants in either group experienced apneic episodes, the bedside

nurse provided tactile stimulation. If the episode did not terminate with tactile

stimulation, facemask ventilation was given.

Eleven infants were dropped from the study because they developed respiratory

failure. The data on 32 infants were analyzed. The control group (n=14) had a mean

birthweight of 1345 grams ($\pm$71) vs 1306 grams ($\pm$ 72) for the treatment group (n=18).

Gestational age for controls averaged 31.4 weeks ($\pm$0.5) vs 30.8 weeks ($\pm$0.5) for the

treatment group. Postnatal age at study entry was 2 days (0.3) for controls vs 2.5 days

(0.3) for the treatment group. Frequency of apnea at baseline was 9.2 ($\pm$2.39) per day vs

11.3 ($\pm$2.40) for the treatment group.

The results did show a significant reduction of the frequency of apnea in the

treatment group (p < .025). In 15 of 18 infants in the treatment group, the frequency of

apnea decreased by 80% within the initial seven days of theophylline treatment. There

was a reduction in the frequency of apnea in the control group but the reduction was not

significant until day 3 of the study (p < .005). The mean ($\pm$SE) serum theophylline level

for the first, second and third weeks were 10 $\pm$0.4 mg/dL, 10.3 $\pm$0.3 mg/dL, and 11.7

$\pm$0.5 mg/dL, respectively. The caffeine levels were consistently < 2 mg/dL. The

investigators concluded that apnea was successfully treated with theophylline.

Although theophylline has been shown to be effective in treating apnea, its use

was limited. Two distinctive groups of infants were identified as patients in whom

theophylline was not effective. One group was premature infants < 31 weeks gestational

age who experience frequent apneic episodes during the first day of life. The other group

was infants whose illness was remarkable for recurrent apnea that persists beyond the

neonatal period.

Muttitt et al. (1988) hypothesized that the clinical response to theophylline may

be related to the dose the premature infant is given. To test this hypothesis, the

researchers conducted a prospective clinical trial. The purpose of the study was to

evaluate the response to incremental doses of theophylline. Premature infants < 32 weeks

gestation who were receiving care at the Royal Alexandria Hospital Children's Pavilion in Alberta, Canada were eligible for the study. In addition, eligible infants had >4 apnea episodes during a 12-hour period. Apnea was defined as cessation of respiration for ≥ 20 seconds associated with drop in heart rate and oxygenation. Each infant's heart rate, respiratory rate, end-tidal CO_2, oxygen saturation, and transcutaneous Po_2 were continuously monitored.

Once parental consent was obtained, airway occlusions and measurements of tidal volume, minute ventilation and respiratory timing were performed. These measurements, obtained at baseline and repeated 24 hours after theophylline dose was increased, were accomplished by applying a face mask with an adapter over the infant's mouth and nose then connecting the adapter to a pneumotachograph. The initial dose (level 1) of theophylline was 4 mg/kg (loading dose) followed by 1 mg/kg every 8 hours (maintenance dose). The computer record of apnea episodes was evaluated 24 hours after the dose was given. If the infant continued to have > 0.33 apneic episodes per hour, an additional theophylline dose (level 2) of 4 mg/kg (loading dose) was given and the maintenance dose was increased to 1.5 mg/kg every 8 hours. If the infant failed after 24 hours on the increased dose, the dose of theophylline was then increased to 2 mg/kg every 8 hours (level 3). If the infant failed again, the maintenance dose was increased to 2.5 mg/kg every 8 hours (level 4). Serum theophylline levels were obtained 2 hours after every loading dose and 24 hours before any additional loading dose.

Twenty-two premature infants were enrolled in the study. The mean birthweight of the sample was 1410 grams (range 920 to 2019 grams), the mean gestational age was 30 weeks (range 26 to 32 weeks, and the postnatal age at study entry was 92 hours (range

24 to 406 hours). At study entry, the mean frequency of apnea episodes was 0.76 per hour (range 0.33 to 2.8 per hour). Of the 22 infants in the study, three responded at level 1 (mean theophylline level = 4.2 mg/L), three responded at level 2 (mean theophylline level = 8.5 mg/L), ten responded at level 3(mean theophylline level = 12.7 mg/L), and 4 responded at level 4 (mean theophylline level = 15.3 mg/L). There was a significant difference between 2 and 24-hour serum theophylline levels at the level 3 dose (p < .001). Analysis of the ventilation measurements (tidal volume, minute ventilation and respiratory timing) revealed no significant improvement with increasing serum theophylline levels. However, there was a significant increase in tidal volume, minute ventilation, and ratio of tidal volume to minute ventilation, and a significant decrease in Pco_2 at the maximum theophylline dose (p < .05). The types of apnea were also documented. Fifty-three percent were central apnea, 39% were mixed apnea and 8% were obstructive apnea. The response to different levels of theophylline dose was not related to the type of apnea. The investigators concluded that a serum theophylline level of 12.7 mg/L is effective in reducing the frequency of apnea in a majority of the premature infants receiving theophylline. In addition, it appears that a higher dose of theophylline does not improve response.

Since some premature infants experiencing apnea are unresponsive to theophylline, it has been recommended that caffeine be prescribed. Research investigations have been done to assess the efficacy of theophylline compared to caffeine in reducing apnea episodes. Davis et al (1987) hypothesized that caffeine, a potent respiratory stimulant, would be more effective than theophylline in treating apnea. To test this hypothesis, the researchers conducted a prospective cohort study to evaluate the

effectiveness of caffeine for treatment of apnea. The purpose of the study was to determine if premature infants who were unresponsive to theophylline would have fewer apnea episodes when caffeine was prescribed. The sample consisted of eleven preterm infants who were experiencing persistent apnea despite therapeutic theophylline level (8-12 mg/liter). During the study, monitoring of the heart rate, thoracic impedance and airflow was recorded via a thermistor-pneumocardiogram system. Measurements were made for a 6-hour period during the daytime. The investigators evaluated the recording for evidence of ≥ 2 central apnea or mixed apnea lasting ≥ 20 seconds while receiving theophylline and theophylline at therapeutic level. If the infant met this criterion, the theophylline was discontinued and caffeine oral loading dose of 10 mg/kg was given followed by a maintenance dose of 2.5 mg/kg once a day. Serum caffeine and theophylline levels were obtained. A caffeine level of 8-20 mg/liter was considered a therapeutic level.

The 11 infants in the sample had a mean birthweight 1660 grams (± 180) and the mean gestational age 31.2 weeks (± 0.7). The mean postnatal age when apnea was first diagnosed was 4.9 days (± 1.1), the mean age when theophylline started was 6.5 days ($+1.8$) and the mean age when caffeine was stated was 20.3 days (± 4.8). After receiving caffeine for 5 to 7 days, the mean ($\pm$SEM) serum theophylline level was 1.2 (± 0.5) and the caffeine level was 11.8 (± 1.1). Overall, there was an 82% reduction in the frequency of apnea when caffeine was started. The number of apnea episodes decreased from 22.8 per 6 hours while on theophylline to 4.8 episodes per 6 hours while on caffeine ($p < .01$). The apnea episodes of >20 seconds occurred 88% less often while on caffeine compared to while on theophylline (1.2 per 6 hour vs 10.1 per 6 hours), ($p < .05$).

The researchers concluded that caffeine is effective in treating apnea when the premature infant is unresponsive to theophylline. The proposed reason for the phenomena is that caffeine has a more direct effect on the central respiratory system and thus a more effective treatment for AOP.

Several neonatal clinicians are in agreement that caffeine is effective in treating apnea but debate the recommended dose (Davis, Spitzer, Stefano, Bhutani & Fox, 1987; Bairam, Boulroy, Badonnel &Vert, 1987; Cattarossi, Colacino, Janes, LoGreco, Rubini, Zilli & Macagno, 1988; Scalon, Morgan, Durbin & Brown, 1992; Lee, Charles, Steer, Flenady & Shearman, 1997; Gannon, 2000). In an effort to evaluate different caffeine dosing regimens, Scalon et al (1992) designed a randomized clinical trial to compare the efficacy of theophylline and caffeine at two different dose regimens on the frequency of apnea of preterm infants. Infants were eligible for enrollment in the study if gestational age was<31 weeks at birth and they were having either >10 apnea episodes in 8 hours or four in one hour. Apnea was defined as a decrease in heart rate >40 beats per minute below baseline in an infant who was not breathing and required stimulation.

After enrollment in the study, the infant was randomly assigned (by random numbers in sealed envelopes) to one of three groups. Infants assigned to Group A received the standard caffeine dose – loading dose of 12.5 mg/kg followed by a maintenance dose of 3mg/kg once a day. The goal was to produce a serum level of 15 mg/ liter (range 13 to 20 mg/liter). Group B infants were given a higher dose of caffeine – loading dose of 25 mg/kg followed by a maintenance dose of 6 mg/kg once a day. The goal serum level was 30 mg/liter (range 26 to 40 mg/liter). Those assigned to Group C received theophylline – loading dose 7.5 mg/kg followed by a maintenance dose of 3

mg/kg every 8 hours. The desired serum theophylline level was 15 mg/liter (range 13 to 20 mg/liter). The desired range for the serum caffeine level was 13 to 20 mg/liter for the standard caffeine dose group and 26 to 40 mg/liter for the higher caffeine dose group. Serum levels were obtained every day for five days, beginning 24 hours after the loading dose. Subsequent levels were measured twice a week for an additional week. The primary outcome of the study was successful reduction in frequency of apnea by 50% or more. The secondary outcomes included detection of tachycardia, diuresis, glucose intolerance and jitteriness as side effects.

Forty-four infants were enrolled in the study over a two-year period. The characteristics of the infants in Group A (n = 16) were mean birthweight of 1140 grams ($\pm$210), mean gestational age 28.7 weeks ($\pm$1.2), and mean postnatal age 5.6 days ($\pm$2.6). Group B (n = 14) were mean birthweight 1200 grams ($\pm$260), mean gestational age 28.2 weeks ($\pm$1.1), and mean postnatal age 6 days ($\pm$2.7). Group C (n = 14) were mean birthweight 1240 grams ($\pm$320), mean gestational age 27.9 weeks ($\pm$1.4), and mean postnatal age 7.6 days ($\pm$4.9). There was no statistically significant difference between the groups. However, there was a significant reduction in the frequency of apnea in all three groups. The number of apnea episodes in Group A decreased from 22.81 ($\pm$0.49) to 6.94 ($\pm$0.69) to 12.50 ($\pm$0.67) between day 0 to day 1 to day 2 ($p < .01$). The number of apnea episodes in Group B decreased from 22.79 ($\pm$0.72) to 6.94 ($\pm$0.69) to 12.79 ($\pm$0.63) between day 0 to day 1 to day 2 ($p < .01$). The number of apnea episodes in Group C decreased from 24.07 ($\pm$0.70) to 13.86 ($\pm$0.86) to 20.36 ($\pm$0.74) between day 0 to day 1 to day 2 ($.01 > p < .001$). There was a greater reduction in the frequency of apnea in the

higher caffeine dose group than the theophylline group. Only one infant in the standard caffeine dose group failed to show a reduction in the number of apneic episodes.

The mean (SD) serum caffeine levels for Group A on days 1, 3, and 5 were 15.43 (5.11), 15.31 (3.93), and 15.81 (2.90) mg/liter. The mean (SD) serum caffeine levels for Group B on days 1, 3, and 5 were 30.42 (4.05), 32.92 (4.88), and 33.36 (5.27) mg/liter. The mean (SD) serum theophylline levels for Group C on days 1, 3, and 5 were 10.87 (3.52), 14.96 (6.00), and 17.22 (3.19) mg/liter. The majority of the infants had serum concentration levels that were within the desired range: 69% of infants in Group A, 73% of Group B infants and 56% of Group C infants. Persistent tachycardia (heart rate >195 beats per minute) was observed when the serum theophylline level was >20 mg/liter. This occurred in approximately 42% of the infants in Group C. The theophylline dose for these infants was adjusted. Only 6% of Group A and none in Group B experienced tachycardia. The other side effects, such as diuresis, glucose intolerance and jitteriness were not detected in any of the three groups.

The investigators confirmed that theophylline and caffeine are effective in reducing the number of apneic episodes. The study results suggested that the neonatal clinician prescribe either theophylline at the standard dose schedule or caffeine at the higher dose. The investigators recommended that caffeine be the first choice since it is better tolerated. Despite these research findings from 1992, many neonatal clinicians are still prescribing theophylline as first-line therapy.

Adverse effects have been reported with the use of theophylline and caffeine. Symptoms that have been observed in the infant receiving methylxanthines include tachycardia, cardiac arrhythmia, vomiting, hyperglycemia, failure to gain weight,

diuresis, irritability, sleeplessness, jitteriness, hyperreflexia, and seizures (Kriter &

Blanchard, 1989; Roberts, 1984). Another effect of methylxanthine, specifically

caffeine, in premature infants is increased oxygen consumption resulting in poor weight

gain (Bauer, Maier, Linderkamp & Hentschel, 2001).

In a case – control study conducted by Bauer et al (2001), the effect of caffeine on

oxygen consumption and metabolic rate was evaluated. Eighteen infants were enrolled in

this study, 9 in the caffeine group and 9 in the control group. The caffeine group

consisted of infants ranging in gestational age from 28 to 33 weeks and birthweight

ranged from 890 to 1680 grams. The control group ranged in gestational age from 29 to

34 weeks and birthweight ranged from 890 to 1640 grams. Postnatal age at entry into the

study was 3 to 6 days for both groups.

The infant was eligible for the study if there was documentation of ≥ 3 apneic

episodes that required pharmacologic therapy. Apnea was defined as a pause in

respiration >20 seconds associated with bradycardia (heart rate < 100 beats per minute).

Episodes of apnea were detected via continuous cardiorespiratory monitoring.

Pharmacologic therapy was the administration of caffeine at a loading dose of 10 mg/kg

followed by a maintenance dose of 5 mg/kg every 24 hours. Serum levels were

maintained between 10 – 15 μg/ml. The primary outcome was the comparison of the

oxygen consumption and carbon dioxide production before and after caffeine therapy. In

addition, parameters of growth and development (parenteral nutrition, enteral nutrition,

daily weight, and behavioral states) were monitored. The measurements of oxygen

consumption and carbon dioxide production were obtained 45 minutes after a feeding had

been given and for 60 minutes in duration. Each infant was studied for a 4-week period.

The results of a paired t test analysis (before and after caffeine was started) did show a significant increase in oxygen consumption within 24 hours after caffeine was started ($p < .05$). There was also a significant increase in carbon dioxide production after caffeine was started ($p < .05$). There was a significant decrease in the number of apneic episodes (20 $\pm$3 before, 8 $\pm$5 after caffeine) for the caffeine treated group ($p < .05$). Oxygen consumption increased significantly in the caffeine group compared to the control group ($p < .05$). However, the weight gain during the 4-week study period for the caffeine group was only 220 grams compared to 433 grams for the control group. The daily weight gain for the caffeine group averaged only 12 ($\pm$2) grams/day compared to 21 ($\pm$4) grams/day in the control group ($p < .01$).

The methylxanthines, theophylline and caffeine, have been shown to be effective therapy for apnea of prematurity (Aranda, Chemtob, Laudignon & Sasyniuk, 1986; Muttitt, Tierney & Finer, 1988; Kriter & Blanchard, 1989; Harrison, 1991; Miller & Martin, 1992). The investigators did demonstrate an association between long-term administration of caffeine and slower weight gain. It was suggested that the neonatal clinician make adjustments in the nutritional plan while the infant is receiving caffeine therapy.

<u>Medication</u>

<u>Doxapram</u>

Several researchers have reported that doxapram is useful in the treatment of apnea that is refractory to methylxanthines therapy (Bairam, Faulon, Monin & Vert, 1992; Barrington, Finer, Peters & Barton, 1986; Barrington, Finer, Torok-Both, Jamali & Coutts, 1987; Beaudry, Bradley, Gramlich & Le Gratt, 1988; Eyal, Alpan, Sagi, Glick,

Peleg, Dgani & Arad, 1985; Jamali, Barrington, Finer, Coutts & Torok-Both, 1988;

Jamali, Coutts, Malek, Finer & Peliowski, 1991). In order to explain the mechanism of

action for doxapram in the treatment of apnea, Barrington et al (1986) conducted a

prospective study. The purpose of this study was to clarify how doxapram works for

infants who were experiencing apnea despite adequate levels of theophylline. Infants

were eligible for the study if they were <34 weeks gestation, receiving theophylline and

had serum theophylline level within therapeutic range (10 to 20 μg/ml). The inclusion

criteria included documentation of >4 apnea episodes in 6 hours or one episode that

required face mask ventilation to terminate the apnea event. Apnea was defined as

cessation of breathing for ≥ 20 seconds associated with a drop in heart rate by $\geq 20\%$ from

baseline and decrease in transcutaneous oxygen (tcPo$_2$).

Once informed consent was obtained, 12 infants were assigned to either Group 1

(n = 8) or Group 2 (n = 4). Group 1 infants were breathing spontaneously and Group 2

infants required mechanical ventilation for poor respiratory drive (secondary to extreme

prematurity or neurologic damage). The heart rate, mean arterial blood pressure, oxygen

saturation, tcPO2, and frequency of apnea were monitored during the study. In addition,

minute ventilation and tidal volume were measured via a pneumotachograph. These

measurements were obtained before and 24 hours after doxapram was started. The dose

of doxapram was 2 - 2.5 mg/hr/hour.

The demographic characteristics of the sample were mean birthweight 1164

grams (±349), mean gestation 28.5 weeks (±2.6) and mean postnatal age at entry into the

study 9.2 days (±8.1). The first five infants entered into the study were given 2

mg/kg/hour and the remaining infants (n=7) were given 2.5 mg/kg/hour. There was no

significant decrease in apnea episodes during the first 6 hours of doxapram infusion but there was a significant decrease in the frequency of apnea during the subsequent 18 hours of therapy ($p < .01$). The minute ventilation increased significantly over the study period of 24 hours ($p < .0025$). There was also an increase in the tidal volume ($p < .05$). There was a significant decrease in the mean Pco_2 ($p < .01$) and the mean arterial blood pressure significantly increased ($p < .01$). The infants were monitored for evidence of adverse effects to the doxapram. Two infants exhibited symptoms such as, jitteriness, irritability, and frequent crying. An additional 17% ($n = 2$) had seizures while the doxapram was infusing. The doxapram was discontinued on only one infant.

