OUTCOMES OF NEONATES TREATED WITH CONTINOUS POSITIVE AIRWAY PRESSURE AT THE UNIVERSITY TEACHING HOSPITAL NEONATAL INTENSIVE CARE UNIT, LUSAKA, ZAMBIA FROM 1st OCTOBER 2015 TO 31st OCTOBER 2016

BY
DR. CHAILUNGA MABO FUNDANGA

A Dissertation submitted to the University of Zambia in partial fulfilment of the requirements for the degree of Master of Medicine in Paediatrics and Child Health

THE UNIVERSITY OF ZAMBIA

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DECLARATION

I, Chailunga Mabo Fundanga hereby declare that this dissertation represents my own work and has not been presented either wholly or in part for a degree at the University of Zambia or any other University.

Date…………………………………………Candidate…………………………………

APPROVAL

This dissertation by Chailunga Mabo Fundanga is approved as a partial fulfilment of the requirements for the award of Master of Medicine in Paediatrics and Child Health by the University of Zambia.

Examiner:

1. Name……………………………………………………………………………………..
   Signature:…………………………………Date:……………………………………………..

2. Name…………………………………………………………………………………….
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Chairperson Board of Examiners……………………………………………………………….
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Supervisor………………………………………………………………………………………
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ABSTRACT

Severe respiratory distress is a common and serious complication in the newborn which may be due to premature birth, neonatal pneumonia and neonatal sepsis, accounting for over one-half of all neonatal deaths globally. Nasal continuous positive airway pressure (CPAP) is a noninvasive form of respiratory assistance that has been used to support spontaneously breathing infants with lung disease. The use of CPAP decreases the need for invasive mechanical ventilation and the combined outcome of death or bronchopulmonary dysplasia (BPD). This was a non-randomized convenience sample study to determine the efficacy of a low-cost bCPAP system in treating newborns with severe respiratory distress in the NICU at the UTH in Lusaka, Zambia. 206 files of Neonates weighing >1,000 g and presenting with severe respiratory distress who fulfilled the inclusion criteria were analyzed using IBM SPSS version 21.0. A greater proportion of the neonates, 145/206 (70.4%) were female compared to 46/206 (22.3%) male. The mean birth weight was 2.1 kg (SD = 1.01). There were 72/206 (35%) neonates with LBW, 69/206 (33.5%) with VLBW, and 65/206 (31.6%) were Term. The mean Apgar at 5 minutes 7.0 (SD = 1.60).There were 47/206 (22.8%) neonates with positive culture results. The mean RR at initial assessment was 71.3 (SD = 8.11).The mean SpO2 at initial assessment was 90.1 (SD = 2.79) and mean SpO2 follow-up was 96.6 (SD = 1.67.The most common sign of respiratory distress was grunting with 174/206 (84.5%) of the neonates, followed by nasal flaring with 149/206 (72.3%) and recessions 140/206 (68%). BCPAP can be safely and successfully administered in Zambian neonates presenting with signs of severe respiratory distress. Since most health care facilities do not have the capabilities to ventilate, this is an optimal alternative.

Key words: bubble continuous positive airway pressure, neonate, respiratory distress syndrome, Premature.

DEDICATION

- To the Neonatal Intensive Care Unit team for teaching me that small lives matter

- My mentors, for their guidance and insight.

- My family and friends; for their patience and support.

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I thank my supervisors, Dr Monica Kapasa and Dr Musaku Mwenechanya for their guidance, encouragement and support throughout this research. I would also like to sincerely appreciate the support from the management at the UNIVERSITY TEACHING HOSPITALS (UTH) for according me the permission to carry out this study.

I acknowledge the assistance of my research assistants Dr Tamikanji Simwanza and Mr Kapambwe Kabinda, as well as the clerks at the neonatal intensive care unit (NICU) for their commitment and effort.

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OPERATIONAL DEFINITIONS AND ACRONYMS

Neonate: New born in the first 28 days of life.

Low Birth Weight Neonates: Babies born with birth weight between 1,500-2,499 grams.

Very Low Birth Weight: Babies born with birth weight between 1000 to 1,500 grams

Extremely Low Birth Weight Neonates (ELBW): babies born with birth weight less than 1000grams.

Small for Gestational Age: neonates with weight below the 10th percentile than for their gestational age.

Preterm Infants: Babies born at less than 37 completed weeks of gestation.

Respiratory Distress: Outwardly evident, physically labored ventilation or respiratory efforts; clinically evident inability to adequately ventilate and/or oxygenate.

Respiratory Distress syndrome (RDS): also known as Hyaline membrane diseaseis a breathing disorder of premature newborns in which the air sacs (alveoli) in a newborn's lungs do not remain open because the production of a substance that coats the alveoli (surfactant) is absent or insufficient.

CPAP: Continuous positive airway pressure (CPAP)

BCPAP: Bubble continuous positive airway pressure (bCPAP) is a low cost nasal CPAP delivery system

VCPAP: Ventilator derived CPAP

Pumani:A low-cost respiratory device for newborns and children used to provide CPAP.

Postmenstrual Age (PMA): Postmenstrual age is the time elapsed between the first day of the last menstrual period and birth (gestational age) plus the time elapsed after birth (chronological age)

Bronchopulmonary dysplasia- as defined according to the physiological definition:

- Receipt of > 30% supplemental oxygen at 36 weeks or
- The need for positive-pressure support or,
- In the case of infants requiring <30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen.

OUTCOMES OF NEONATES TREATED WITH CPAP AT THE NICU AT UTH, LUSAKA ZAMBIA FROM 1ST OCTOBER 2015 TO 31 OCTOBER 2016

CHAPTER ONE

1.1 BACKGROUND

Severe respiratory distress is a common and serious complication in the new born which may be due to premature birth, neonatal pneumonia, and neonatal sepsis, accounting for over one-half of all neonatal deaths globally .The WHO factsheet of 2016, shows that forty per cent of global child deaths occur in the neonatal period.[(1)] Of these, ninety eight percent of neonatal deaths arise in less developed countries[(2).] Two-thirds of these neonatal deaths arise in Africa and South-east Asia. The main direct causes of neonatal death are estimated to be preterm birth (28%), severe infections (26%), and asphyxia (23%)[(1).] Nasal continuous positive airway pressure (CPAP) is a noninvasive form of respiratory assistance that has been used to support spontaneously breathing infants with lung disease for nearly forty years. Following reports that mechanical ventilation contributes to pulmonary growth arrest and the development of chronic lung disease, there is a renewed interest in using CPAP as the prevailing method for supporting newborn infants[5]. The most frequent cause of admission for special care in both term and preterm infants are respiratory disorders[21]. A wide variety of pathologic lesions may be responsible for respiratory disturbances including hyaline membrane disease (HMD; respiratory distress syndrome [RDS]), aspiration syndrome, pneumonia, sepsis, and metabolic disturbances[21].

It is sometimes difficult to distinguish cardiovascular from respiratory causes or sepsis on the basis of clinical signs alone. Any sign of postnatal respiratory distress warrants an immediate examination and diagnostic evaluation. Tests involved such as a blood gas determination, are not readily available at the UTH. Timely and appropriate therapy is essential to prevent ongoing injury and improve outcome. Successful establishment of adequate lung function at birth is dependent on unobstructed anatomy and maturity of respiratory control. Fluid filling the fetal lungs must be removed, gas containing functional residual capacity (FRC) established and maintained, and a ventilation-perfusion relationship developed that will provide optimal exchange of oxygen and carbon dioxide between alveoli and blood.

At the NICU-UTH, a neonate that is in respiratory discomfort will initially be placed on nasal oxygen therapy. When further ventilation assistance is required, that neonate will be put on BCPAP, failure to which the neonate will be intubated and mechanically ventilated. Though we no longer use the head box for oxygen at the NICU-UTH, Buckmaster and colleagues conducted an RCT comparing CPAP with head box oxygen for neonates > 31 weeks born in non-tertiary hospitals and found CPAP reduced the need for transfer to a neonatal intensive care unit (NICU) [25].

A delicate balance of chest compressions, lung fluid resorption occurs before and during birth. When delivered vaginally, intermittent compression of the thorax facilitates removal of lung fluid. The surfactant lining the alveoli enhances the aeration of gas-free lungs by reducing surface tension, thereby lowering the pressure required to open alveoli.

When compared with term neonates, low birth weight (LBW) neonates who have a compliant chest may be at a disadvantage at drawing the first breath [23]. This is because the FRC is least in the immature neonates because of the presence of atelectasis and the presence of a ventilation-perfusion mismatch. As a result LBW infants may have a low $PaO_2$and an elevated $PaCO_2$ as a result of atelectasis, intrapulmonary shunting, and hypoventilation.

More than 50% of babies born at ≤31 weeks of gestation will develop respiratory distress syndrome (RDS) [3].Respiratory distress is associated with over 80% of cases of neonatal pneumonia [4] and most cases of neonatal sepsis [5].

An Australian Professor Colin Sullivan and his team invented the first CPAP machine in 1981. The invention was inspired by the idea of reversing how a vacuum works, blowing out air instead of sucking it in. The team then applied this idea to a ventilation mask that a sleep apnea patient can wear as they sleep.

CPAP, or continuous positive airway pressure, is a treatment that uses mild air pressure to keep the airways open. Due to the harmful effects of mechanical ventilation, continuous positive airway pressure (CPAP), a non-invasive mode of respiratory support delivered through a nasal mask or prongs, has been used to treat RDS.[9] This form of respiratory support helps to prevent lung collapse by enabling neonates to breathe spontaneously while receiving a baseline level of continuous pressure. Its use in preterm neonates with RDS has been found to help prevent respiratory failure and reduce the need for mechanical ventilation[32]

General Outlook

In bubble CPAP (bCPAP), pressure is safely regulated by submerging the end of the tubing in a bottle of water. The depth of water determines the pressure in the system. This pressure helps recruit alveoli and increase functional residual lung capacity [12], thus lowering the baby's work of breathing. The result is better compliance, reduced airway resistance, conservation of surfactant, and stabilized chest and diaphragm [13]. Bubble CPAP has been used in developed countries for decades [8]. It reduces morbidity [6] and mortality [5], [8], as well as the need for mechanical ventilation [6], [7], [9]–[11], [14], [15]. It can be administered by trained nurses [14], [16], and is safer than mechanical ventilation [6], [14]. A study carried out at Queen Elizabeth Central Hospital (QECH), in Malawi, evaluated the efficacy and safety of a novel, low-cost bCPAP device to treat neonatal respiratory illness in a low-resource setting; Pumani device. It showed that use of the Pumani to treat neonatal respiratory distress resulted in 27% absolute improvement in survival, as compared to patients treated with oxygen therapy[18]. There are a number of Pumani units also being evaluated in partnership with Rice 360 at the UTH-NICU, in Zambia.

The burden of LBW, VLBW and ELBW pre-term neonates in Zambia is unknown. Audits done at the University Teaching Hospital (UTH)-NICU of Zambia in 2015, revealed that pre-term neonates make up sixty percent of all NICU admissions and are the leading cause of death followed by asphyxia. ELBW and VLBW neonates make up for more than two thirds of these deaths with case fatality rates of eighty-eight and sixty-eight percent respectively. Quarterly reports at UTH, Department of Pediatrics have consistently shown that about 70% of neonates admitted to NICU have some form of respiratory distress that requires intervention of surfactant administration, intubation and ventilation or CPAP. Though surfactant has been available at the NICU-UTH, there is a lack of surfactant usage due to the lack of adequate sizes of endotracheal tubes and enough expertise. It is for this reason that I undertook this study with the aim of establishing the types of neonates that are most likely to have success on bubble CPAP. With the evidence gathered, I hope to further improve and guide management of neonates in need of this respiratory support.

1.2. Statement of the Problem

Quarterly reports at UTH, Department of Paediatrics show that about 70% of neonates admitted to NICU have some form of respiratory distress that requires intervention of surfactant administration, intubation and ventilation or CPAP. Though surfactant has been available at the NICU-UTH, there is a lack of surfactant usage due to the lack of adequate sizes of endotracheal tubes and enough expertise. The limited number of ventilators and monitoring capacity due to inability to do blood gases has led to the use of CPAP as the leading intervention.