The investigators concluded that doxapram is effective in the treatment of refractory apnea by increasing respiratory center output. However, doxapram has been associated with significant cardiovascular (increase in arterial blood pressure) and central nervous system adverse effects (seizures, jitteriness, and irritability). The adverse effects were observed when the infant received the higher dose of doxapram (2.5 mg/kg/hour). Therefore, the investigators recommended that doxapram be prescribed with caution.

Doxapram has been shown to be effective in the treatment of refractory apnea but requires a continuous IV route to be administered. Research was then directed toward testing an enteral preparation of doxapram (Tay-Uyboco, Kwiatkowski, Cates, Seifert, Hasan & Rigatto, 1991; Bairam, Akramoff-Gershan, Beharry, Laudignon, Papageorgiou & Aranda, 1991). Tay-Uyboco et al (1991) hypothesized that an enteral preparation of doxapram would be just as effective as intravenous infusion in reducing the frequency of apnea without adverse effects. To test this hypothesis, the researchers conducted a clinical trial. Premature infants <34 weeks gestation and having >10 episodes of apnea in

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a 24 hour period were eligible for the study. The apnea episodes were defined as cessation of breathing >15 seconds with or without bradycardia (heart rate <100 beats per minute). Infants were enrolled consecutively into either doxapram alone group or doxapram with theophylline group. The doxapram alone group was enrolled first.

The study procedure was intravenous (IV) administration of doxapram with loading dose of 2.5mg/kg followed by a maintenance dose of 1 mg/kg/hour. If the infant did not show the desired effect of a 50% reduction in the frequency of apnea episodes, the doxapram was increased at a rate of 0.5 mg/kg/hour to a maximum of 3 mg/kg/hour until the desired effect was attained. Once the apnea was controlled with IV doxapram, the route of administration was changed to enteral (nasogastric) still using the same total dose that was then divided into 6-hour intervals. Serum doxapram levels were obtained at 1, 6, and 12 hours after the IV doxapram was started. Subsequent serum levels were drawn every 48 – 96 hours. The weaning procedure was a 25% reduction of the doxapram every day. Throughout the study, there were measurements of apnea episodes, heart rate, Po_2, Pco_2, minute ventilation, tidal volume, ventilatory response to inhalation of 3% CO_2 and 100% oxygen and sleep states using electroencephalogram and electrooculogram. In addition, the infant was monitored for evidence of adverse effects such as blood in stool, feeding intolerance, seizures, irritability, jitteriness, excessive sweating, and excessive salivation.

The investigators studied 16 infants, 10 in the doxapram alone group and 6 in the doxapram and theophylline group. The mean birthweight for the doxapram alone group was 1520 grams (±102), the mean gestational age was 30 (±0.7), and the postconceptional age was 32 weeks (±1.9). They differed from the doxapram alone

group who had a birthweight of 1020 grams ($\pm$35) and gestational age 26 weeks ($\pm$0.5). The duration of the treatment was 31.6 days ($\pm$1.9) for the doxapram alone group and 28.8 days ($\pm$1.6) for the doxapram and theophylline group. The mean dose of doxapram was 1.5 mg/kg/hour (range 0.8 – 3 mg/kg/hour) for the doxapram alone group and 1.4 mg/kg/hour (range 0.8 – 2.1 mg/kg/hour) for the doxapram and theophylline group. The serum level in the doxapram alone group ranged 0.5 – 2 mg/liter and 0.85 – 2,25 mg/liter in the doxapram and theophylline group.

There was a significant reduction in the frequency of apnea episodes in both groups ($p < .001$). Because of the small sample size, there was a marginally statistically significant increase in minute ventilation in both groups ($p <. 07$) but it was a clinically significant increase from 0.18 L/min/kg ($\pm$0.013) to 0.213 L/min/kg ($\pm$0.017). There were non-significant changes in heart rate, P_{O_2} and responses to 100% oxygen. However, there was a ventilatory response to 3% CO_2. There was no correlation between doxapram dose and the decrease in frequency of apnea episodes. Twelve (75%) of the 16 infants experienced one or more adverse effects while receiving doxapram. The most common symptoms were jitteriness, hypertension, feeding intolerance, blood in stool, necrotizing enterocolitis, and premature eruption of teeth. For some of the infants the symptoms resolved without intervention and others resolved once theophylline was discontinued.

The investigators concluded that doxapram alone is effective in treating apnea and enteral administration of doxapram is a possible option for long-term treatment of apnea. The proposed mechanism of action for doxapram is an increase in alveolar ventilation. Despite these promising results, many infants experienced adverse effects. For this reason, the investigators recommended that doxapram be prescribed with caution.

There have been studies that compared doxapram and theophylline in treating apnea. Eyal et al (1985) conducted a double-blinded clinical trial comparing the effect of theophylline and doxapram on reducing the frequency of apnea. The objectives of this investigation were to test the efficacy of doxapram as single therapy in reducing the frequency of apnea and whether the addition of doxapram along with theophylline would be beneficial. This study was conducted in two parts. During Part 1, the infant was randomly assigned, using a random numbers table, to either doxapram alone or theophylline alone. In Part 2 of the study, the infant was randomly assigned to receive theophylline with doxapram or placebo. Infants were eligible for either study if there was documentation of ≥ 3 apnea episodes in 8 hours. Apnea was defined as a cessation of respiration associated with cyanosis and bradycardia with heart rate < 100 beats per minute. The demographic characteristics were mean birthweight 1289 grams (± 460), mean gestational age 30.1 weeks (± 2.2), and mean age at enrollment 61.8 hours (± 38).

After enrollment in Part 1, the infant was assigned to either doxapram treatment or theophylline treatment. Doxapram dose was 2.5mg/kg/hour continuous intravenous (IV) and theophylline was given initial as loading dose of 6 mg/kg followed by maintenance dose of 1.5 mg/kg every 8 hours. To ensure that type of treatment was blinded, placebo vials containing normal saline were added to each treatment regimen. The duration of each treatment was 48 hours. The primary outcome variable was reduction in the frequency of apnea episodes. Sixteen infants were studied in Part 1, nine in doxapram treatment group and 7 in the theophylline group.

The study procedure for Part 2 was random assignment to either doxapram with theophylline treatment or placebo with theophylline treatment. The doxapram dose was

the same as the dose given in Part 1. The duration of this treatment was 48 hours. The primary outcome was the same as Part 1. Ten infants were studied in Part 2, six infants in doxapram treatment group and 4 infants in the placebo group. The demographic characteristics were mean birthweight 808 grams ($\pm$200), mean gestational age 27.5 weeks ($\pm$1.8), and mean age at enrollment 11.4 hours ($\pm$6.4). During each part of the study, the infant was connected to a heart rate and respiratory monitor to detect apnea episodes. The trained neonatal nurses would record the apnea episodes on the infant's chart.

There was a reduction in frequency of apneic episodes for the both groups during Part 1 of the study. The difference between the groups, doxapram compared to doxapram with theophylline, was not statistically significant. However, in Part 2 of the study, theophylline/placebo compared theophylline/doxapram, there was also a significant reduction in apnea episodes ($\chi^2 = 12.44$, p < .001). The investigators concluded that doxapram is equally as effective as theophylline in treating apnea. The primary disadvantage of using doxapram is the route of administration, continuous IV while theophylline may be given either IV or by mouth.

<u>Continuous Positive Airway Pressure (CPAP)</u>

Occasionally, apneic episodes are not controlled with medication alone and infants require ventilatory support— either continuous airway positive pressure (CPAP) or mechanical ventilation. Nasal CPAP delivers air under pressure through nasal prongs inserted into the nares secured to the face via a strap surrounding the head. The proposed mechanisms of action by which nasal CPAP reduce apnea include the following: support of the nasopharyngeal structures, alteration of Hering-Breuer deflation reflex,

maintenance of lung inflation, and stabilization of the chest wall (Miller & Martin, 1992; Ariagno, 1995). This results in an increase in the functional residual capacity (FRC) and improves oxygenation (Miller & Martin, 1992; Ariagno, 1995). If apnea episodes continue despite nasal CPAP treatment, the infant may require intubation and mechanical ventilation (Miller & Martin, 1992).

In order to evaluate if nasal CPAP is effective in treating all types of apnea (central, obstructive and mixed), Miller et al (1985) conducted a prospective clinical trial to determine whether nasal CPAP is equally effective in treating obstructive and nonobstructive apnea. Premature infants experiencing apnea episodes ≥ 1 per hour associated with bradycardia were eligible for this study. Some of the eligible infants (N = 5) were receiving theophylline and some were already on nasal CPAP 4 – 6 cm H_2O pressure (N = 4). Apnea was defined as respiratory pause ≥ 5 seconds occurring during sleep and classified as central, obstructive or mixed. Central apnea was defined an absence of chest wall movement as well as airflow. Obstructive apnea was defined as chest wall movements without nasal airflow. Mixed apnea was defined as a combination of absence of nasal airflow with chest wall motion and central pause of breathing >2 seconds.

The study intervention was the application of nasal CPAP ± 4 cm H2O pressure. The duration of the intervention was three 45-minute time periods, on CPAP, off CPAP then on CPAP. Throughout the study period the following measurements were obtained: airflow via a pneumotachometer, heart rate, respiratory rate, and transcutaneous Po_2, tidal volume and minute ventilation.

Fourteen premature infants with mean gestational age 28 weeks (range 26 – 32), mean weight 1150 grams (range 680 – 2000) and mean postnatal age 11 days (range 2 – 30) participated in the study. Ten of the 14 infants in the study experienced ≥ 1 episode of apnea during the study. There were 252 episodes recorded during the study. During the time period when nasal CPAP was in place, there was a reduction in the frequency of mixed apnea (p < .01). The apneic episodes classified as obstructive were completely abolished while nasal CPAP was in place (p < .03). However, there was no reduction in central apneic episodes during nasal CPAP therapy. For the entire sample, there was an increase in the transcutaneous Po_2 ($tcPo_2$) and a decrease in the respiratory rate. There was no change in heart rate, tidal volume or minute ventilation while the infants were on nasal CPAP.

The investigators concluded that nasal CPAP is effective in the treatment of obstructive and mixed apnea but ineffective for central apnea. It was suggested that nasal CPAP maintained airway patency by either dilating the upper airway muscles or by splinting the upper airway structures.

Ryan et al (1989) agreed that nasal continuous positive airway pressure (CPAP) is effective in treating apnea episodes experienced by premature infants but hypothesized that intermittent positive airway pressure ventilation (IPPV) would also be useful in preventing apnea and possible intubation for respiratory failure. Therefore, the researchers conducted a prospective, randomized crossover clinical trial to test this hypothesis. Only infants with gestational age <32 weeks being treated with nasal CPAP were eligible to be included. All infants were receiving theophylline at the time of the study.

Once informed consent was obtained, the 20 infants were randomly assigned to one of two treatment groups by using a computerized generated randomization schedule. The treatment groups were either nasal CPAP or nasal IPPV. An arterial blood gas was obtained after 2 and 6 hours on either nasal CPAP or nasal IPPV. The infant was then switched to the alternate mode of treatment, nasal CPAP → nasal IPPV or nasal IPPV → nasal CPAP.

During the study, the heart rate, respiratory impedance, transcutaneous Po_2 ($tcPo_2$), transcutaneous Pco_2 ($tcPco_2$), and proximal airway pressures were monitored. The number of apnea episodes was recorded. Apnea was defined as cessation of respiration for ≥ 15 seconds associated with decrease in $tcPo_2$ of ≥ 5mm Hg and or decrease in heart rate of $> 20\%$ from baseline heart rate.

The demographic characteristics of the sample included mean birthweight 923 grams (± 292), mean gestational age 26 weeks (± 2), weight at entry into the study 979 grams (± 315) and age at entry into the study 25 days (± 15.6). The infants received a mean fractional of inspired oxygen (FiO_2) of 0.29 (+0.1) (range 0.21 – 0.6). While on nasal CPAP the end- expiratory pressure ranged 2 – 4 cm H_2O pressure and the peak pressure ranged 8 –21 cm H_2O with end- expiratory pressure of 2 – 4 cm H_2O pressure for 20 breaths per minute while on nasal IPPV. There was no significant difference in the frequency of apnea when comparing the two 6-hour periods of nasal CPAP or nasal IPPV. The lack of significance was unlikely an issue of small sample size and lack of power. When the effect size was calculated, there was a very weak effect: the infants on nasal IPPV did not do any better than the infants on nasal CPAP (e. s. = .13 SD units). In

addition, there was no significant decrease in the $tcPCO_2$ when comparing nasal CPAP

and nasal IPPV 6-hour periods (e. s. = .15 SD units; CI = -1.04 – 0.72)

The conclusion was that nasal IPPV offers no advantage over nasal CPAP in

preventing apnea episodes. The investigators would not recommend nasal IPPV as a

mode of therapy because of potential hazards of gastric distention and possible gastric

perforation.

Lin et al (1998) proposed that the reason for these unfavorable results might be

related to the sample selection that was not clearly defined. The researchers hypothesized

that nasal intermittent positive pressure ventilation (NIPPV) would be a potential

alternative to nasal continuous positive airway pressure (nasal CPAP) or mechanical

ventilation via an endotracheal intubation. To test this hypothesis, the investigators

conducted a randomized clinical trial. The inclusion criteria included documentation of

apnea episodes >2 per hour that failed to respond to a) tactile stimulation and/or

supplemental oxygen and b) theophylline therapy. Apnea was defined as cessation of

respiration for ≥20 seconds associated with bradycardia (heart rate <100 beats per

minute) or hypoxemia (O2 saturation $\leq$ 85%).

After enrollment, 34 infants were randomly assigned (number of group in sealed

envelope) to one of two study intervention groups, either nasal CPAP group (N = 16) or

NIPPV group (N = 18). The study intervention was the application of either nCPAP or

nIPPV for a 4-hour period. The nCPAP was end- expiratory pressure of 4 – 5 cm H_2O

pressure and NIPPV was peak pressure of 12 cm H_2O initially and increased to 20 cm

H_2O pressure until there was adequate chest excursion. The end- expiratory pressure for

NIPPV was 4 –5 cm H_2O pressure with a respiratory rate of 20 breaths per minute. The

outcome variables for this study were arterial blood gas change from the beginning and end of the study, heart rate, oxygen saturation (SaO_2), and the frequency of apnea.

The clinical characteristics of the nCPAP group were mean birthweight 1022 grams ($\pm$174), mean gestational age 27.3 weeks ($\pm$1.4), age at entry into study 15.7 days ($\pm$10.2), mean FiO2 0.31 ($\pm$0.07), hemoglobin 12.3 g/dL ($\pm$2.6), and theophylline level 7.7 µg/mL ($\pm$3.4). The clinical characteristics of the NIPPV group were mean birthweight 1020 grams ($\pm$327), mean gestational age 27.8 weeks ($\pm$2.2), age at entry into study 15.5 days ($\pm$10.1), mean FiO_2 0.35 ($\pm$0.16), hemoglobin 12.8 g/dL ($\pm$5.1), and theophylline level 7.9 µg/mL ($\pm$2.3). The differences between the groups on clinical characteristics were not statistically significant.

There was a reduction in the frequency of apneic episodes when the infant was receiving either treatment modality. However, the reduction of apneic episodes was significantly ($p < .02$) greater in the NIPPV group compared to the nCPAP group (e. s. = .85 SD units, CI = .15 – 1.55). The difference in the value of the Po_2 and Pco_2 between both groups was not statistically significant (e. s. = .07 SD units; CI = -.6 – .74).

Research investigations have shown that nCPAP is effective in treating apnea (Kattwinkel, Nearman, Fanaroff, Katona & Klaus, 1975; Miller, Carlo & Martin, 1985; Ryan, Finer & Peters, 1989; Lin, Wang, Lin & Yeh, 1998). The investigators concluded that the findings of this study are suggestive that NIPPV is effective in treating apnea. The possible reason for the positive response to NIPPV may be that infants received a sigh breath. The benefits comes when the positive sigh breath works in asynchrony with the infant's own respiratory effort thereby reducing the working of breathing and improving pulmonary function. However, if the breaths that are given with NIPPV result

in high airway pressure, problems such as pneumothorax and barotrauma may occur. Therefore, NIPPV therapy should be prescribed with caution.

Mechanical Ventilation

If the premature infant continues to experience apneic episodes despite interventions previously discussed (tactile stimulation, vestibular-proprioceptive stimulation, medications or nCPAP), insertion of an endotracheal tube is the final, most invasive measure to provide respiratory support. A study conducted by Sims et al (1989) demonstrated the need for mechanical ventilation for premature infants who had central apnea and failed treatment with medications, theophylline and caffeine.

Even though nCPAP and mechanical ventilation are two methods effective in treating and preventing apnea, significant side effects may occur. Nasal trauma has been reported as a complication of CPAP (Martin, 1993; Robertson, McCarthy, Hamilton, & Moss, 1996). The pressure on the nares and nasal septum causes tissue damage that may require surgical repair. Pulmonary barotrauma, resultant chronic lung disease and reduced cardiac output as a result of positive pressure to the thorax are documented side effects of mechanical ventilation (Duncan, Oh & Hillman, 1986; Monin & Vert, 1987; deLemos & Coalson, 1992). These issues have prompted investigators to seek less invasive alternative methods to keep the airway open and reduce episodes of apnea.

Nasal Cannula

As an alternative method for treating AOP, clinicians have suggested using the nasal cannula to deliver airflow as the initial therapy. If effective in maintaining a patent airway, the nasal cannula would provide a more gentle airflow to the nasopharyngeal area in a non-intrusive and comfortable manner.

In an attempt to wean the infant off the nasal cannula oxygen, most clinicians decrease the inspired oxygen by varying the liter flow and keeping the percent of oxygen constant. The clinician estimates the oxygen concentration the infant is receiving. In a previous study, it was shown that the hypopharyngeal concentration is similar to the tracheal oxygen concentration (Kaye, Summers, Monast & McEnany, 1981). Building on this information, Vain et al (1989) suggested measuring the hypopharyngeal oxygen concentration in order to determine the oxygen concentration reaching the infant's airway. These investigators conducted a prospective randomized clinical trial to provide a guide for the clinician in weaning from the nasal cannula oxygen.

The infants eligible for the study were clinically stable and receiving supplemental oxygen via nasal cannula (Salter Infant Nasal Cannula 1601). The physiologic parameters monitored throughout the study were the heart rate, respiratory rate, transcutaneous oxygen tension (tcPo2) and oxygen saturation. The hypopharyngeal oxygen concentration (FhO_2) was measured by using the nasal oxygen sampler (12F suction catheter inserted into the hypopharynx). FhO_2 was measured at various gas flow rates (0.25, 0.5, 0.75, and 1.0 Liter/minute) and at different oxygen concentrations (100%, 80%, 60%, 40%, and 21%). Once parental consent was obtained, 10 infants were randomly assigned to start at one of the gas flow rates and oxygen concentrations. Each infant was studied at the various gas flow rates and oxygen concentrations.

Birthweight ranged from 825 to 4090 grams, weight at entry into the study was 1780 to 4090 grams, gestational age was 25 to 39 weeks, and postnatal age was 19 to 123 days. The FhO_2 was approximately .35 at 0.25 L/m and 1.0 oxygen concentration and approximately .65 at 1.0 L/m and 1.0 oxygen concentration. When an infant was

breathing room air at 0.25 to 1.0 L/m, the FhO_2 ranged 0.16 to 0.18. There was minimal change in the FhO_2 when the oxygen concentration was decreased below 80% at the various gas flow rates.

There was a statistically significant difference between the FhO_2 and gas flow rate and oxygen concentration ($p < .001$) indicating lower oxygen concentration at the tracheal. There was a linear relationship between the FhO_2 concentration and oxygen flow rates, such that FhO_2 concentration decreased as the oxygen flow rates decreased. The weaning guidelines suggested by the investigators were to initially decrease the gas flow rate from 1.0 to 0.25 L/m then reduce the oxygen concentration from 100% to 80%.

Neonatal clinicians have often observed an improvement in the respiratory status after starting nasal cannula O_2 therapy. Locke et al (1993) hypothesized that the improvement observed with nasal cannula O_2 therapy may be related to delivering end-distending pressure. To test this hypothesis, a randomized prospective clinical trial was conducted with 13 infants who had a mean birthweight of 1377 $\pm$705 grams and who were 30 $\pm$4 weeks mean gestational age. Each infant was randomly assigned to use either the 0.2-cm nasal cannula or 0.3-cm nasal cannula at flow rate of 0.5, 1 1.5 and 2 L/minute. The primary outcomes for this study were airway end-distending pressure (as measured by esophageal pressure) and pulmonary mechanics (as measured by thoracoabdominal motion).

The investigators detected no relationship between the mean esophageal pressure and the various flow rates when the 0.2-cm nasal cannula was used. However, there was a positive linear relationship between the mean esophageal pressure and the various flow rates when using the 0.3-cm nasal cannula ($r = .92$). The thoracoabdominal motion was

not significantly different with the 0.2-cm nasal cannula as the flow rate increased but the thoracoabdominal motion was significantly reduced with the 0.3-cm nasal cannula as the flow rate increased ($p < .02$).

These data demonstrate that the 0.3-cm nasal cannula can deliver positive end-distending pressure resulting in improved lung volume and chest wall forces. The investigators caution against the indiscriminate use of the nasal cannula as therapy for respiratory problems affecting premature infants because of the potential side effects of positive end-distending pressure, such as barotrauma and pneumothorax.

Sreenan et al (2001) conducted a crossover study to evaluate the possibility of using the O_2 nasal cannula as treatment of apneic episodes. If effective, the nasal cannula could be used as an alternative therapy to nCPAP, thus avoiding adverse effects such as nasal trauma. Forty premature infants 28.7 (± 0.4) weeks gestation, 1256 (± 66) grams birthweight and 30.3 +0.6 weeks postconceptual age, initially received nCPAP. After 6 hours they were switched to nasal cannula at various flow rates, 0.5, 1 and 2 L/m. The primary outcome for this study was also airway end-distending pressure. As in the Locke et al (1993) study, Sreenan et al (2001) measured the esophageal pressure as an indication of airway end-distending pressure. The secondary outcome was the frequency of apneic, bradycardia and desaturation episodes. For the purpose of the study, apnea was defined as cessation of breathing lasting at least 10 seconds associated with bradycardia (decrease in heart rate to <70% of the baseline heart rate) and desaturation (oxygen saturation <88%). The investigators reported that the nasal cannula delivered positive airway pressure ranging 1.4 to 9.8 cm at the various flow rates, 0.5, 1 and 2 L/m. There was no statistically significant difference in the frequency of apnea, bradycardia and desaturation

between the two-treatment methods, nCPAP (1.6 ± 0.8) and nasal cannula (2.0 ± 0.5) but the effect size difference was more than .5 SD units. On average, the infant who received nCPAP had fewer apneic episodes than 70% of the infants who received the nasal cannula therapy. However, they concluded that the nasal cannula was as effective as nCPAP in treating apnea, based on the lack of statistical significance in their small sample (type II error).

In these studies, the nasal cannula at O_2 flow rates of 0.5, 1 and 2 L/m were shown to reduce apneic episodes with 1 L/m delivering approximately 4-5 cm positive airway pressure. It has been shown that nCPAP of 4-5 cm positive airway pressure is therapeutic in reducing apneic episodes.

Conclusions

AOP affects approximately 80% of infants born before 37 weeks gestation. The primary cause of AOP is immaturity of the respiratory system and poor airway compliance. An apneic episode is identified by an audible alarm from the bedside cardiorespiratory monitor that indicated a lack of an electrical respiratory wave signal for ≥ 20 seconds. The sound of the alarm prompts the bedside nursing staff to assess the infant and initiate appropriate action to assist the infant to resume breathing. Then the bedside nursing staff records these episodes in the infant's bedside medical chart. Korner et al (1975) extracted information regarding the frequency of apneic events from the bedside medical chart only. Saigal et al (1986) documented apneic events using both chest wall impedance monitoring system and the bedside medical chart. They found a discrepancy between the two documentation techniques. It was recommended that the

chest wall impedance monitoring system be used along with the nursing documentation in the bedside medical chart of apneic episodes.

When an apneic episode occurs, there is a decrease in heart rate, initially an increase in blood pressure followed by a decrease in blood pressure and decrease in oxygen saturation. Investigators have described two scenarios in the sequence of events as a result of an apneic episode. In the scenario described by Henderson-Smart et al (1986), apnea occurs, oxygen saturation decreases then the heart rate decreases (bradycardia). The investigators hypothesized that hypoxia from the lack of respiratory effort leads to bradycardia. Whereas, Poets et al (1993) described the same events in a different sequence; apnea occurs, the heart rate decreases, which leads to a decrease in oxygen saturation. The time it takes for these events to occur ranges from 1.5 to 8 seconds. It may be difficult to definitively state the true sequence of these events. However, all investigators agree that the hypoxia that results from an apneic episode could lead to cellular damage and prompt treatment is essential.

Current therapies include tactile stimulation, medication that stimulates the respiratory center, and mechanical respiratory support. These therapies have been shown to be effective in reducing the frequency of apneic episodes but have unwanted side effects. For example, Kattwinkel et al (1975) did show tactile stimulation to be effective in reducing apneic events but required constant nursing attention. This technique is useful as short-term management.

The oscillating bed is another technique used to management apneic episodes. Korner et al (1975), Jirapaet (1975), Tuck et al (1982) reported the oscillating bed applied over a short period of time was effective in reducing apnea. However, the sample size in

each study was consistently small and the study intervention was applied over short duration (hours) and in combination with aminophylline. Therefore, the positive results should be taken with caution.

In contrast, Jones (1981) and Saigal et al (1986) reported the oscillating bed ineffective in reducing apneic episodes. These studies were conducted over a longer study period (days) with two separate treatment groups, one receiving the oscillating bed and the other receiving theophylline. This design truly tested the effect of the study intervention, oscillating bed. The investigators advised neonatal clinicians to only use the oscillating bed as short-term management of AOP.

Many researchers and clinicians describe theophylline, caffeine and doxapram to be effective therapy in the treatment of AOP. Repeatedly, the investigators report these respiratory stimulants are effective a significant reduction in the frequency of apnea. However, the researchers reported symptoms of intolerance such as, tachycardia, jitteriness, vomiting, irritability, and most importantly an increase in oxygen consumption.

It has been documented that mechanical respiratory support techniques, such as nCPAP and mechanical ventilation are also effective in reducing the frequency of apneic episodes. However, these techniques have been shown to result in unwanted effects. For example, Robertson et al (1996) has shown nCPAP causes trauma to the nasal septum nasal trauma. Duncan et al (1986), Monin et al (1987), and deLemos et al (1992) reported evidence of barotrauma after using mechanical ventilation.

Fan et al (1983), Locke et al (1993), and Vain et al (1989) described the feasibility of the nasal cannula in delivering supplemental oxygen to infants. Despite these small sample sizes, they all did show clinical relevance for using the nasal cannula.

Locke et al (1993), Sreenan et al (2001), and Wilson et al (1996) described the similarity between the nasal cannula and nCPAP. They stated that the nasal cannula was as effective as nCPAP in reducing the frequency of apnea. These studies were also completed using small samples and the subjects were given aminophylline, in addition to the nasal cannula. It is unclear if the nasal cannula therapy actually made a difference in the frequency of apnea. Perhaps the reduction in the frequency was a result of the aminophylline. The nasal cannula researchers used various levels of flow of oxygen via the nasal cannula. Oxygen has been shown to be effective in reducing apneic episodes (Gerhardt & Bancalari, 1984). Again it is unclear which therapy was effective in reducing the episodes of apnea. Research is needed to test the effect of the nasal cannula as single therapy in the management of apnea.

Future studies should be directed toward the description and documentation of the apneic episodes in nursing bedside notes as well as the management of AOP. Currently, there are general guidelines to help the neonatal bedside nurse to describe and then to document an apneic episode. But these guidelines are subject to individual interpretation. For example, fifteen UCSF NICU nurses were asked during in an informal survey to describe an apneic episode and the management of these episodes. The description was similar, cessation of breathing for >20 seconds. But the procedure they followed after an apneic episode occurred was different. The nurses with >10 years NICU experience

watch to see if the episodes will terminate without intervention. The nurses with <5 years NICU experience applied tactile stimulation immediately.

The degree of tactile stimulation also varied. Normally tactile stimulation is described using terms such as none (or no), mild, moderate or vigorous (Kattwinkel et al, 1975). The term none or no stimulation is used when it is not necessary for the nurse to intervene to terminate the episode. The term mild stimulation is used when the nurse gently touches the infant to terminate the episodes. The term moderate stimulation is used when the infant requires a more forceful touch to terminate the episode. Neither the nurses with >10 years NICU experience nor the nurses with <5 years NICU experiences used the same term to describe the degree of tactile stimulation that was provided to terminate the apneic episode. Research to support evidence-based guidelines is needed.

Research is also needed on the management techniques, such as caffeine, theophylline and doxapram, used to treat AOP. Often apneic episodes are controlled with either caffeine or theophylline. But for some infants, medications are ineffective and further pharmaceutical treatment is required, such as doxapram. A clinical investigation needs to be conducted to describe the characteristics of the infants who are responsive to caffeine and theophylline and those who are not responsive to these drugs. If the neonatal clinician is aware of these characteristics, appropriate treatment could be prescribed without delay.

In addition to medications, research is also needed on maneuvers that support the premature infant's respiratory system. Currently, maneuvers, such as nCPAP and mechanical ventilation have adverse effects, which include nasal trauma, barotrauma and chronic lung disease. The focus of the research could be directed toward the discovery of

new techniques that support the premature infant's respiratory system. One such technique is the use of the nasal cannula to deliver air and splint the airway to reduce the frequency of apneic episodes without adverse effects. The study should test the effect of the nasal cannula as a single therapy. It is recommended that one flow rate of the nasal cannula be selected without any other mode of treatment such as caffeine, theophylline or doxapram in order to test the effect of the nasal cannula therapy in reducing the frequency of apnea.

The proposed research questions are as follows: 1) Is air delivered by the nasal cannula effective in reducing the frequency of apneic episodes?, 2) Is the nasal cannula effective in reducing the duration of the apneic episodes?, and 3) Is the nasal cannula effective in reducing the severity of apneic episodes?.

CHAPTER 3

METHODOLOGY

Study Design

The study design was a randomized interrupted time series clinical trial (Figure 1 and Figure 2). The purpose of the study was to evaluate the feasibility and effect of airflow (FiO_2 21%) via the nasal cannula a 1L/min as a treatment for premature infants with the diagnosis of apnea of prematurity to reduce the frequency, duration, and severity (change in oxygen saturation) of apneic episodes.

Setting

This investigation was conducted in the Neonatal Intensive Care Unit (NICU) at Children's Hospital University of California, San Francisco (UCSF) Medical Center, a tertiary academic medical center.

Sample

Ten premature infants, with the diagnosis of apnea of prematurity and whose parents or legal guardian consent to participate, were recruited for this study. Criteria for inclusion of infants were 1) between 28 and 32 weeks gestation, 2) between birthweight 1200 and 1800 grams, 3) primary diagnosis of apnea of prematurity at time of eligibility, and 4) having apneic episodes associated with bradycardia and requiring treatment. Criteria for exclusion of infants were 1) grade III or IV intraventricular hemorrhage, 2) major congenital anomalies, and 3) participating in another therapeutic clinical trial.

Instruments

The heart rate, respiratory rate, and oxygen saturation (SaO_2) were monitored on a continuous basis. The Hewlett-Packard Model 1176A-monitor system was used to record

the heart rate and respiratory rate by impedance pneumography and the Nellcor N-200 pulse oximeter measured the SaO_2.

<div align="center">Measurement of Heart Rate</div>

The heart rate was detected with continuous non-invasive monitoring of electrocardiographic (ECG) activity using the Hewlett-Packard monitor (Model 66, Hewlett-Packard Co., CA). The ECG measures changes in electrical energy on the body surface that reflects underlying cardiac electrical activity.

The infant was monitored using three electrodes configured in Lead II. This configuration involved placement of the electrodes on the right chest, on the left chest and on the abdomen. The right arm electrode was placed at the level of the 2nd intercostal space near the right mid-clavicular line directly below the clavicle. The left arm electrode was placed at the level of the 2nd intercostal space near the left mid-clavicular line directly below the clavicle. The left leg electrode is placed at the level of the 6th or 7th intercostal space below the left mid-clavicular line (see Figure 3).

There are several parameters that were adjusted to reflect the neonatal patient's heart rate. These parameters include waveform size, bandwidth, and QRS detection mode. The waveform was set at gain x1, which the displayed waveform with 1000 magnification. The monitor bandwidth was selected. The QRS detection has either an auto or manual mode selection. The auto mode was used to detect the QRS waveform. The high and low alarm limits were also set.

The high limit was set to call attention to a heart rate > 200 beats per minute (bpm) and the low limit was set to indicate a heart rate < 100 bpm. There was both a visual display of the heart rate as well as an audible sound of violation of the alarm limits.

The audible tone volume of the alarm sound was set at 120 dB, a standard tone for monitors used in the NICU.

To ensure accuracy of the information displayed on the Hewlett-Packard Monitor, there was a recent (within 1 month prior to study entry) calibration testing performed on the monitors by the biomedical engineer. The testing procedure entails evaluation of the heart rate monitor accuracy and response to irregular rhythm generated by a heart rate simulator. The simulator displays heart rate waveforms at various levels, 80, 90, 60, and 120 bpm. The primary evaluation of the monitoring system is the time required for the monitor to respond to an increase or decrease in the simulator heart rate waveform. In order to be valid and reliable, the Hewlett-Packard Monitor must display the various heart rate levels, respond to an increase in heart rate in 8.6 seconds, and respond to a decrease in heart rate in 8.2 seconds.

<u>Measurement of Respiration</u>

The Hewlett-Packard (Model 66, Hewlett-Packard Co., CA) was used to continuously monitor the respiratory rate. This monitoring system measured the respiratory rate by detecting the change in resistance (or impedance) between the chest and the two electrodes (see Figure 4). The change in resistance measured between these two electrodes produces a respiratory waveform on the monitor screen (see Figure 5).

A series of settings were adjusted while monitoring the respiratory rate. These settings included respiration detection mode, alarm limit, and apnea alarm limit. The respiration detection auto mode was used to count the frequency of respiration. Both a high alarm and low alarm were selected. A count >60 breaths per minute was chosen as the high alarm limit with adjustments based on the infant's clinical status. The low alarm

limit was set at <20 breaths per minute. An apnea alarm limit was also set for 20 seconds. This means that an audible alarm will sound if there is no detected respiration after a 20-second time interval. The volume of the alarm tone was 120 dB, a standard tone for monitors used in the NICU.

<div align="center">Measurement of Oxygen Saturation</div>

The Nellcor N-200 (Nellcor Inc., Hayward, CA), pulse oximeter was the instrument used to obtain a noninvasive and continuous estimate the SaO_2. The patient module provides a connector for the oximetry sensor and provides initial pulse oximeter signal processing. The pulse oximeter probe was connected to the infant's hand. Once connected to infant and turned on, it provided immediate information about the infant's SaO_2 and heart rate with visible and audible display.

Each SaO_2 and heart rate parameter has separate alarm settings. The high limit for the SaO_2 for the premature neonatal patient was set at 96% and the low limit was set at 88%. The high heart rate alarm limit was set at 200 bpm and low alarm set at 100 bpm. A visual and audible display indicated the SaO_2 and heart rate reached the alarm limits. The volume of the audible alarm tone was 120 dB, a standard tone for monitors used in the NICU.

There is no need for the Nellcor N-200 pulse oximeter to be calibrated or configured on a regular basis. This system has automatic self-test and automatic oximetry calibration; the automatic calibration is performed each time the monitor is turned on, at periodic intervals thereafter, and whenever a new sensor is connected.