The purpose of this study was to retrospectively investigate the length of stay on bubble CPAP (bCPAP) considering gestational age, birth weight, and sepsis in the neonatal population admitted at the NICU-UTH, Lusaka Zambia.

Bubble CPAP is often used, as a means to avoid mechanical ventilation, however, guidelines as to what the most optimal variables are to predict length on bCPAP have yet to be determined. The desired outcome of this study is to increase awareness of these parameters and to aid in determining the suitable candidates from the neonatal populations whom bCPAP use would be most successful.

1.3. Study Justification

This study aimed at establishing the types of neonates that are most likely to have success on bubble CPAP, and helps to propose guidelines. Data is now available to help in rolling out the usage of CPAP not just in our Department of Paediatrics but across our country. At this time, a prospective study would be costly with regards to consumables, and time required for follow up of individual patients. However, this remains a fertile avenue for further studies.

1.4. Research Question

What are the outcomes of neonates placed on bCPAP in the NICU at UTH, Lusaka Zambia?

1.5. Objectives

1.5.1 General objectives

To investigate neonatal outcomes with usage of CPAP at the NICU, UTH

1.5.2. Specific objectives

The following outcomes will be determined:

1. factors associated with neonatal outcomes with usage of CPAP
2. Determine the magnitude of mortality

CHAPTER TWO

2.1 LITERATURE REVIEW

In 1987, Avery et al[3, 15] published a small observational study suggesting that using continuous positive airway pressure (CPAP) as the primary mode of respiratory support reduced the need for supplemental oxygen at 28 days of life. More recent randomized clinical trials have demonstrated that, in comparison with prophylactic or early use of surfactant, the use of CPAP decreases the need for invasive mechanical ventilation and the combined outcome of death or BPD[4,5].

The causes of neonatal deaths are represented in a figure 1 below.

Figure 1. Causes of Neonatal Deaths

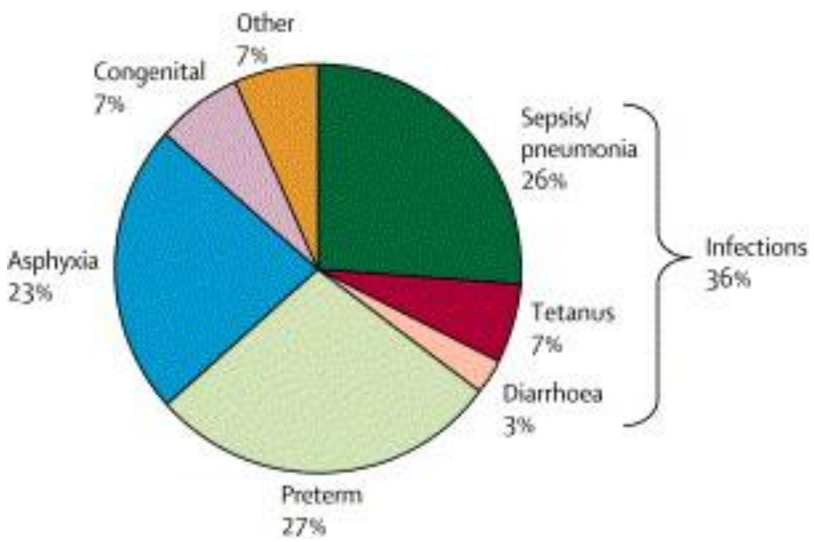

Figure 1 above is the estimated distribution of direct causes of 4 million neonatal deaths for the year 2000 based on vital registration data for 45 countries and modelled estimates for 147countries[(1)]

Table 1

Studies on feasibility and/or effectiveness of CPAP therapy in LMIC settings

Author, year	***Country***	***Setting***	***Study design***	***Study population***	***CPAP Strategy***	***Results***	***Comments***
Studies with a control group							
Koyamaibole, 2005[15]	Fiji	Referral hospital (only hospital providing NICU services in Fiji)	Comparison of two time periods—before and after introduction of bCPAP	Median weight 2765 g (1785–3300); 70 (12.6%) were 1000–1500 g	CPAP was considered for neonates with grunting, severe chest indrawing, severe respiratory distress and hemoglobin in oxygen saturation <90% despite oxygen	Among the 105 neonates who received CPAP, 24 (22.8%) failed and required mechanical ventilationTrend towards lower mortality in the period when bCPAP was used (OR 0.74; 95% CI 0.52 to1.03; *P*=0.06)	Not a randomized trial; ventilator assistance was available as backup if required so the findings may not be translated to a scenario where it is used in isolation

Respiratory distress is common immediately after birth, and is typically caused by abnormal respiratory function during the transition from fetal to neonatal life. Tachypnea, nasal flaring, intercostal or subcostal retractions, audible grunting, and cyanosis manifest it.

The burden of LBW, VLBW and ELBW pre-term neonates in Zambia is unknown. In our NICU, at UTH, we have over 4000 admissions (for the years 2014 and 2015, there were a total number of 4000, and 4200 respectively) per year.

The 2014 audit done in NICU-UTH revealed that pre-term neonates make up sixty percent of all admissions and are the second leading cause of death after asphyxia. Quarterly reports since then have consistently shown that about 70% of neonates admitted to NICU have some form of respiratory distress that requires intervention of assisted ventilation.

It is well recognized that applying continuous positive airway pressure (CPAP) in respiratory distress in neonates is a reasonable alternative to intubation and ventilation[2]. CPAP is generally well tolerated, and usually effective, in part because infants are preferential or "obligatory nasal-breathers,"[3] and pressure is maintained in the lungs due to the anatomic seal that forms between the infant's tongue and the soft palate. CPAP is most frequently applied in premature infants with respiratory distress syndrome (RDS). However, CPAP has also been used to treat infants with other respiratory disorders, including transient tachypnea of the newborn[9], meconium aspiration syndrome[10, 11], primary pulmonary hypertension[11], pulmonary hemorrhage[12], patent ducts arteriosus[13] and consequent pulmonary edema[12].

CPAP mimics the natural physiologic reflex, "grunting," that is frequently exhibited in infants with low lung compliance and low end-expiratory lung volume. Grunting is the dynamic expiratory braking phenomenon, resulting from vocal cord adduction and diaphragmatic contraction, which limits airflow during exhalation and maintains trans-pulmonary pressure and end-expiratory lung volume above the critical closing pressure of the lungs[15, 16,17]

2.2 CPAP

Nasal CPAP has been adopted by many NICUs as a way of reducing rates of broncho-pulmonary dysplasia in premature neonates, but assessment of its benefits is complicated by questions about the simultaneous effects of concomitant surfactant treatments and other NICU interventions [27]. Most research into the potential benefit of CPAP has used a study population of very preterm or extremely preterm neonates who were delivered in tertiary referral hospitals. Little is known about the benefits of CPAP use in more mature neonates in tertiary NICUs. The Buckmaster trial compared CPAP use with supplemental oxygen in neonates > 30 weeks gestation in non-tertiary centers [25] to prevent transfer of neonates for intensive care. The study showed a reduction in both treatment 'failure' and the rate of up-transfer, but did not show any statistically significant reduction in outcomes such as length of admission. The results also showed an increased risk of pneumothorax in the CPAP arm but the confidence interval is wide (RR = 2.76; 95% CI 1.02, 7.48). The possibility of increased rates of pneumothorax has been a concern with use of CPAP, and the COIN trial [11] reported a rate of pneumothorax three times higher in the CPAP group compared with the mechanical ventilation group. However, the recently published results of the SUPPORT trial found no difference in the rates of pneumothorax for extremely preterm neonates randomized to initial treatment with either CPAP or endotracheal administration of surfactant [26].

Buckmaster and colleagues conducted a Randomised controlled trial comparing CPAP with head box oxygen for neonates > 31 weeks born in non-tertiary hospitals and found CPAP reduced the need for transfer to a neonatal intensive care unit (NICU) [25]. Trials in very preterm babies published since 2008 suggest that starting CPAP at birth may have important benefits, with 50% of babies 25-28 weeks gestation never requiring intubation and ventilation, and that neonates of this gestational age who commence CPAP from birth have no increased risk of death or bronchopulmonary dysplasia, and in fact are less likely to be on oxygen at 28 days of age[26,11]. A review of RCTs up to 2010 by Christine Roberts et al in 2011, demonstrated that CPAP reduces need for intubation and ventilation for infants born at 25-28 weeks gestation, and at > 32weeks, in non-tertiary hospitals, CPAP reduces need for transfer to NICU. Other potential advantages of CPAP compared with intubation and subsequent conventional mechanical ventilation include lower costs, easier operation, potentially fewer risks, and less training [9].

Sinha, Gupta, and Donn in 2007 evaluated several different studies using CPAP, intubation and mechanical ventilation, and surfactant. The authors observed that the frequency and severity of RDS was inversely proportional to the gestational age of the neonate. A large number of neonates were put on mechanical ventilation and of those, 30-40% developed chronic lung disease (CLD). The authors deduced that neonates born after 28 weeks did well on CPAP and surfactant if needed, however those under 28 weeks required mechanical ventilation[31]. In addition, the authors felt early use of CPAP and surfactant may have a synergistic effect when used together, because CPAP seems to conserve the existing surfactant, which ultimately reduces morbidities, with the exception of BPD.

2.3. Neonate's birth weight

In a retrospective analysis carried out by Ammari et al. to determine which variables differentiate those who succeeded versus failed on CPAP, The authors found that the factors associated with early CPAP failure were those related to the small birth size (birth weight <750 g), immaturity (PMA <26 weeks), severe RDS on the initial chest x-ray and need for PPV at delivery. These factors essentially define a ‘‘small, sick baby’’ who may be somewhat depressed at birth.

It must be noted though; none had a positive predicted value above 55%, meaning they were poor predictors of CPAP failure. Overall, successful neonates on CPAP were on average 3 gestational weeks older and weighed 300 grams more. The researchers agreed that part of the difficulty in predicting failure was due to the difficulty in diagnosing severity of RDS at birth. When comparing BCPAP to VCPAP, there is limited data available. However, in a retrospective study carried out by Amit et al results indicate that BCPAP was more successful than VCPAP in managing preterm neonates with early onset moderate to severe respiratory distress in their set up. They concluded that overall, BCPAP is a safe and effective method of treating early respiratory distress in preterm neonates but a definitive large trial is needed to confirm these findings[33].

2.4. Gestational age

Morley et al. performed a randomized trial to test whether nasal CPAP was superior to intubation and ventilation directly after birth in 610 preterm neonates of 25-28 gestational weeks of age. After 28 days, the results showed there was little variation in the general mortality of the neonates. However, of the survivors, those on CPAP required less need for oxygen and had fewer days of overall ventilation. Pertaining to gestational age and weight differences, Chan and Chan[33] studied short-term outcomes of 80 premature neonates supported on CPAP with a birth weight of less than 1500g. The aim of the study was to evaluate respiratory outcomes with the hypothesis that bubble CPAP would create less apnea post extubation and improved non-respiratory outcomes. Neonates born between October 2000, and March 2002, (period 1) were compared to neonates born between October 2002, and March 2004, (period 2). The neonates in period 1 were treated with ventilator CPAP, while the neonates in period 2 were treated with bubble CPAP. The results were separated into two birth weights of <1499g VLBW and <1000g extremely low birth weight (ELBW).There was no increased incidence of intra-ventricular hemorrhage (IVH) or CLD on BCPAP with less apnea as well, although these neonates were on BCPAP longer than ventilator CPAP. There was also no increase in non-respiratory morbidities with BCPAP, and 33% of the VLBW neonates were successful with BCPAP alone. The authors noted though that most neonates were initially intubated before receiving CPAP, which could have skewed results. Therefore, the scientists agreed a study with more samples, would be needed to determine long-term effects.