Study Procedure

Once permission was obtained from the parents of the infant for study participation, the infant was randomly assigned to either Order 1 or Order 2. To control for time of day, developmental changes and sleep state, each group alternated the order of nasal cannula treatment. Order1 started with the nasal treatment on and Order 2 started with the nasal cannula treatment off. (See Appendix E.) After each 60-minute segment, the treatment alternated. The nasal cannula treatment was the delivery of airflow (FiO_2 21%) at 1-liter per minute via a nasal cannula system. The nasal cannula system is an infant size apparatus manufactured by Salter Labs reference number 1601. The study intervention was administered during one 6-hour period, which was divided into six 60-minute segments. Initially, there was a 30-minutes of baseline monitoring that followed by the random assignment to the order of the treatment, either Order 1 or Order 2. The infant received the routine medical and nursing care during the study period.

During the 6-hour study period the documentation of the heart rate, respiratory rate and oxygen saturation were recorded. (See Appendix F.) The time periods for obtaining impedance pneumography measurements were at entry into the study and then continuously during the 6-hour study period. The frequency (count) and duration (seconds) of apnea, as well as mean SaO_2 during the each 60-minute segment, were the primary outcomes. A pause in breathing >20 seconds indicated an apneic episode. These episodes of apnea were documented in the nursing notes and saved in the memory of the Hewlett-Packard monitor. Then the number of apneic episodes recorded on the monitor was counted.

If an apneic episode >20 seconds occurred during the study period, the initial intervention was the application of tactile stimulation. If tactile stimulation alone was not effective in terminating the episode, oxygen therapy and/or bag mask ventilation was administered. The infant exited the study if oxygen and/or bag mask ventilation is required to terminate the apneic episode. Alternative treatments, such as medications or nasal CPAP were started immediately.

In addition, a retrospective chart review was conducted to collect information that included demographic characteristics about the infant. The demographic characteristics included gender, admission diagnosis, ethnicity, birthweight, gestational age, age at enrollment, and severity of illness score. The severity of illness score was estimated by calculating the Score for Neonatal Acute Physiology (SNAP) (Richardson, Gray, McCormick, Workman & Goldman, 1993). The SNAP is a 26-item scoring system that is completed within 24 hours after birth. The 26 items obtained from the chart review include: physiologic measures (heart rate, blood pressure, respiratory rate, and temperature), laboratory measures (complete blood count, electrolytes, glucose, blood gases, hematocrit, indirect bilirubin, and direct bilirubin), apnea (responsive to stimulation, unresponsive to stimulation or complete apnea), and seizure (single or multiple).

Data Analysis

Descriptive statistics were used to present the results of all study variables. Independent categorical demographic variables, such as gender, admission diagnosis, and ethnicity, were summarized with frequencies and percentages. The continuous independent variables, such as birthweight, weight at entry into the study, gestational age,

severity of illness score, age at enrollment, heart rate, respiratory rate, and oxygen saturation, caffeine dose, and hematocrit were summarized with means and standard deviations. The three demographic independent variables were correlated with the ten continuous independent and three dependent variables (frequency, duration, and severity of apneic episodes).

A repeated measures analysis of variance (RM-ANOVA) with one between subjects factor, group, with two levels (order 1 and order 2) and one within subjects factor, condition, with two levels (nasal cannula therapy versus no cannula therapy) was used to address the three hypotheses (See Figure 2). Testing the main effect of condition was used to determine if nasal cannula therapy does decrease the number of apneic episodes and/or decrease the duration and severity (change in oxygen saturation) of apneic episodes. The main effects of group and the interaction of group by condition were also tested, but only to determine if order of therapy did not affect the outcomes. An alpha level of <0.05 was considered statistically significant.

CHAPTER 4

RESULTS

Study Results

This randomized interrupted time series clinical trial evaluated the effectiveness of nasal cannula treatment in reducing the frequency of apneic episodes in premature infants. Demographic characteristics and the results of the study are presented in this chapter.

Demographic Data

The study sample consisted of 10 infants admitted to the Neonatal Intensive Care Unit (NICU) at the Children's' Hospital at UCSF Medical Center. Table 1 shows the demographic characteristics of these infants.

Eighty percent of the infants were male (n = 8). The ethnicity of the infants who participated in the study varied with African American, Hispanic, White, and Asian. In addition to the admission diagnosis of prematurity, three of the infants had a diagnosis of respiratory distress syndrome and one was diagnosed with cleft palate and one with patent ductus arteriosus. All infants had the diagnosis of apnea of prematurity in order to be eligible for the study. Five of the infants were randomly assigned to protocol order 1 and 2 (Figure 1). Protocol order 1 start the study on the nasal cannula and protocol order 2 started the study off the nasal cannula.

Descriptive Data

The infants were premature with a mean (SD) gestation 30.4 weeks (1.35) and mean (SD) birthweight 1504 grams (178.54). The mean (SD) age at time of entry into the study was 9.4 days (3.92) and with the mean (SD) corrected gestational age of 31.9

weeks (1.37). The mean (SD) severity of illness (SNAP) score was 12.4 (3.4) and the range was 8 to 20. The mean (SD) weight 24 hours before starting the study was 1499 grams (252.67) and mean (SD) weight on study day 1 was 1481 grams (252.26). Table 2 shows the descriptive data for these infants. The mean heart rate, respiratory rate and oxygen saturation for each infant is outlined in Table 3. The descriptive data has normal distribution (Figures 6 through 12).

Hypotheses

Hypothesis 1: **There will be no change in the frequency of apneic episodes when the preterm infant receives one-liter airflow (FiO$_2$ 21%) by nasal cannula.**

The mean (SD) frequency of apneic episodes 24 hours before study entry was 10.6 (4), during the study was 3 (1.82) and 24 hours after completing the study was 6.1 (4.2) (See Table 3). Since the sample met the required assumptions of random sampling of differences, paired samples, independent samples and sample from normal distribution, a paired t-test was conducted. The paired t-test demonstrated a statistically significant difference between the frequency of apneic episodes 24 hours before entering into the study and 24 hours after the study was completed (t$_9$ = 3.551, p = 0.006). The mean frequency of apneic episodes was lower 24 hours after the study compared to 24 hours before the study.

The required assumption for Repeated Measures ANOVA are random sample from normally distributed population, repeated observations of each subject, independence of each observation, and non-significant test of variance. Since the required assumptions for this sample were met, RM-ANOVA was used to test the main effect of group (order), condition (nasal cannula), and the interaction of group * condition

with the frequency of apneic episodes as the dependent variable. RM-ANOVA

demonstrated a statistically significant effect of the condition (nasal cannula) on the

frequency of apneic episodes as the dependent variable ($F_{(5,45)}$ = 3.423, p = 0.011). There

was no statistically significant effect of group (order1 versus order 2) ($F_{(1,8)}$ = 4.0, p =

0.081) or interaction of condition * group ($F_{(1,8)}$ = 0.027, p = 0.874) (Figure 13).

Hypothesis 2: **There will be no change in the duration of apneic episodes when the**

preterm infant receives one-liter airflow (FiO$_2$ 21%) by nasal cannula.

The mean (SD) duration of apnea before starting the study was 39.5 (8.317)

seconds, during the study treatment was 31.0 (5.676) seconds, and 24 hours after study

was 36.7 (6.056) seconds. There was no statistically significant difference in the duration

of apneic episodes 24 hours before the study and 24 hours after the study ($t_{(9)}$ = 1.007, p =

0.34) (Table 4). However, the duration of apneic episodes was significantly longer

before the intervention (39.5 (8.317) seconds) compared to after the intervention (36.7

(6.056) seconds).

Hypothesis 3: **There will be no change in the severity (oxygen desaturation [SaO$_2$]) of**

apneic episodes when the preterm infant receives one-liter airflow (FiO$_2$ 21%) by

nasal cannula.

The mean (SD) level of desaturation, the lowest SaO$_2$, before starting the study

was 64.9% (12.87), the lowest level of desaturation during the study treatment was 75.1%

(7.5), and the lowest level of desaturation after the study was 67% (10.055). There was

no statistically significant difference between the level of desaturation between the time

24 hours before study and 24 hours after the study ($t_{(9)}$ = -2.003, p = 0.076) (Table 5).

Influence of Demographic Characteristics on Study Outcome

Research has shown that there is an inverse relationship between the frequency of apneic episodes and gestational age, birthweight, and SNAP score. Statistical analysis was conducted using Pearson Product-Moment correlation to determine the associations between gestational age and birthweight and the study outcome (frequency of apneic episode).

<u>Gestational Age, Birthweight, and SNAP Score</u>

The gestational age of the infants in the study was not correlated with the frequency of apneic episodes ($r = -0.135$, $p = 0.709$) (See Figure 14). There was a negative correlation between birthweight of the study infants and the frequency of apneic episodes 24 hours after the study treatment ($r = -0.765$, $p = 0.01$) (See Figure 15). The infants with higher birthweight had fewer episodes of apnea. There was no significant correlation between the SNAP score of the study infants and the frequency of apneic episodes ($r = 0.283$, $p = 0.428$) (See Figure 16).

Additional Findings

The apneic episodes that occurred during the study treatment were successfully treated with tactile stimulation. None of the infants required oxygen therapy or bag/mask positive ventilation.

After completing of the study, all 10 of the infants were prescribed nasal cannula 1 Liter/minute FiO_2 .21 on a continuous basis as treatment for their apneic episodes. Four infants were given caffeine in addition to the nasal cannula.

CHAPTER 5

CONCLUSION, DISCUSSION AND RECOMMENDATIONS

INTRODUCTION

The findings of this study suggest that the nasal cannula is effective in reducing the frequency of apneic episodes of premature infants. The results are discussed in relationship to the effect the nasal cannula has on the frequency of apneic episodes, the duration as well as the severity of these episodes. The nursing implications, limitations of the study and recommendations for future research are also discussed in this chapter.

CONCLUSION

There were three significant findings in this 6-hour study that evaluated the effect of the nasal cannula treatment. First, the nasal cannula 1 Liter/minute reduced the frequency of apneic episodes in premature infants with the diagnosis of Apnea of Prematurity (AOP). For most infants, there was approximately 50% to 75% reduction in the frequency of apneic episodes from the 24 hours before entering the study to the time in the study (6 hours). In all but one infant, this reduction in apneic episodes continued for 24 hours after the study was completed.

Second, there was also a reduction in the duration (seconds) of the apneic episodes for the infants using the nasal cannula 1 liter per minute room air to treat apneic episodes. During the 24 hours before entering the study, the duration of the apneic episodes ranged from 30 – 50 seconds. In comparison, the duration of the apneic episodes during the study treatment was reduced and ranged 25 – 40 seconds.

Third and most importantly, the severity, O_2 desaturation level, of the apneic episodes was less during the study period. The lowest O_2 desaturation level before the

study ranged from 40 – 82%. The lowest O_2 desaturation level improved during the study period to range from 63 – 86%.

The apneic episodes that did occur during the study resolved with tactile stimulation. There was no drying of the nasal mucosa and no nasal trauma was noted during the study. Therefore it is recommended that the nasal cannula 1 Liter/minute be used to treat premature infants with the diagnosis of AOP.

DISCUSSION

This study investigated the effect of the nasal cannula on the frequency, duration and severity of apneic episodes. This was the only study thus far that tested the effect of the nasal cannula as single therapy for Apnea of Prematurity.

The results did show that there was a reduction in the frequency of apneic episodes. There was a reduction in the duration of these episodes. The level of desaturation was not as low while on the nasal cannula. Overall, while on the nasal cannula treatment, the apneic episodes were fewer, shorter and less severe. It is unclear how the nasal cannula treatment is effective in reducing the frequency apneic episodes. However, it is hypothesized that the nasal cannula delivers positive pressure similar to nasal continuous positive pressure (nCPAP). The positive pressure improves functional residual capacity, thereby improving oxygenation and ventilation. Therefore, the physiologic effect of the nasal cannula treatment will be the focus of future research studies.

These findings are consistent with previous research that described the effect of nasal cannula treatment in reducing apneic episodes (Locke et al (1993) and Sreenan et al

(2001). In these studies, the nasal cannula treatment with oxygen was found to be as effective in reducing the episodes of apnea as nCPAP.

Locke et al (1993) hypothesized that the reduction in the frequency of apneic episodes was related to the nasal cannula delivering end-distending pressure. To test this hypothesis, the investigators conducted a prospective clinical trial with 13 premature infants. The nasal cannula (0.2 cm versus 0.3 cm) delivered oxygen and was set at various liter flows (0.5, 1.and 2 liter/minute). They demonstrated that the 0.3-cm nasal cannula could deliver positive end-distending pressure resulting in improved lung volume and chest wall forces. Results of this study support the findings of Locke et al that the flow pressure from the nasal cannula improves lung volume.

Sreenan et al (2001) conducted a crossover study that compared nasal cannula oxygen with nCPAP oxygen as treatment for apneic episodes. Each of the 40 premature infants that participated in this study received 6 hours of initial nCPAP then 6 hours of nasal cannula treatment. They concluded that there was no difference in the frequency of apneic episodes between the two treatment groups (nCPAP versus nasal cannula).

These studies did show that the nasal cannula was effective in reducing the frequency of apneic episodes. However, in the study conducted by Locke et al (1993), it is unclear the exact liter flow that was the most effective in reducing the frequency of apneic episodes.

In the study conducted by Sreenan et al (2001), each infant in the study received both nasal cannula as well as the nCPAP. There is potential for carryover effect of each intervention. In contrast, the current study was conducted only using the nasal cannula

treatment, thereby testing the effectiveness of the nasal cannula in reducing the episodes of apnea.

NURSING IMPLICATIONS

The neonatal nurse is responsible for the recognition and prompt treatment of apneic episodes. This study has shown that the nasal cannula, a soft two-prong system that administers oxygen, is effective in treating apnea of prematurity.

After the medical team has prescribed the nasal cannula treatment for AOP, it will be the neonatal nurse who applies the nasal cannula apparatus and assesses whether the nasal cannula continues to be effective in reducing the apneic episodes.

Based on the results of this study, the following is the recommended standard of care for nasal cannula treatment:

1. **Indication:** Treat apneic episodes that require treatment in addition to tactile stimulation for premature infants < 35 weeks gestation with the diagnosis of AOP.

2. **Contraindication:** Upper airway obstruction, such as choanal atresia or cleft palate.

3. **Equipment:**

   a. Nasal Cannula – Salter Labs Infant Nasal Cannula #1601

   b. Flow Meter

   c. Oxygen blender

   d. Skin Prep – Hollister Skin gel protective dressing swipe

   e. 2 pieces of 2cm x 5cm DuoDERM – Convatec Extra Thin DuoDERM

   f. 2 pieces of 2cm x 5cm Tegaderm – 3M Tegaderm

4. **Application of the Nasal Cannula:**

   a. Cleanse cheeks with warm water

   b. Assess each nostril for patency (suction each nostril if necessary)

   c. Apply skin prep

   d. Place 1 piece of DuoDERM strip on each cheek in space between outer nare to ear lobe

   e. Insert soft two-prong nasal cannula into each nostril (one prong in each nostril)

   f. Apply 1 piece of Tegaderm over DuoDERM and Nasal Cannula tubing

   g. Connect end of Nasal Cannula to flow meter

   h. Start flow at 1-liter room air (FiO$_2$ 21%)

5. **Criterion of Effectiveness:**

   a. Frequency of apneic episodes – evaluate the frequency of apneic episodes within 3 to 6 hours after starting nasal cannula treatment then daily while infant is receiving nasal cannula treatment.

   b. Monitor physiologic parameters, such as, mean heart rate, mean respiratory rate and mean oxygen saturation 3 to 6 hours after nasal cannula is started then daily. Compare mean heart rate, mean respiratory rate and mean oxygen saturation 24 hours before nasal cannula treatment and mean heart rate, mean respiratory rate and mean oxygen saturation 24 hours after nasal cannula treatment.

6. **Length of Treatment:** Continue nasal cannula treatment until the infant has no episodes for 7 days.

7. **Monitor for side effects** of drying of the nasal mucosa and trauma to face/cheek and nose.

The neonatal nurse will also help identify clinical signs of side effects of the nasal cannula treatment. It is important for the neonatal nurse to monitor infants for evidence of drying of the nasal mucosa. She/he will evaluate the infant for changes in the respiratory pattern or O_2 saturation levels that may indicate possible in airway obstruction. To help prevent dry nasal mucosa the nasal cannula oxygen will be warmed and humidified.

In addition, the neonatal nurse will also assess the infant for signs of trauma to the face and nares. This can be done by frequently inspecting the skin of the face and nares looking for redness and breakdown.

The procedure the neonatal nurse follows when applying and maintaining the nasal cannula treatment will result in minimal disturbance to the infant. This may provide the infant longer uninterrupted rest periods to promote growth and development.

The additional nursing care of the infant with this treatment is minimal. Thereby, affording the neonatal nurse an opportunity to spend more time caring for the infant and his/her parents.

LIMITATIONS OF THE STUDY

Interpretation of the results of this study may be limited by several factors. First, every attempt was made to recruit premature infants of gestational age ranging 24 to 35 weeks. However, the group of infants enrolled in the study was one that have been described in the literature to have less frequent apneic episodes. Unfortunately, this limits

the generalizability of the findings to a small group of premature infants who were 28 to 32 weeks gestation and birthweight 1240 grams to 1890 grams.

A second limitation to the study is the small sample size. A power analysis performed before starting the study indicated that a sample size of 50 (25 infants in each group) was needed to provide greater than 90% power to detect a difference at an alpha level of .05. The sample size was 10 because of limited eligible infants for this study because of low census in the NICU. Subjects were enrolled between the months of March and November in the year 2003.

Third, the improvement in SaO_2 levels may have been confounded by the fact that the infants were in prone position before, during, and after the study. The reason the infants were in the same position was to minimize the effect of position on SaO2 during the study. It has been described in the literature that prone positioning enhances oxygenation (Maynard, Bignall, & Kitchen, 2000). Future studies should include both supine and prone position to determine if position has an effect on the frequency of apneic episodes.

Fourth, it is possible that the duration of the apneic episodes may have been shorter that expected. Since the neonatal nurse was present at the bedside throughout the study, the nurse may have responded to monitor alarms quicker than usual. Thereby, the duration of the apneic episodes may have been shorter for the study participants than non-study participants.

Lastly, the reduction in the frequency of apneic episodes may have been due to the fact that the study was only 6 hours during which time the infant may have naturally

had fewer episodes. In future studies, the duration of the study should be extended to a period of 24 hour in order to capture all possible episodes of apnea.