CHAPTER THREE:
METHODOLOGY

3.1. Study Design

Retrospective Descriptive Cohort

3.2. Study Site

Neonatal Intensive Care Unit (NICU) at University Teaching Hospital (Situated close to the maternity block at UTH) is the main/primary referral site for all premature neonates in Lusaka, with a bed capacity of 40 to 60; Staffing on average includes 8-10 doctors and 22 nurses, nurse: patient ratio of 1:38. It is also the primary site with bCPAP.

3.3. Study Population

All neonates admitted to the NICU that meet inclusion (to the study) criteria

3.4. Sampling

A non-randomized convenience sample study to test the efficacy of a low-cost bCPAP system treating newborns with severe respiratory distress in the neonatal ward of the UNIVERSITY TEACHING HOSPITAL in Lusaka, Zambia. Neonates weighing >1,000 g and presenting with severe respiratory distress who fulfilled the inclusion criteria received nasal bCPAP.
Eligible babies whose files are complete and fit the inclusion criteria.

3.5. Sample size

The sample size was calculated using EpiInfo version 7 making the following assumptions:

- α = 95% CI
- Population of neonates admitted per annum- 4000
- Expected Mortality on bCPAP =30% based on file review of 60 patients put on CPAP in January 2016.

Sample size required: minimum required 214

3.6. Inclusion criteria

1. Files of neonates with birth weight >1000 grams admitted to NICU at UTH.
2. Neonates files that are complete and meet inclusion criteria
3. Files of neonates placed on BCPAP.

3.7. Exclusion criteria- files of:

1. Neonates with low APGAR scores (<3 at 5 minutes).
2. Neonates with congenital defects.
3. Incomplete file (i.e. pages missing)

3.8. Procedures

1. Consent was sought from the Head of Department Paediatrics and Child Health, and Senior Medical Superintendent, UTH for the use and analysis of files from the NICU at UTH.
2. All files were screened to determine which neonates were placed on bCPAP and met the eligibility criteria.
3. Once identified, files were divided into bands based on gestational age and weight.
4. Data was then extracted from the files onto my data collection sheet.

3.8.1. Limitations

1. Not all patients had chest x-rays and other imaging modalities routinely done.
2. Retrospective study-loss of files and inability to interview primary care givers (doctors and nurses managing the patients).
3. Lack of record of adverse events (nasal/cosmetic trauma) in the files reviewed.
4. Inter use of improvised bCPAP, PUMANI machines. and other types of CPAP
5. Patient information was collected on data collection sheets.

3.8.2 Data Entry

1. Patient’s information was assigned study identification numbers and filled out on a form.
2. The forms were then checked for inconsistencies and completeness. Double entry was then used to enter the data on the Epidata software database.

3.8.3 Ethical Considerations

Permission to conduct the study at the UTH was sought from the Senior Medical Superintendent of the UTH.

Ethical approval was granted by the ERES Board.

Confidentiality was maintained at all levels of the study. Files were given an identification code rather than their name for identity purposes. Data obtained was kept under lock and key in the NICU and only accessible to the investigator, supervisor and the Ethical regulation board if need arose.

CHAPTER FOUR: RESULTS AND ANALYSIS

4.1. Statistical Analysis

IBM SPSS version 21.0 was used for statistical analysis and to produce some graphical output. All statistical tests were at 5% significance level. Independent samples T-test was used to compare mean values between groups and the Pearson's chi-squared test was used for comparison of proportions between groups. The Fisher's exact test was used when one or more of the cells had an expected frequency of five or less. Some variable categories with less frequency were collapsed together accordingly. Study variables were checked for evidence of co-linearity based on a correlation coefficient >0.8. The relationship between study variables and clinical outcome was examined using backward logistic regression. The selection for entry into the logistic regression model was considered at level $p<0.20$ or known clinical significance from literature.

4.2. Results

Data on 206 neonates treated with CPAP was analyzed for this study, 15 files rejected as incomplete. A greater proportion of the neonates, 145/206 (70.4%) were female compared to 46/206 (22.3%) male and this difference was in sex distribution proportion was significant ($P<0.001$) [Table 1]. Maternal age was about normally distributed with mean age 24.6 years (SD = 3.99). The youngest mother was aged 16 years and oldest 35 years [Figure 1.1]. The mean parity was 2 (±1). There were 147/206 (71.4%) mothers with parity = 2 or less and 59/206 (28.6%) with parity 3 or more. The mean Apgar score at 1 minute was 5.4 (SD = 2.07) and the mean Apgar at 5 minutes 7.0 (SD = 1.60). In the course of my review of literature, I did not identify any randomized trial that had compared the effect of CPAP with other methods such as oxygen by prongs or head box on neonatal mortality. However, a total of 13 observational studies had reported the effect of CPAP therapy on in-hospital or neonatal mortality in preterm neonates (Table 2).

These studies can be broadly categorized into three groups: time-series/comparison with historical controls, case-control studies ('typical' case-control or analysis of prospective data like a case-control study) and prospective observational studies of CPAP therapy. Time series/comparison with historical controls: one study from Fiji evaluated mortality data from two time periods–18 months before and 18 months after the introduction of bubble CPAP (bCPAP).[15] In the former period, there were 79/1106 deaths (7.1%) while in the latter there were 74/1382 deaths (5.4%), suggesting a trend toward lower mortality (OR 0.74, 95% CI 0.52

to 1.03; *P*=0.06).Case–control studies: a retrospective chart review from South Africa found that the use of nasal CPAP was associated with lower mortality among very low birth weight neonates (16.7 vs 32.8% OR 0.22, 0.08 to 0.63) [16] which was similar to the findings of this study (37% for VLBW vs 22% for term).The confounding effect of other variables was, however, unclear. My study findings had a significantly higher clinical success rate (57 % vs 43.%; 95% CI 0.12 to 0.83) One non-randomized study from Malawi compared the effects of nasal CPAP with oxygen therapy by nasal cannulae. The study reported a significantly lower mortality in the CPAP group as compared with the control group (29.0 vs 56.0% OR 0.32, 95% CI 0.12 to 0.83). [18] When compared to the retrospective study from South Africa, outcomes of neonates manages with CPAP as against invasive ventilation [19] reported mortality in the CPAP group (25%) was comparable to the group that received ventilation (39%). The authors remarked that mortality in neonates successfully managed with CPAP was 18% and this dropped to 9% after correcting for neonates who were not offered ventilation. This was similar to my findings that mortality 35.4%, dropped to 18% for the neonates not offered ventilation. Adjusting for confounding factors, such as culture confirmed sepsis (22.8%) reduced the mortality rate to 10%. The mean birth weight was 2.1 kg (SD = 1.01). There were 72/206 (35%) neonates with LBW, 69/206 (33.5%) with VLBW, and 65/206 (31.6%) were Term. A greater majority of the neonates were delivered through SVD, 175/206 (85%), compared to 31/206 (15%) delivered through other means including Caesarean section, and this proportional difference was statistically significant (P<0.001) [Figure 1.2]. The parity of the mother did not show any significance value to the outcome. The mode of delivery however, showed a higher likely hood of babies born via LSCS or instrument delivery to end up on CPAP (67%) and most likely culture positive (45%).

Slightly over half of the neonates, 107/206 (51.9%) were discharged home while 73/206 (35.4%) neonates died, and status for those transitioned to mechanical ventilation was 26/206 (12.6%). A greater majority of the neonates had improved respiratory distress 159/206 (77.2%) compared to 9/206 (4.4%) who did not. There were ultimately 117/206 (56.8%) neonates with clinical success outcome. There was a significant difference in proportion between clinical success and clinical failure (P = 0.001). The mean number of days on CPAP was 2.8 days (SD = 0.95). There were 85/206 (41.3%) neonates that spent 1-2 days on CPAP, 72/206 (35%) that spent 3 days, and 49/206 (23.8%) that spent 4 or more days.

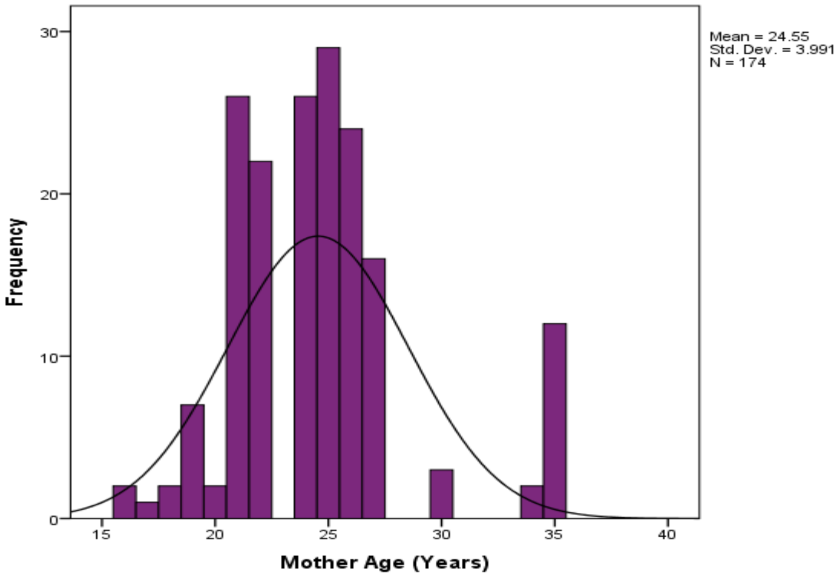

Figure 2. Mother age distribution

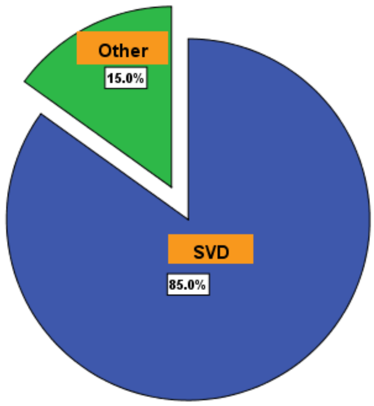

Figure 3. Mode of delivery

There were 79/206 (38.3%) neonates with 1-minute Apgar score less than 5, 63/206 (30.6%) with score from 5 to 6, and 64/206 (31.1%) with score 7 or greater. There were 23/206 (11.2%) neonates with 5-minute Apgar score less than 5, 39/206 (18.9%) with score 5 to 6, and 144/206 (69.9%) with score 7 or greater. The mean RBS was 4.5mmols (SD = 1.22) [Figure 1.3]. There were 47/206 (22.8%) neonates with positive culture results, 115/206 (55.8%) with negative results, and culture was not done for 44/206 (21.4%). About 76% of the culture organism was staphylococcus.

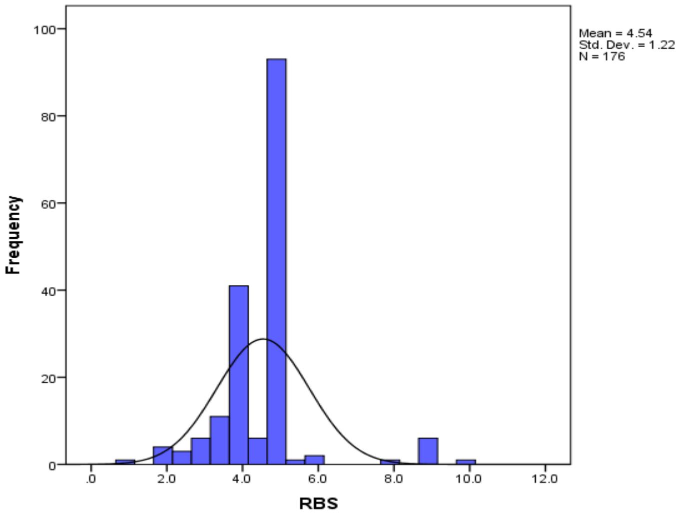

Figure 4. RBS distribution

The mean gestation age of the neonates was 31.6 weeks (SD = 3.60). The mean RR at initial assessment was 71.3 (SD = 8.11) and mean RR at follow-up assessment 48.9 (SD = 12.44), and this drop in mean RR between the assessment points was statistically significant (P<0.001) [Figure 1.4]. The mean HR at initial assessment was 156.0 (SD = 9.93) and follow-up assessment 138.5 (6.89), and this drop in HR was also significant (P<0.001). The mean SpO2 at initial assessment was 90.1 (SD = 2.79) and mean SpO2 follow-up was 96.6 (SD = 1.67), and this increase in SpO2 was statistically significant (P<0.001) [Figure 1.5]. The mean body temperature at initial assessment was 35.9 Celsius (SD = 0.62) and mean follow-up assessment body temperature 36.9 Celsius (SD = 0.33), and the increase in body temperature was significant (P<0.001). The most common sign of respiratory distress was grunting with 174/206 (84.5%) of the neonates, followed by nasal flaring with 149/206 (72.3%) and recessions 140/206 (68%).