RECOMMENDATIONS FOR FUTURE RESEARCH

Recommendations for future research include:

1. Repeat this study with a larger sample size documenting the frequency, duration and severity of apneic episodes. In addition, the sample would include those in the gestational age range of 24 to 28 weeks to ensure generalizability of the research findings.

2. Describe the mechanism for action of nasal cannula treatment in order to evaluate the effect of the nasal cannula on lung volume.

3. Describe the effect of nasal cannula treatment on frequency of apneic episodes throughout the infant's hospitalization while receiving this treatment. This study design would help answer other research questions not addressed in this study such as:

- Length of study would be extended to include time period with the diagnosis of Apnea of Prematurity.

- To understand the long-term effects of nasal cannula treatment and potential habituation after 24 hours.

4. Conduct a randomized clinical trial comparing nasal cannula treatment and caffeine treatment with the primary outcome of frequency of apneic episodes.

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NASAL CANNULA TREATMENT
SCREENING SHEET

Infant's Name: _____

UC Unit #: _____

Sex: M   GA: _____

       F

Date of Birth: _____

INCLUSION CRITERIA:
YES   NO

☐   ☐   <35 Weeks Gestational Age
☐   ☐   Primary Diagnosis of Apnea of prematurity
☐   ☐   >6 but no more than 12 apnea episodes in 24 hours
☐   ☐   Not receiving theophylline or caffeine

EXCLUSION CRITERIA:
YES   NO

☐   ☐   Grade III or IV IVH
☐   ☐   Major congenital anomalies
☐   ☐   Participating in another clinical trial
☐   ☐   No parental consent signed

If yes is checked, infant is excluded.

Meets entry criteria for study: YES   NO

CONSENT

☐   Approached
      Date: _____
☐   Approached but declined
      Date: _____
☐   Consent obtained
      Date:_____

STUDY ID# _____

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

NASAL CANNULA TREATMENT FOR APNEA OF PREMATURITY

A. PURPOSE AND BACKGROUND

Abbey Alkon, RN, PhD, Assistant Professor, UCSF School of Nursing, Dolores Quinn, RN, NNP, PhD(c), Doctoral Student, UCSF School of Nursing, and Robert Piecuch, MD, Attending Neonatologist, UCSF Medical Center are conducting a research study to understand if the nasal cannula will decrease the number of apneic spells.

Apneic spells are when the premature baby briefly stops breathing. At the same time the baby's heart rate and the amount of blood oxygen may drop. It is important to treat the apneic spells to prevent any damage to the baby's growing body, especially the brain.

Currently, the therapies used to treat apneic spells are stimulation with touch, medicines, caffeine and theophylline, nasal continuous positive airway pressure (CPAP) and nasal cannula. There are problems with most of these therapies, for example: 1) touch stimulation may not be enough to stop these spells, 2) medicine (caffeine or theophylline) may make the baby jittery and not able to sleep, 3) nasal CPAP, a soft two-prong plastic device that fits snuggly inside the nostrils, may cause injury to the nose, and 4) nasal cannula is a soft two-prong plastic device fits loosely inside the nostrils. The nasal cannula is currently being used to deliver oxygen but it is not known if it is useful in treating apneic spells.

You have been asked to give permission for your baby to participate in this study because your baby was born prematurely and needs treatment for his/her apneic spells.

B. PROCEDURES

If you agree to have your baby participate in this study the following will occur:

1) Your baby will receive the intervention for the apneic spells using a soft plastic two-prong respiratory device (nasal cannula) that delivers airflow at 1 liter per minute at 21% oxygen that will be in the nostrils for 1 hour and off for 1 hour. When your baby is off for 1 hour, the nasal cannula will be removed from the nostrils.

2) Your baby will have a 50% chance of being assigned to either a group who receives the nasal cannula intervention first or a group who receives the nasal cannula intervention second.

3) If your baby is assigned to the group that receives the nasal cannula first, he/she will be:
on the nasal cannula for 1 hour,
off the nasal cannula for 1 hour, then
on the nasal cannula for 1 hour,
off the nasal cannula for 1 hour then,
on the nasal cannula for 1 hour,
off the nasal cannula for 1 hour.

4) If your baby is assigned to the group that receives the nasal cannula second, he/she will be:
off the nasal cannula for 1 hour,
on the nasal cannula for 1 hour, then
off the nasal cannula for 1 hour,
on the nasal cannula for 1 hour then,
off the nasal cannula for 1 hour,
on the nasal cannula for 1 hour.

5) The number of apneic spells will be recorded using the cardio-respiratory monitor. This type of monitor records and shows your baby's heart rate and breathing rate. Small adhesive patches with wires are placed on your baby's chest and abdomen. If the heart rate or breathing rate goes outside of the limits set on the monitor, an alarm will alert the investigator and the nursing staff to check on your baby's heart rate and breathing rate. The blood oxygen level (oxygen saturation) will be measured using the pulse oximeter. The pulse oximeter is a small red light that senses the amount of oxygen in blood. The pulse oximeter will be taped to your baby's hand or foot. If the amount of oxygen is too high or too low, the monitor will alarm, alerting the investigator and nursing staff to check on your baby.

6) Your baby's chart will be reviewed to obtain information about his/her admission diagnosis, ethnicity, birthweight, gestational age, age at enrollment, and severity of illness score. The severity of illness score is an estimation of how sick your baby was during the first few days after he/she was born. This score includes his/her heart rate, blood pressure, respiratory rate, and temperature, complete blood count, electrolytes, glucose, blood gases, hematocrit, indirect bilirubin, and direct bilirubin, apnea, and seizure.
Each day for 2 weeks your baby's weight, age, number of apneic episodes, feeding and urine output will be recorded and each week your baby's hematocrit will be recorded.

C. RISKS/DISCOMFORTS

Your baby will be assigned to an intervention order by chance. The nasal cannula intervention your baby receives may prove to be less effective or to have more side

effects than standard treatment. This will not be known until after the study is completed and the data has been analyzed.

It is possible that the nasal cannula intervention may increase the number of apneic spells. Your baby will receive appropriate treatment if an apneic spell should occur during either the time when he/she is on the nasal cannula or off the nasal cannula, appropriate treatment will be given. The number of apneic spells will be recorded to monitor the risk.
On the other hand, the nasal cannula intervention may prove to be effective in decreasing the number of apneic spells and increase the oxygen level.

It is also possible that there may be irritation to the skin as a result of applying the nasal cannula. To reduce the risk of skin irritation, DuoDERM, a soft thin dressing, will be placed on the skin of the just washed cheeks and tape will be placed over the DuoDERM.

Participation in research will involve loss of privacy; however, your baby's research records will be handled as confidentially as possible. All records will be coded, and kept in locked files so that only the study investigators have access to them. No individual identities will be used in any reports or publications resulting from this study.

If your baby is injured as a result of being in this study, intervention will be available. The costs of such interventions may be covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, contact the office of the Committee on Human Research, Box 0962, UCSF, San Francisco, CA 94143.

D. BENEFITS

There may or may not be a direct benefit to your baby from participating in this study. The information learned may also help health professionals better understand the usefulness of the nasal cannula for treating apneic spells in premature babies.

E. ALTERNATIVES

If you choose not to have your baby participate in this study, your baby may receive alternative treatment for his/her apneic spells. The possible alternative treatment may be either stimulation with touch, medicine, nasal continuous positive airway pressure (CPAP) or nasal cannula. Stimulation with touch is when your baby's nurse gently strokes his/her body. The medicine may be either caffeine or theophylline. The medicine stimulates your baby to breathe. Nasal CPAP is a two-prong plastic device that fits tightly inside the nostrils and sends pressure into your baby lungs. The nasal cannula is a soft two-prong plastic device fits loosely inside the nostrils and sends oxygen into your baby lungs.

F. COSTS

There will be no costs to you as a result of your baby's participation in this study.

G. PAYMENT

You will not be paid for your baby's participation in this study.

H. QUESTIONS

Dolores Quinn or the person who signed below explained the study, answered questions, and showed you a nasal cannula and the DuoDERM. If you have any other questions, you may call Dolores Quinn 415-353-1565.

I. CONSENT

You have been given copies of this consent form and the Experimental Subjects Bill of Rights to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to have your baby participate or to withdraw your baby at any point in this study without jeopardy to your baby's medical care.

If you wish to have your baby participate, you should sign below.

Date

Parent's signature/Legal guardian
Relationship:_____

Date

Interpreter's signature

Date

Person obtaining consent

Date

Witness

**UNIVERSIDAD DE CALIFORNIA, SAN FRANCISCO
CONSENTIMIENTO PARA PARTICIPAR EN UN ESTUDIO DE
INVESTIGACION**

TRATAMIENTO DE CÁNULA NASAL PARA APNEA DE PREMATURIDAD

A. PROPÓSITO Y ANTECEDENTES

Los doctores especialistas Abbey Alkon, RN, Ph.D., Profesor Agregado, Facultad de Enfermería de la UCSF, Dolores Quinn, RN, NNP, Ph.D.(c), Doctorando, Facultad de Enfermería de la UCSF, y Robert Piecuch, MD, Neonatólogo Adscrito, Centro Médico UCSF, se encuentran llevando a cabo un estudio de investigación para comprender si la cánula nasal disminuirá el número de episodios de apnea.

Los episodios de apnea son momentos cuando el bebé prematuro deja de respirar. En el mismo momento, el ritmo cardíaco y la cantidad de oxígeno en la sangre pueden bajar. Es importante tratar los episodios de apnea para prevenir cualquier daño al cuerpo creciente del bebé, sobre todo al cerebro.

Actualmente, las terapias que se usan para tratar los episodios de apnea son estímulo por tacto, medicinas, cafeína y teofilina, presión positiva nasal continua de las vías respiratorias y cánula nasal. La mayoría de estas terapias conlleva problemas, por ejemplo 1) el estímulo por tacto puede ser insuficiente para parar estos episodios, 2) la medicina (cafeína y teofilina) pueden ponerlo intranquilo al bebé e incapaz de dormir 3) la presión positiva nasal continua de las vías respiratorias, un aparato plástico, blando, de dos dientes, que cabe de manera ceñida dentro de las fosas nasales, puede lesionar la nariz, y 4) la cánula nasal es un aparato plástico, blando, de dos dientes, que cabe de manera ceñida dentro de las fosas nasales. La cánula nasal se usa actualmente para llevar oxígeno pero no se sabe si es útil para tratar los episodios de apnea. Le hemos pedido a Ud. que permita que su bebé participe en este estudio ya que su bebé nació prematuramente y necesita tratamiento para sus episodios de apnea.

B. PROCEDIMIENTOS

Si Ud. acepta que su hijo participe en este estudio sucederá lo siguiente:

1) Su bebé recibirá la intervención para los episodios de apnea utilizando un aparato respiratorio, plástico, blando, de dos dientes (cánula nasal) que proporciona un flujo de aire de 1 litro por minuto con 21 % de oxígeno que estará en las fosas nasales por una hora y se quitará otra hora. Cuando se apague por una hora, se le quitará a su bebé la cánula nasal de las fosas nasales.

2) Su bebé tendrá un chance del 50 % de que lo asignen a un grupo que reciba la intervención de cánula nasal primero o bien a un grupo que reciba la intervención de cánula nasal después.

3) Si se asigna a su bebé al grupo que recibe la cánula nasal primero, estará:
con la cánula nasal por 1 hora,
sin la cánula nasal por 1 hora, luego,
con la cánula nasal por 1 hora,
sin la cánula nasal por 1 hora luego,
con la cánula nasal por 1 hora,
sin la cánula nasal por 1 hora.

4) Si se asigna a su bebé al grupo que recibe la cánula nasal después, estará:
sin la cánula nasal por 1 hora,
con la cánula nasal por 1 hora, luego,
sin la cánula nasal por 1 hora,
con la cánula nasal por 1 hora, luego,
sin la cánula nasal por 1 hora,
con la cánula nasal por 1 hora,

5) Se registrarán el número de episodios de apnea por medio del monitor cardiorespiratorio. Este tipo de monitor registra y muestra el ritmo cardíaco tanto como el respiratorio de su bebé. Se colocan pequeños parches adhesivos con alambres en el pecho y en el abdomen de su bebé. Si el ritmo cardíaco o el respiratorio salen de la gama de los límites establecidos en el monitor, una alarma alertará al investigador y al personal de enfermería para que revisen el ritmo cardíaco y el respiratorio de su bebé. El nivel de oxígeno en la sangre (saturación de oxígeno) se medirá usando el oxímetro de pulso. El oxímetro de pulso es una pequeña luz roja que detecta la cantidad de oxígeno en la sangre. El oxímetro de pulso se sujetará con cinta adhesiva a la mano o el pie de su bebé. Si la cantidad de oxígeno es demasiado alta o baja, el monitor sonará, alertando al investigador y al personal de enfermería para que atiendan a su bebé.

6) El grafíco de su bebé sera repasado para obtener información acerca de su diagnosis al ser admitido, etnicidad, peso de nacimiento, edad gestacional, edad al tiempo de participación, y un valor de severidad de enfermedad. El valor de severidad de enfermedad es un estimado de cuan enfermo/a estaba su bebé durante los primeros dias despues de nacido/a. Este valor incluye el ritmo cardiáco, pression de las sangre, ritmo respiratorio, y temperatura, un recuento de sangre completo, electrólitos, glucosa, gases en la sangre, hematócrito, bilirubina indirecta, y bilirubina directa, apnea, y ataques repentinos.
Cada dia por dos semanas el peso de su bebé, edad, número de episodios de apnea, alimentación y rendimiento de orina seran registrados, y cada semana la hematócrita de su bebé sera registada.

C. RIESGOS/MOLESTIAS

Se asignará al azar a su bebé a un orden de intervención. La intervención de cánula nasal que recibe su bebé podría resultar menos efectivo o tener más efectos secundarios que el tratamiento estándar. No lo sabremos hasta que se complete el estudio y se analicen los datos.

Es posible que la intervención de cánula nasal podría aumentar el número de episodios de apnea. Si ocurre un episodio de apnea mientras está con o sin la cánula nasal, recibirá el tratamiento indicado su bebé. Se registrará el número de episodios de apnea para controlar el riesgo.

Por otra parte, la intervención de cánula nasal podría ser efectiva en disminuir el número de episodios de apnea y en aumentar el nivel de oxígeno.

También es posible haya irritación de la piel como resultado de la aplicación de la cánula nasal. Para reducir el riesgo de irritación de la piel, DuoDERM, un apósito suave y fino se pondrá en la piel recién lavada de las mejillas y se colocará cinta adhesiva sobre el DuoDERM.

La participación en la investigación incluirá una pérdida de privacidad, sin embargo los informes de investigación de su bebé se manejarán lo más confidencialmente posible. Se codificarán todos los informes y permanecerán bajo llave para que sólo los investigadores del estudio tengan acceso a ellos. No se utilizará ninguna identificación individual en ninguno de los reportes o publicaciones que resulten de este estudio.

Si su bebé se lesiona como resultado de estar en este estudio, tendrá tratamiento disponible. Los costos de tales tratamientos se podrían cubrir por la Universidad de California, dependiendo de una variedad de factores. La Universidad normalmente no provee ninguna otra forma de compensación por lesiones. Para mayor información sobre este tema, comuníquese a la oficina Committee on Human Research [Comité de Investigación Humana], Box 0962, UCSF, San Francisco, CA 94143.

D. BENEFICIOS

Puede ser que haya o no haya beneficios directos para su bebé por participar en este estudio. La información que se obtenga podría ayudar también a los profesionales de la salud a comprender mejor la utilidad de la cánula nasal para el tratamiento de episodios de apnea en bebés prematuros.

E. ALTERNATIVAS

Si elige usted que su bebé no participe en este estudio, su bebé puede recibir tratamientos alternativos para sus episodios de apnea. Los tratamientos alternativos posibles pueden ser estímulo por tacto, medicina, presión positiva nasal continua de las vías respiratorias o

cánula nasal. El estímulo por tacto es cuando la enfermera de su bebé le toco suavemente el cuerpo. La medicina puede ser cafeína o teofilina. La medicina le estimula a su bebé a que respire. La presión positiva nasal continua de las vías respiratorias es un aparato plástico, de dos dientes, que cabe de manera ceñida dentro de las fosas nasales y manda oxígeno a los pulmones de su bebé.

F. COSTOS

No habrá costos para Ud. como resultado de la participación de su bebé en este estudio.

G. PAGO

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

H. PREGUNTAS

Dolores Quinn o la persona que firma debajo le explicó este estudio, le respondió a sus preguntas y le mostró una cánula nasal y el DuoDERM. Si tiene cualquier otra pregunta puede llamar a Dolores Quinn al 415-353-1565.

I. CONSENTIMIENTO

Se le ha dado a usted copias de este formulario de consentimiento y de la Carta de Derechos de los Sujetos Experimentales, las cuales puede conservar.

LA PARTICIPACIÓN EN LAS INVESTIGACIONES ES VOLUNTARIA. Tiene usted el derecho de negarse a hacer participar a su bebé, o bien, de retirarlo en cualquier momento de este estudio sin perjudicar el cuidado médico de su bebé.

Si desea que su bebé participe, debe firmar a continuación.

_____   _____
Fecha   Firma del Padre/Madre/Tutor Legal
                       Relación:_____

_____   _____
Fecha   Firma del Intérprete

_____   _____
Fecha   Persona que obtiene el consentimiento

_____   _____
Fecha   Testigo

Appendix D. Data Collection Sheet

id#	mr#	dob	ga	bw	race	dx	prdx	snap	order	doe	doe	dae	cga

id#	wtae	wtd	hr	hr1	hr2	rr	rr1	rr2	sat	sat1	sat2	apnea

id#	apnea1	apnea2	feeding	urine	urine1	hct	hct1

Appendix E: Application of Nasal Cannula Procedure

Equipment:

Nasal Cannula – Salter Labs Infant Nasal Cannula #1601
Flow Meter
Oxygen blender
Skin Prep – Hollister Skin gel protective dressing swipe
2 pieces of 2cm x 5cm DuoDERM – Convatec Extra Thin DuoDERM
2 pieces of 2cm x 5cm Tegaderm – 3M Tegaderm

Procedure:

Wash cheeks with warm water
Suction nares
Apply skin prep
Place 1 piece of DuoDERM strip on each cheek in space between outer nare to ear lobe
Insert Nasal Cannula into nares
Apply 1 piece of Tegaderm over DuoDERM and Nasal Cannula tubing
Connect end of Nasal Cannula to flow meter
Start flow at 1-liter (FiO$_2$ 21%)
Every 10 – 15 minutes check of nasal cannula position, liter flow, room air (FiO$_2$ 21%), and nasal patency.