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	RR1	71.31	202	8.110	.571
	RR2	48.88	202	12.444	.876

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	RR1 & RR2	202	.139	.049

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	RR1 - RR2	22.431	13.880	.977	20.505	24.356	22.968	201	.000

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	SpO2_1	90.06	171	2.794	.214
	SPO2_2	96.55	171	1.670	.128

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	SpO2_1 & SPO2_2	171	-.038	.618

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	SpO2_1 - SPO2_2	-6.491	3.310	.253	-6.991	-5.992	-25.643	170	.000

Table 2. SpO2 Paired Samples Test Output

Slightly over half of the neonates, 107/206 (51.9%) were discharged home while 73/206 (35.4%) neonates died, and discharge status was unknown for 26/206 (12.6%). A greater majority of the neonates had improved respiratory distress 159/206 (77.2%) compared to 9/206 (4.4%) who did not and 38/206 (18.4%) who transitioned to palliative care. There were ultimately 117/206 (56.8%) neonates with clinical success outcome and 73/206 (35.4%) with clinical failure, with 16/206 (7.8%) transitioning to mechanical ventilation. [Figure 1.7]. There was a significant difference in proportion between clinical success and clinical failure (P = 0.001). The mean number of days on CPAP was 2.8 days (SD = 0.95). There were 85/206 (41.3%) neonates that spent 1-2 days on CPAP, 72/206 (35%) that spent 3 days, and 49/206 (23.8%) that spent 4 or more days [Figure 1.8]. Table 1 shows a summary of the demographic and clinical characteristics of the patients.

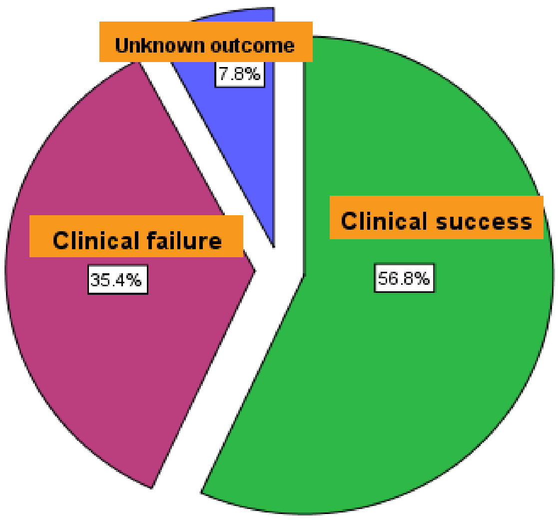

Figure 5. Neonatal clinical outcome

Table 3. Description of patient characteristics.

Variable	Frequency	Percent
Sex		
Female	145	70
	61	
Male		30
Birth weight		
LBW	72	35
VLBW	69	33.5
Term	65	31.6
Mode of delivery		
SVD	175	85
Other(instrument/LSCS)	31	15
Parity		
2 or less	147	71.4
3 or more	59	28.6
Apgar 1 min		
Apgar1min < 5	79	38.3
Apgar1min 5 -6	63	30.6
Apgar1min 7+	64	31.1
Apgar 5 min		
Apgar5min < 5	23	11.2
Apgar5min 5 -6	39	18.9
Apgar5min 7+	144	69.9
Culture		
Positive	47	22.8
Negative	115	55.8
Not done	44	21.4
Discharge status		
Died	73	35.4

Discharged Home	107	51.9
Intubated	26	12.6
Improved RD		
Yes	159	77.2
No, Died	9	4.4
No	38	18.4
Clinical Outcome		
Success	117	57
Failure	89	43

Table 3 (continued). Description of patient characteristics

Variable	Frequency	Percent
Days on CPAP		
1-2 days	85	41.3
3 days	72	35
4 or more days	49	23.8
Maternal age		
(mean, SD)	24.6, 3.99	
Birthweight		
(mean, SD)	2.1, 1.01	
Parity		
(mean, SD)	2, 1	
Apgar 1min		
(mean, SD)	5.4, 2.07	
Apgar 5min		
(mean, SD)	7.0, 1.60	
RBS		
(mean, SD)	4.5, 1.22	
GA (weeks)		
(mean, SD)	31.6, 3.60	

RR1	
(mean, SD)	71.3, 8.11
RR2	
(mean, SD)	48.9, 12.44
HR1	
(mean, SD)	156.0, 9.93
HR2	
(mean, SD)	138.5, 6.89
SpO2-1	
(mean, SD)	90.1, 2.79
SpO2-2	
(mean, SD)	96.6, 1.67
Temp-1	
(mean, SD)	35.9, 0.62
Temp-2	
(mean, SD)	36.9, 0.33
Days on CPAP	
(mean, SD)	2.8, 0.95