Appendix F: Placement of Monitor Electrodes

Equipment:

1 package of 3 leads

Procedure:

Place leads 2 on chest and 1 on abdomen
White Chest lead – mid-clavicular 1 cm below nipple on right chest
Black Chest lead – mid-clavicular 1 cm below nipple on left chest
Red lead – mid-clavicular 1 cm below umbilicus on right abdomen

Demographic Characteristics	
	N(%)
Gender	
Male	8 (80%)
Female	2 (20%)
Ethnicity	
Black	1 (10%)
Hispanic	2 (20%)
White	3 (30%)
Asian or Pacific Islander	4 (40%)
NICU Admission Diagnosis	
Prematurity	10 (100%)
*RDS	2 (30%)
Other (Cleft Lip, **PDA)	2 (20%)
Diagnosis at entry into study	
Apnea of Prematurity	10 (100%)

Table 1. Demographic characteristics of all infants in the study (N = 10). (*RDS = Respiratory Distress Syndrome; **PDA = Patent Ductus Arteriosus.)

Descriptive Data	Mean (SD)
Gestational Age (weeks)	30.4 (1.35)
Birthweight (gms)	1504 (178.54)
Age at entry (days)	9.4 (3.921)
Corrected Gestational Age (weeks)	31.9 (1.37)
SNAP score (range 8 – 20)	12.4 (3.438)
Weight at entry into study	1481.5 (252.268)
Weight 24 hours after study complete	1508.8 (252.29)

Table 2. Descriptive Data for all infants in the study (N = 10).

Mean Heart Rate per minute			
Subject	24 hours Before study	During study	24 hours After study
1	150	140	144
2	146	155	149
3	156	154	165
4	162	166	159
5	156	157	155
6	142	141	145
7	136	139	121
8	156	155	152
9	135	147	145
10	147	153	158

Mean Respiratory Rate per minute			
Subject	24 hours Before study	During study	24 hours After study
1	62	48	48
2	36	41	46
3	47	41	58
4	54	69	54
5	51	53	50
6	53	43	44
7	52	52	70
8	41	36	30
9	44	39	43
10	51	46	44

Mean O_2 Saturation (%)			
Subject	24 hours Before study	During study	24 hours After study
1	94	97	96
2	94	95	96
3	96	92	95
4	96	96	95
5	92	92	93
6	96	95	97
7	93	95	97
8	97	98	98
9	97	100	98
10	99	98	98

Table 3. Physiologic Measures (Heart Rate, Respiratory Rate and O_2 Saturation) for each subject 24 hours before, 6 hours during and 24 hours after study treatment.

	Frequency (#)		
	24 hours Before study*	6 hours During study	24 Hours after study*
Subject			
1	12	6	11
2	8	1	12
3	9	2	4
4	8	4	1
5	15	5	10
6	8	2	2
7	5	1	4
8	14	4	5
9	18	4	10
10	9	1	2
Total	**106**	**30**	**61**
Mean (SD)	**10.6 (4)**	**3 (1.82)**	**6.1 (4.2)**

Table 4. Frequency (#) of apneic episodes before, during study treatment, and after study. (* paired t-test before and after study, $t_{(9)}$ = 3.551, p = 0.006)

	Longest Duration (seconds) of Apnea		
	24 hours Before study*	6 hours During study	24 hours After study*
Subject			
1	50	35	45
2	35	30	35
3	40	30	40
4	50	40	40
5	30	30	30
6	30	30	30
7	50	25	45
8	50	40	32
9	40	25	40
10	30	25	45
	Mean (SD)	Mean (SD)	Mean (SD)
Total	39.5 (8.317)	31 (5.676)	36.75 (6.056)

Table 5. Longest duration (seconds) of apneic episodes before, during study treatment and after study. (* paired t-test before and after study, $t_{(9)}$ = 1.007, p = 0.34)

	Lowest SaO$_2$ (%)		
	24 hours Before study*	**6 hours During study**	**24 hours After study***
Subject			
1	68	79	70
2	60	86	65
3	63	77	68
4	60	64	62
5	73	82	74
6	82	74	79
7	81	80	80
8	40	63	48
9	52	70	55
10	70	76	69
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Total	**64.9 (12.87)**	**75.1 (7.5)**	**67 (10.055)**

Table 6. Lowest Oxygen Saturation (SaO$_2$ %) with apneic episodes before, during study treatment, and after study. (* paired t-test before and after study, $t_{(9)}$ = -2.003, p = 0.076)
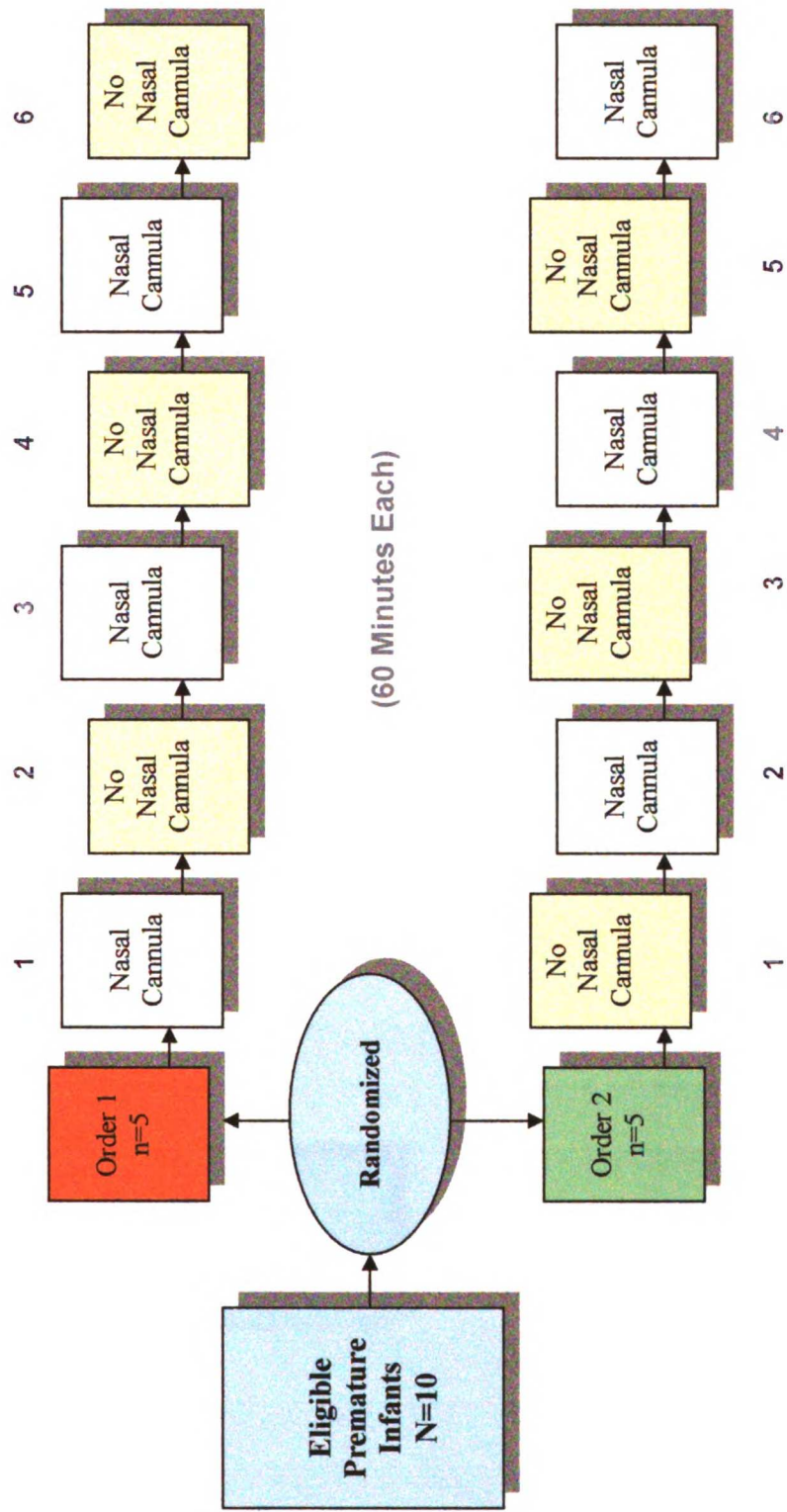
Figure 1. Study Design
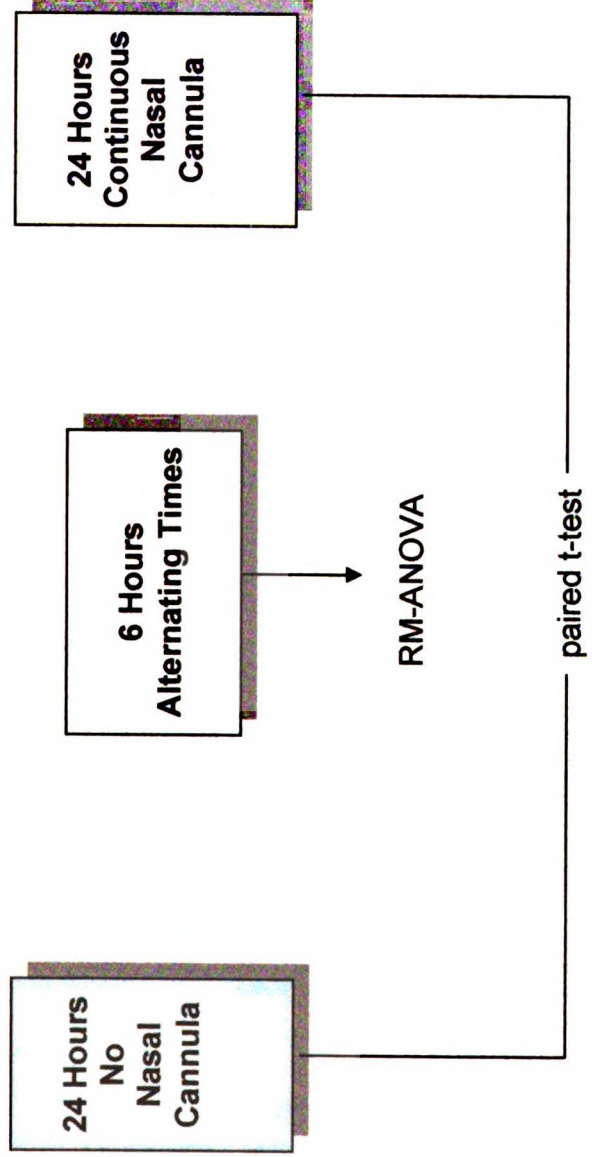
Figure 2. Data Analysis

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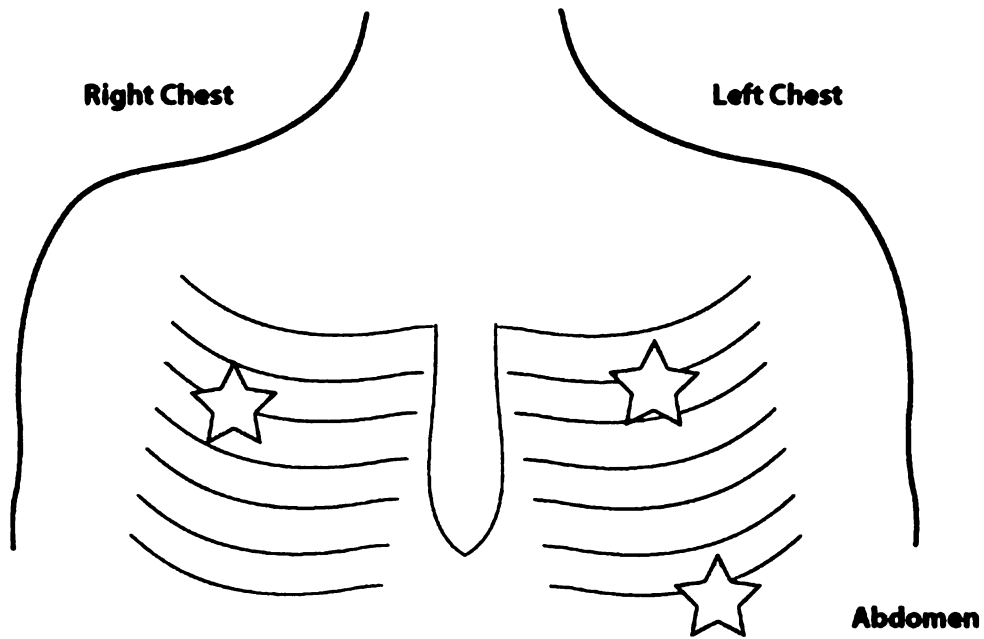
Figure 3. Electrode Placement for monitoring the heart rate. Berne, R. M. &
Levy, M. N. (2001). <u>Cardiovascular Physiology</u> (pp 1 – 53). St Louis: Mosby.
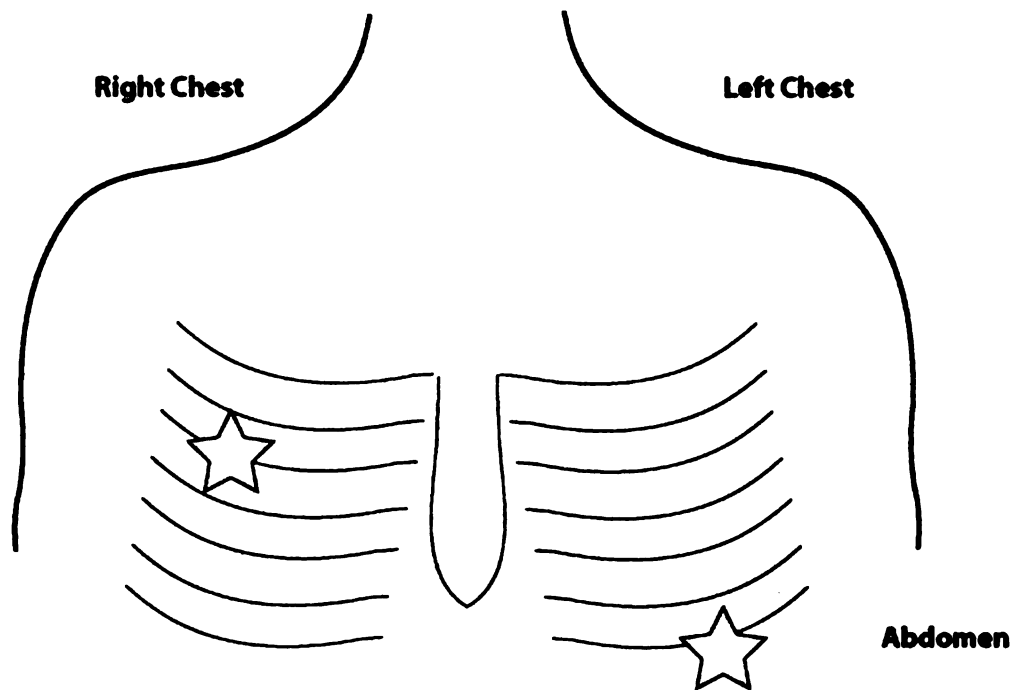
Figure 4. Electrode Placement to monitor respiration. Stein, I. M. & Shannon, D. C. (1975). The pediatric pneumogram: A new method for detecting and quantitating apnea in infants. Pediatrics 55 (5), 599 – 603.
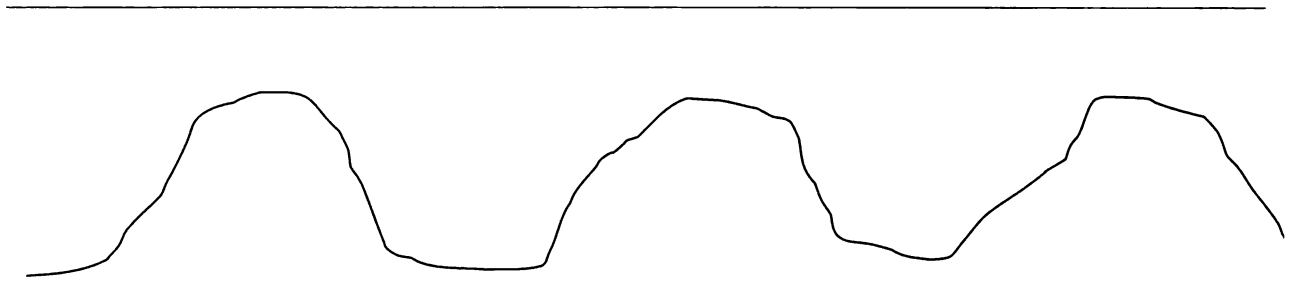
Figure 5. Respiration Waveform. Stein, I. M. & Shannon, D. C. (1975). The pediatric pneumogram: A new method for detecting and quantitating apnea in infants. Pediatrics 55 (5), 599– 603.
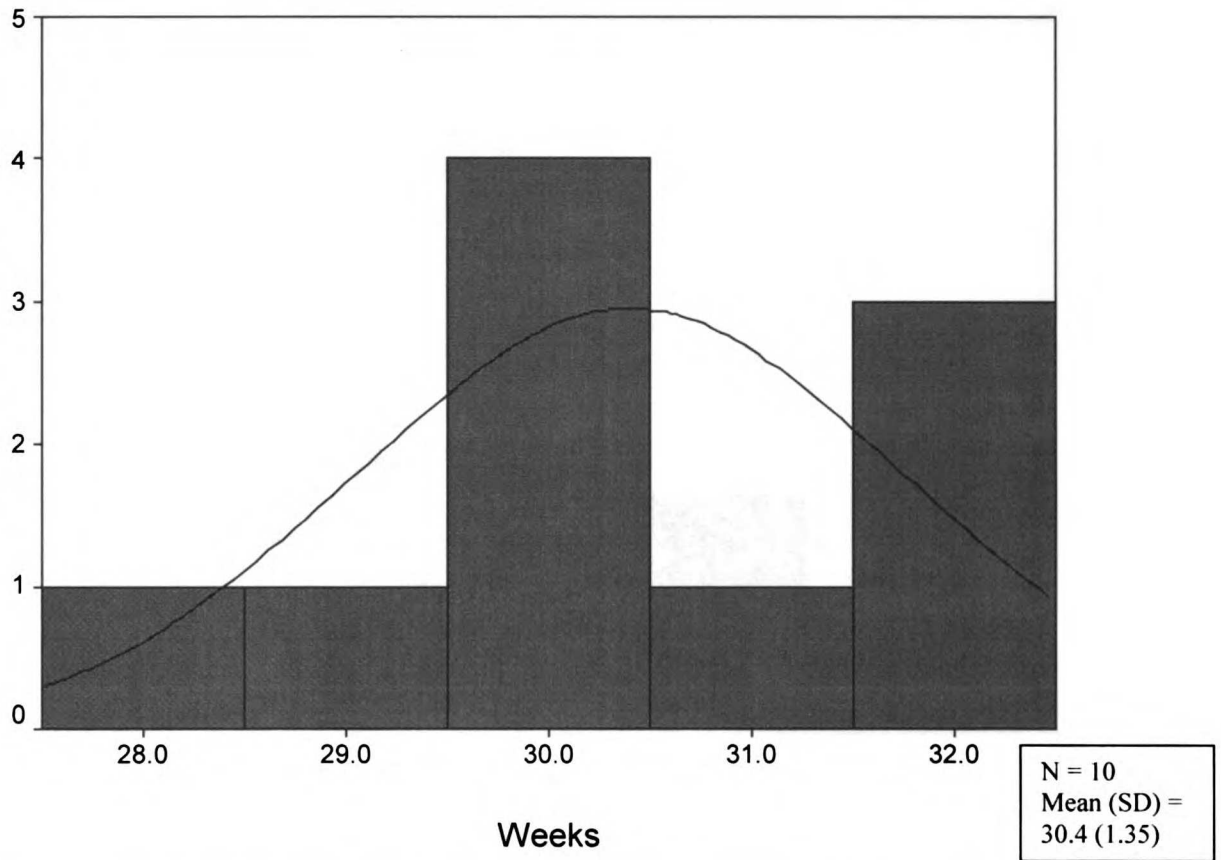
Figure 6. Gestational age (weeks) at time of delivery for all infants in the study.
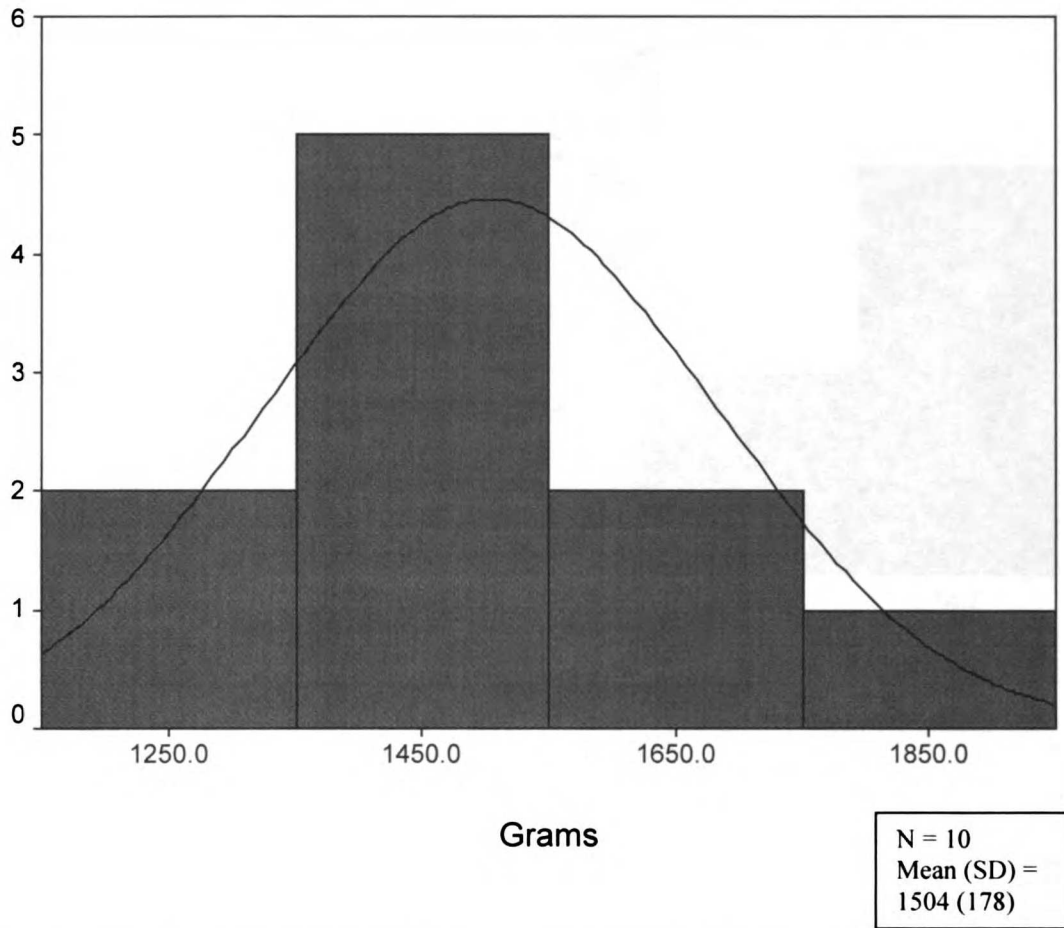
Figure 7. Birthweight (Grams) for all infants in the study.
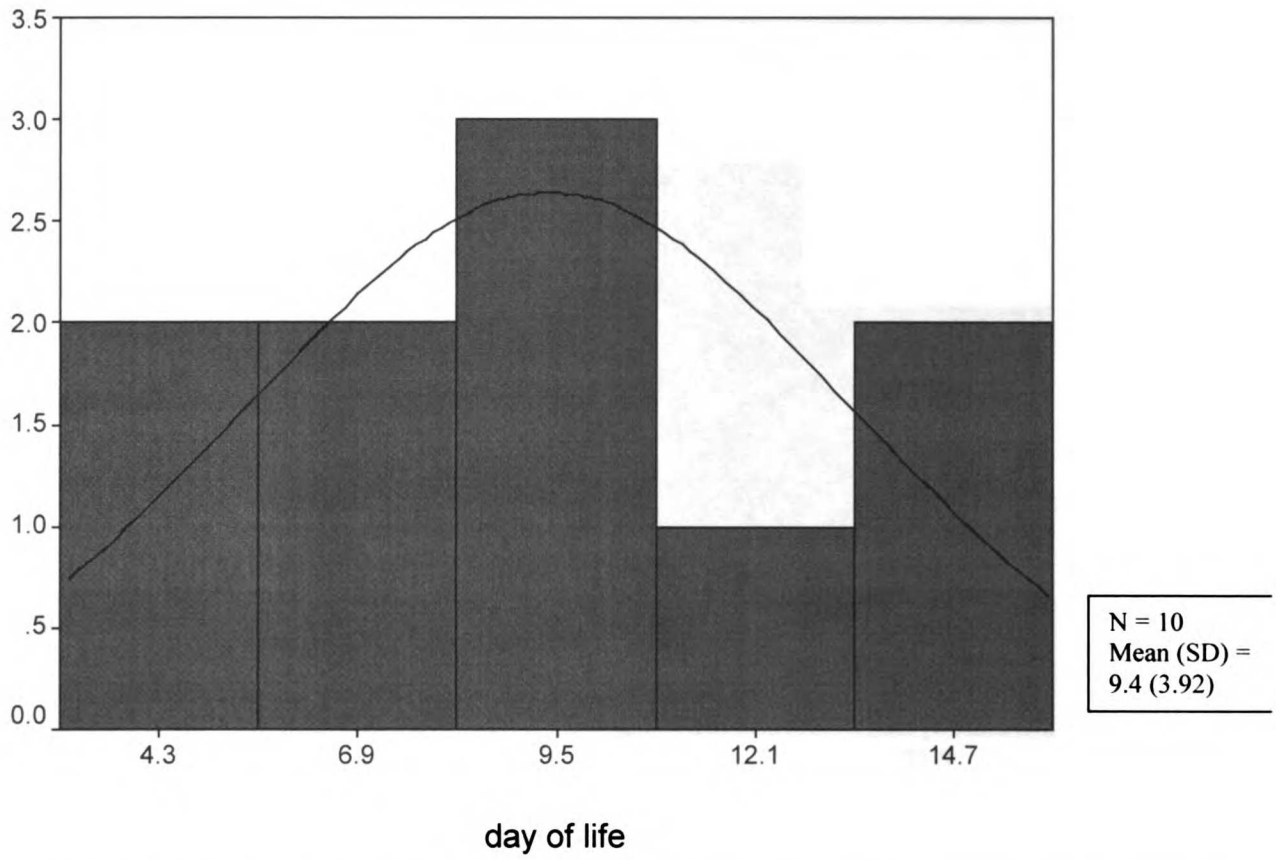
Figure 8. Age (day of life) of the infants at study entry.
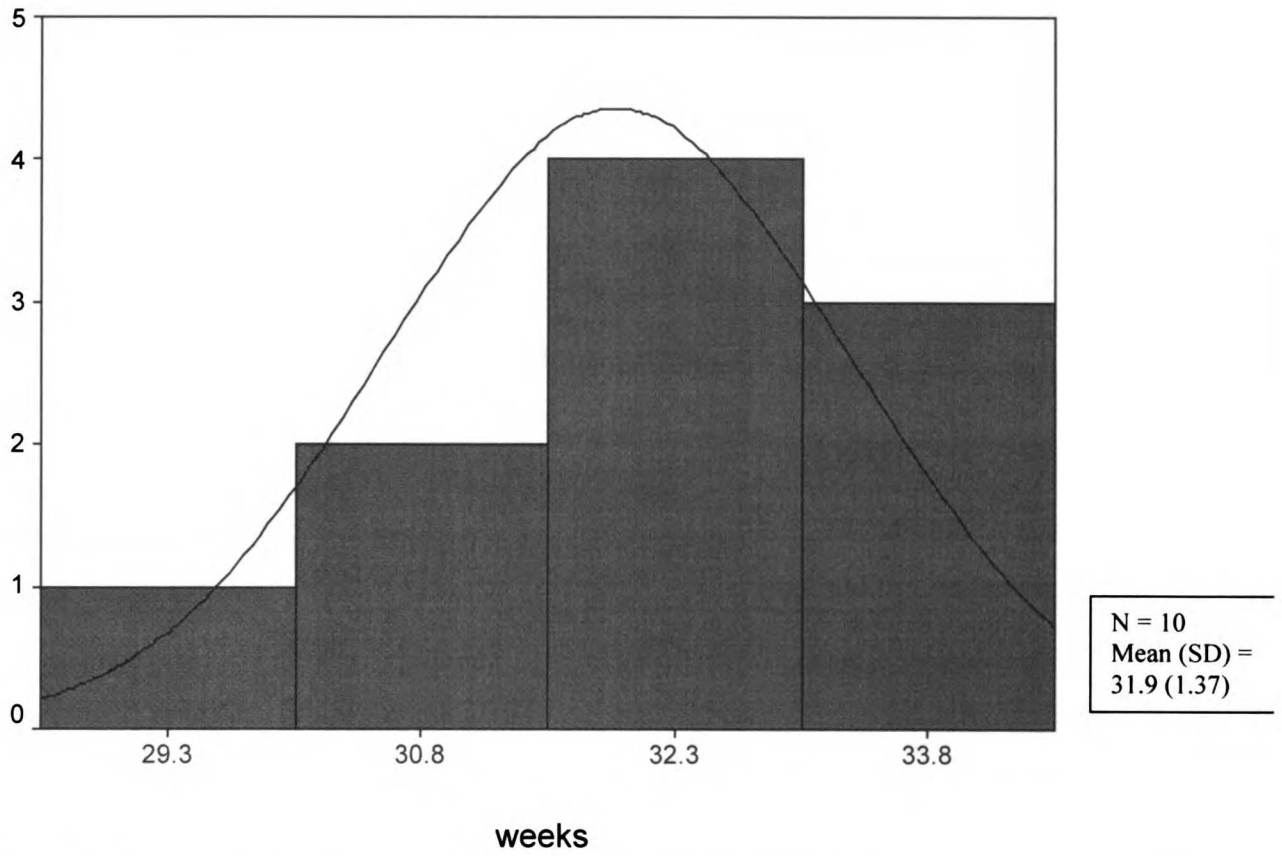
Figure 9. Corrected gestation age (weeks) of all infants in the study.

N = 10
Mean (SD) =
31.9 (1.37)
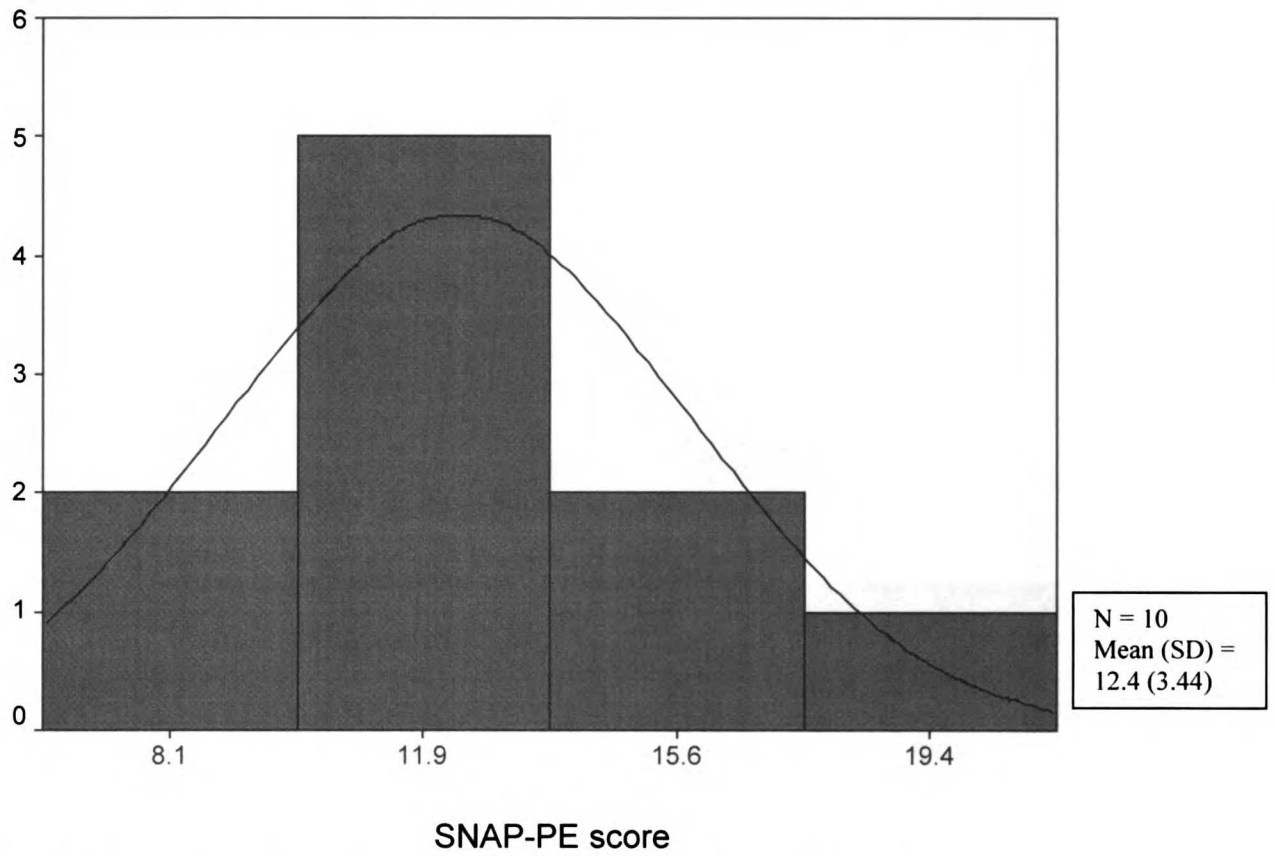
Figure 10. Severity of illness (SNAP) score for all the infants in the study.
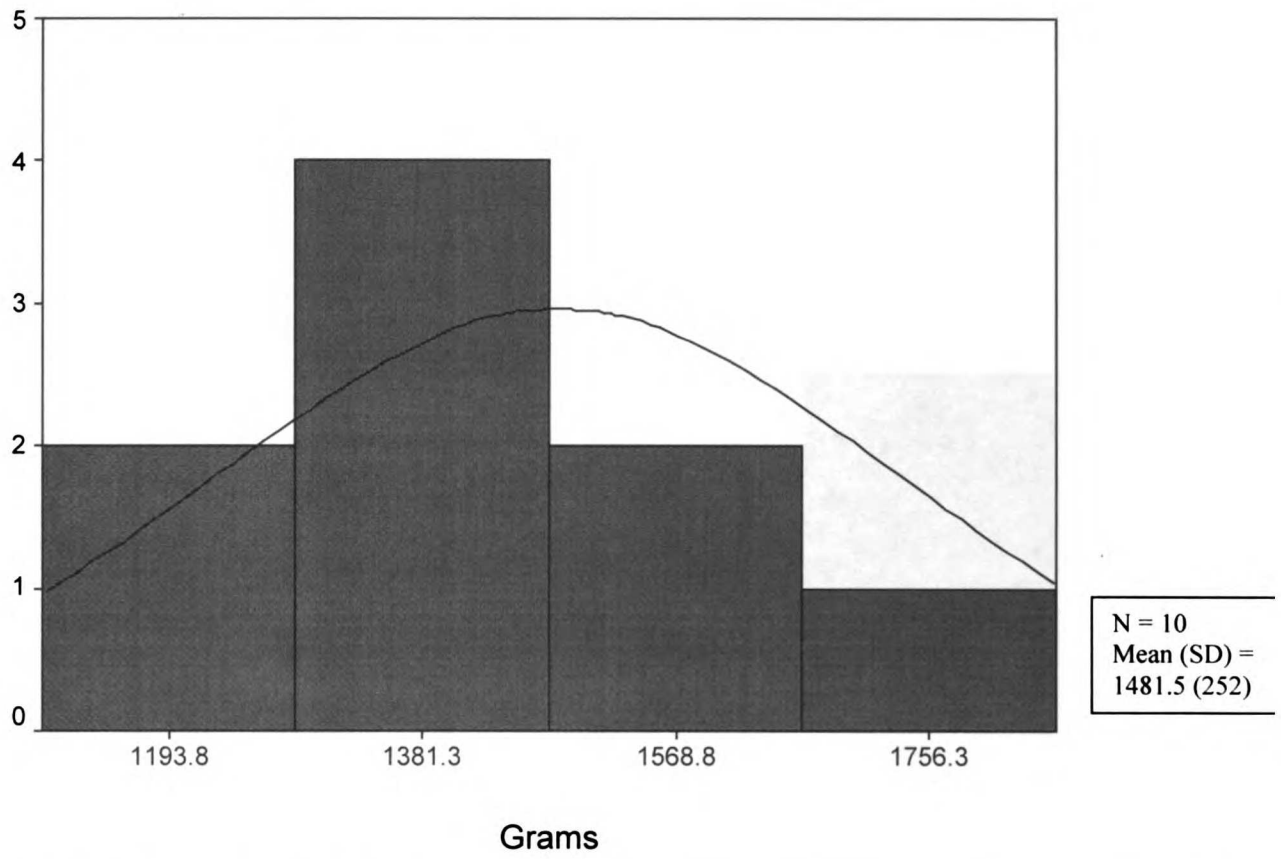
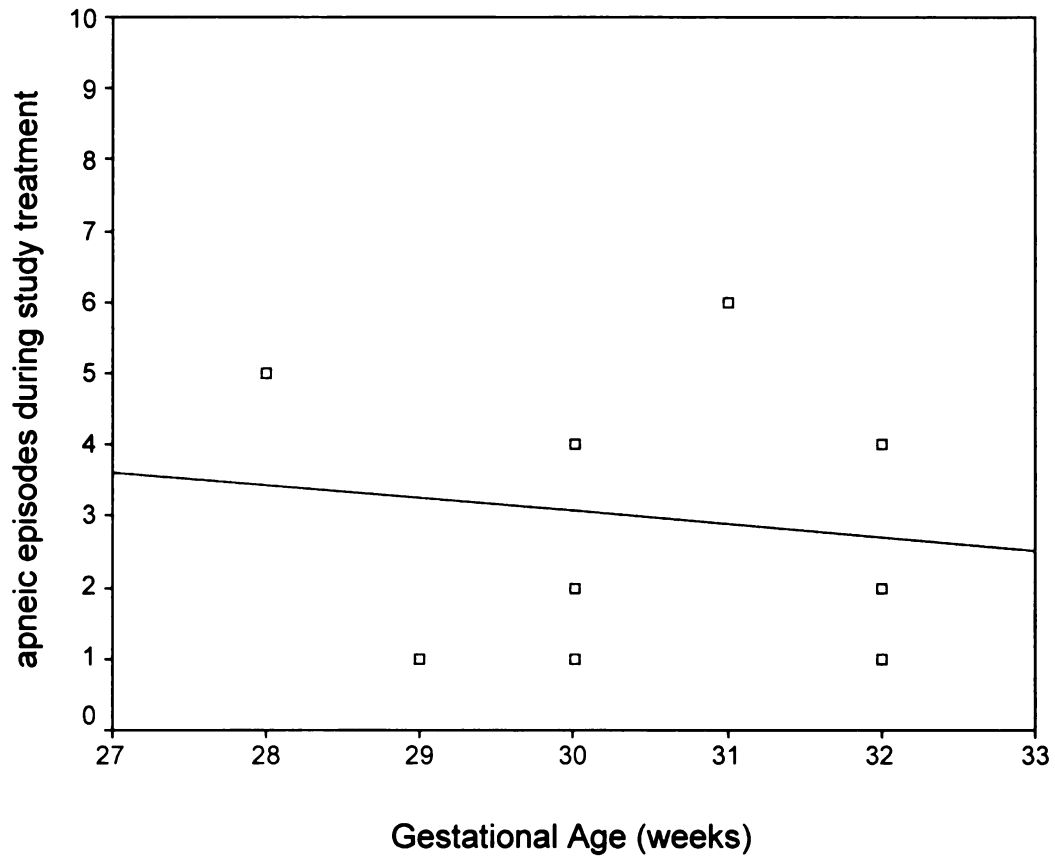**Figure 11.** Weight (Grams) of all infants at study entry.
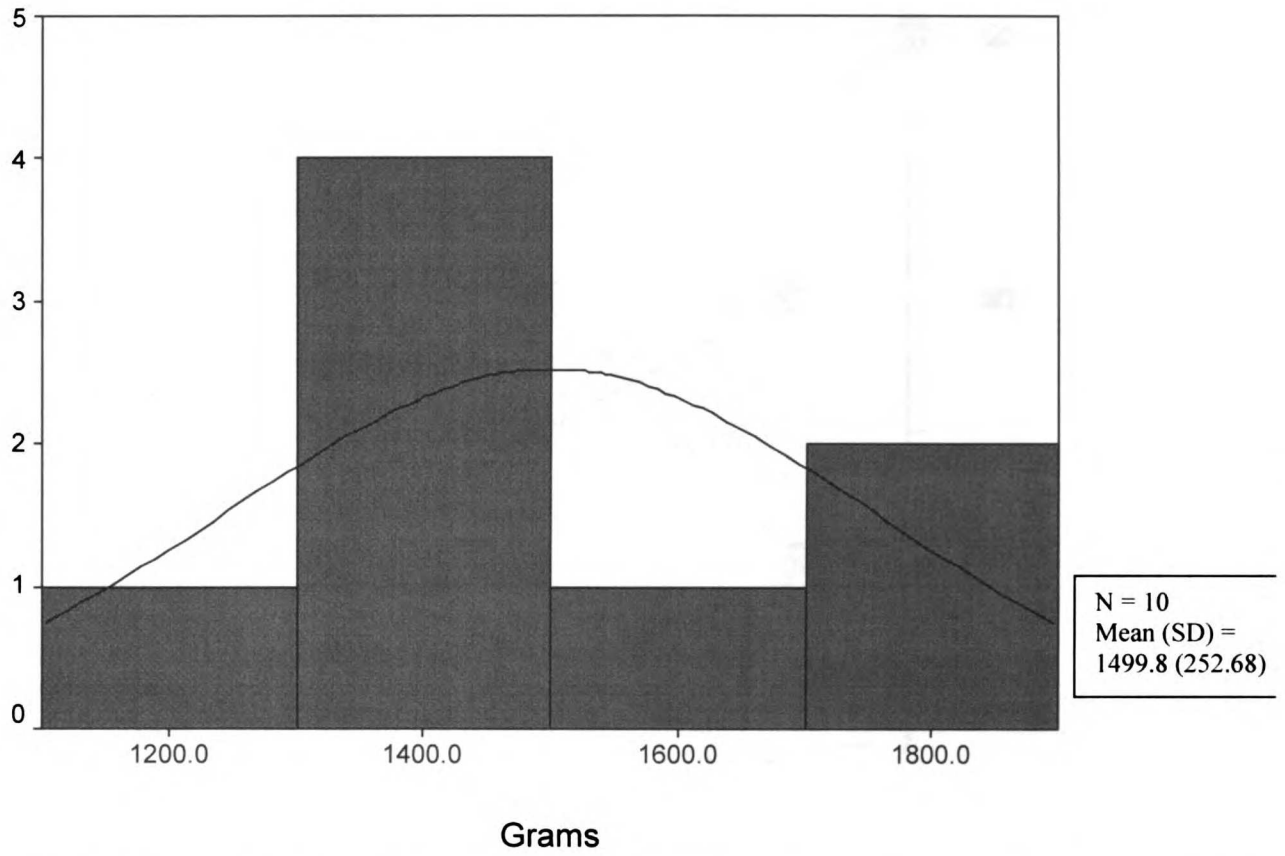
Figure 12. Weight (Grams) of all infants 24 hours after study.

N = 10
Mean (SD) =
1499.8 (252.68)
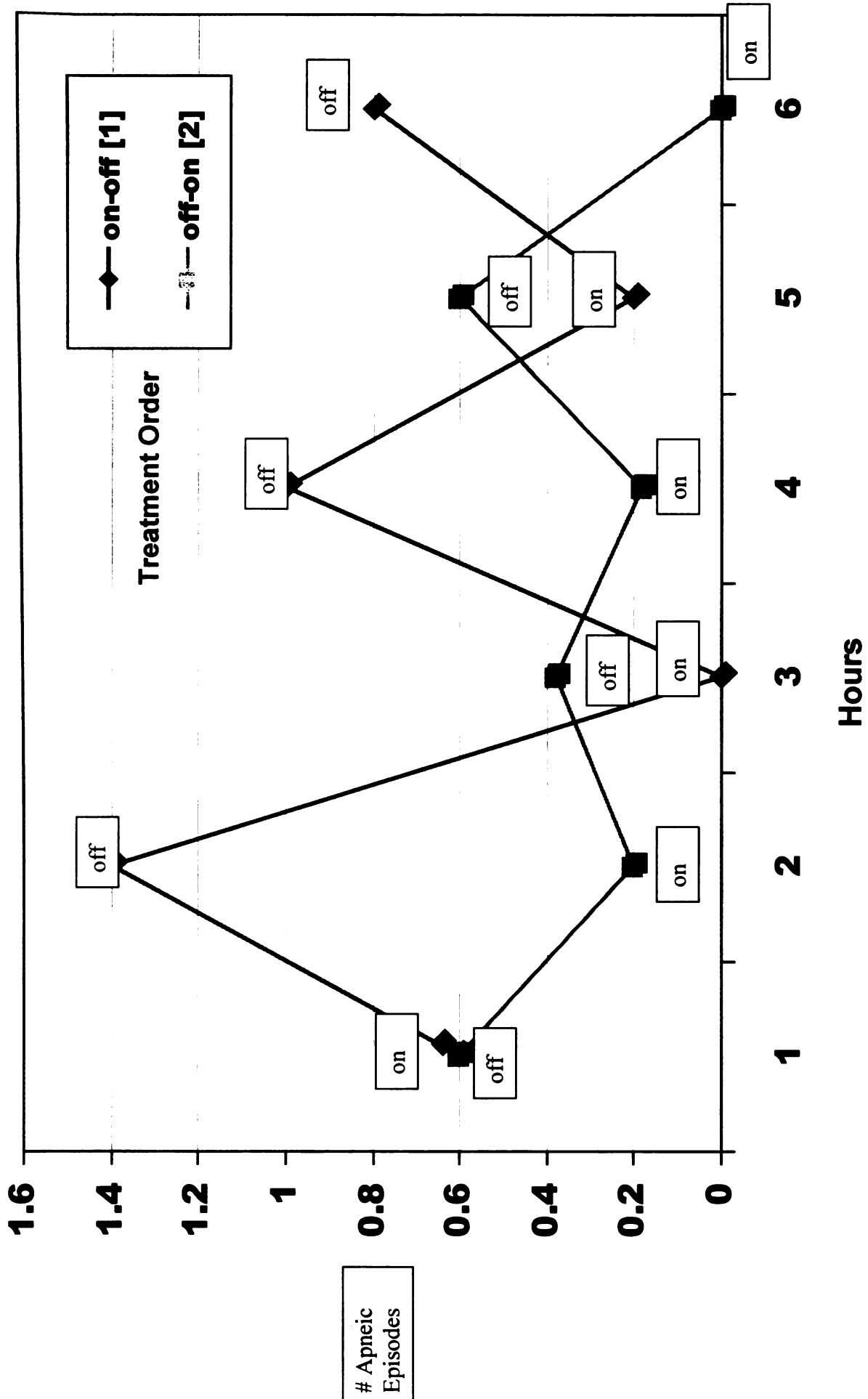
Figure 13. Apneic episodes over 6 hours of study treatment with alternating use of nasal cannula 1 Liter/min each cycle 1 hour in length (N=10, treatment Order 1 n=5, treatment Order 2 n =5.) (*RM-ANOVA: $F_{(5,45)} = 3.423$, p = 0.011)

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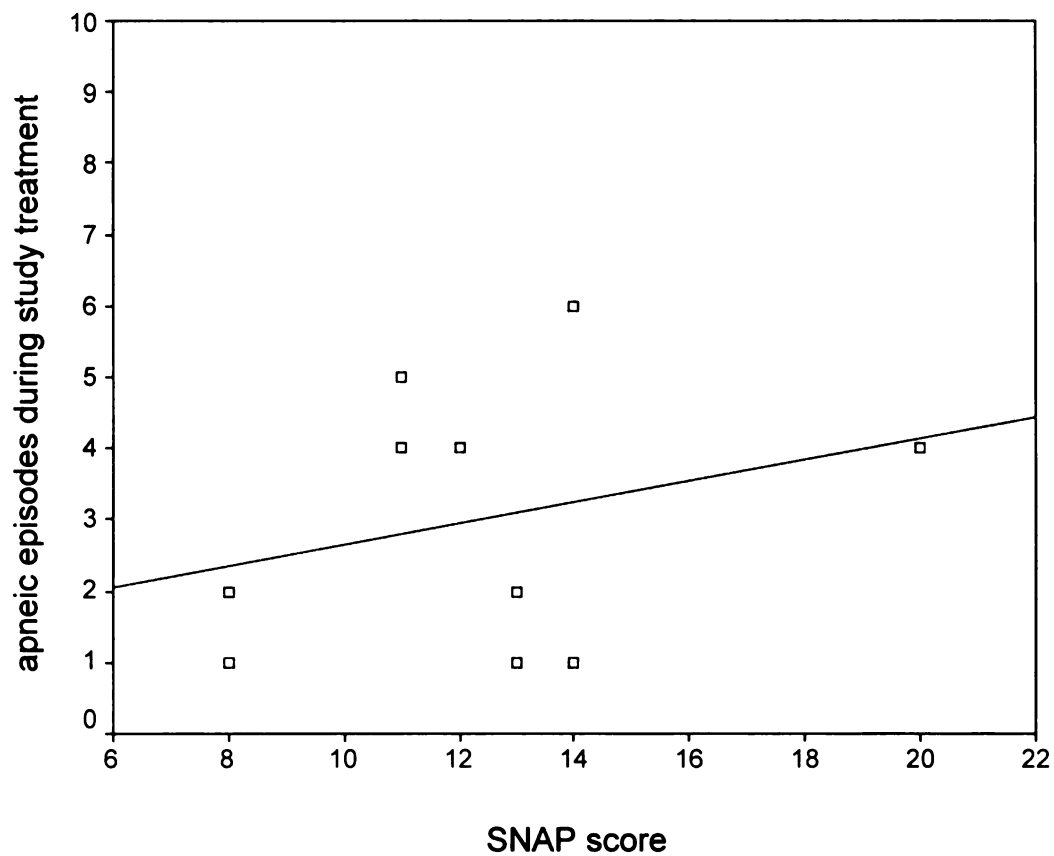**Figure 14.** Relationship between gestational age and frequency of apneic episodes during 6 hours of study treatment (N=10, r = -0.135, p = 0.709).
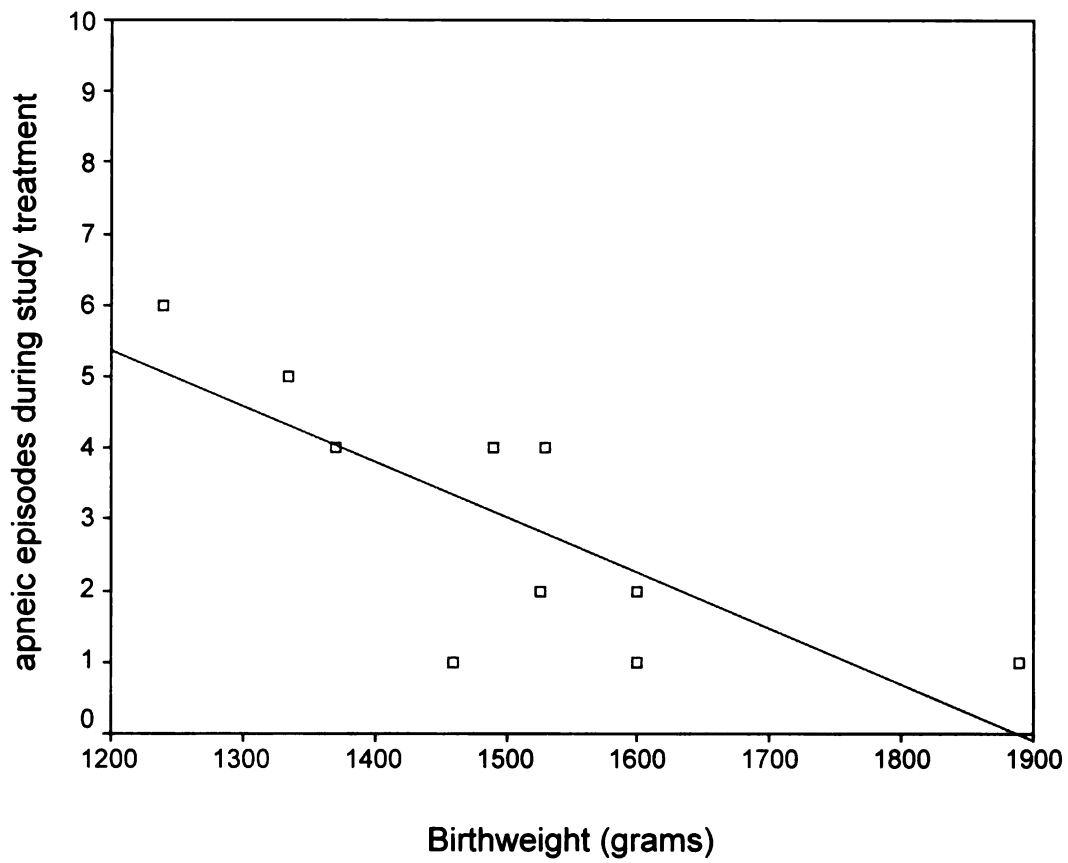
Figure 15. Relationship between birthweight and frequency of apneic episodes during 6 hours of study treatment (N=10, r = -0.765, p = 0.01).

Figure 16. Relationship between SNAP score and frequency of apneic episodes during 6 hours of study treatment (N=10, r = 0.283, p = 0.428).