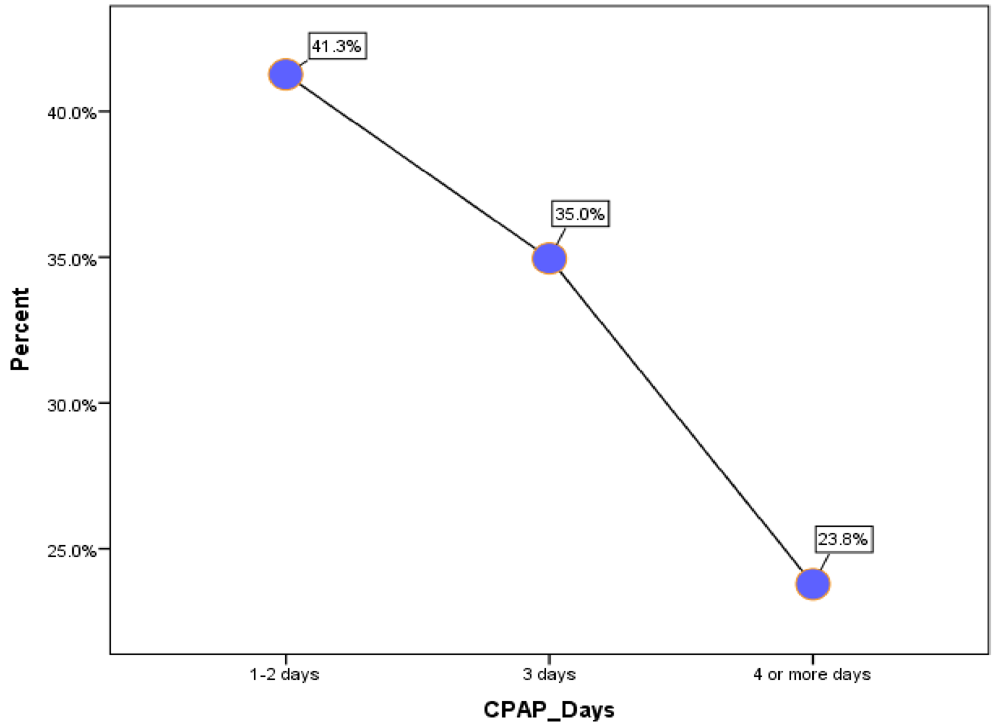

Figure 6. Duration on CPAP

4.3. Bivariate Analysis

Table 2 shows bivariate analysis results for association with clinical outcome. At 5% significance level the following variables were significantly associated with clinical outcome:

a) Sex of neonate (P=0.04)
b) Birth weight (P<0.001)
c) Apgar score at both 1 min and 5 min (P<0.001 in each case)
d) Number of days on CPAP (P<0.001)
e) RBS (P<0.001).

Table 4. Bivariate analysis for association with clinical outcome

Variable	Clinical Success		Clinical Failure		P-value
	N	%	n	%	
Sex					
Female	88	85.4%	53	72.6%	0.04
Male	15	14.6%	20	27.4%	
Birth weight					
LBW	47	40.2%	14	19.2%	<0.001
VLBW	44	37.6%	20	27.4%	
Term	26	22.2%	39	53.4%	
Mode of delivery					
SVD	95	81.2%	64	87.7%	0.24
Other	22	18.8%	9	12.3%	
Parity					
2 or less	88	75.2%	54	74.0%	0.85
3 or more	29	24.8%	19	26.0%	
Apgar 1 min					
Apgar1min < 5	7	6.0%	61	83.6%	<0.001
Apgar1min 5 -6	54	46.2%	9	12.3%	
Apgar1min 7+	56	47.9%	3	4.1%	
Apgar 5 min					
Apgar5min < 5	0	0.0%	23	31.5%	<0.001
Apgar5min 5 -6	4	3.4%	24	32.9%	

Apgar5min 7+	113	96.6%	26	35.6%	
Culture					
Positive	5	6.2%	42	63.6%	<0.001
Negative	76	93.8%	24	36.4%	
Discharge status					
Died	0	0.0%	73	100.0%	<0.001
Discharged Home	92	100.0%	0	0.0%	
Improved RD					
Yes	117	100.0%	42	82.4%	<0.001
No	0	0.0%	9	17.6%	
Days on CPAP					
1-2 days	69	59.0%	12	16.4%	<0.001
3 days	33	28.2%	39	53.4%	
4 or more days	15	12.8%	22	30.1%	
Maternal age					
(mean, SD)	24.9 (4.95)		24.1 (2.55)		0.16
Birth weight (Kg)					
(mean, SD)	2.0 (0.98)		2.6 (1.1)		<0.001
Parity					
(mean, SD)	1.9 (0.83)		2.1 (0.74)		0.08
Apgar 1min					
(mean, SD)	6.5 (1.51)		3.8 (1.55)		<0.001
Apgar 5min					
(mean, SD)	8.1 (0.83)		5.8 (1.43)		<0.001
RBS					
(mean, SD)	4.3 (0.91)		5.0 (1.42)		<0.001
GA (weeks)					
(mean, SD)	31.4 (3.69)		34.5 (2.52)		0.12
RR1					
(mean, SD)	66.5 (6.99)		77.7 (4.0)		<0.001
RR2					

(mean, SD)	47.0 (6.89)	53.6 (18.11)	0.005
HR1			
(mean, SD)	154.7 (10.07)	155.6 (6.59)	0.47
HR2			
(mean, SD)	138.4 (5.92)	139.2 (8.61)	0.47
SpO2-1			
(mean, SD)	90.0 (3.11)	90.1 (1.96)	0.91
SpO2-2			
(mean, SD)	96.7 (1.26)	96.3 (2.34)	0.24
Temp-1			
(mean, SD)	35.9 (0.80)	35.8 (0.51)	0.23
Temp-2			
(mean, SD)	36.9 (0.40)	36.9 (0.17)	0.16

4.4. Logistic Regression Analysis

Table 3 shows the backward logistic regression output predicting clinical failure. Adjusting for confounders, female neonates had average reduced odds for clinical failure of 99% (OR = 0.001, P-value = 0.011). For every increase of 1mmol in RBS above 7mmols, the odds for clinical failure increased by an average 93% (OR = 1.93, P-value = 0.048). This was also consistent in those neonates whose RBS dropped below 3mmols. For every increase by 1 in Apgar score at 5 minutes, the odds for clinical failure reduced on average by 93% (OR = 0.07, P-value = 0.005). For every increase in duration on CPAP by 1 day the odds for clinical failure reduced by 91% (OR = 0.095, P-value = 0.018).

Table 5. Logistic regression analysis predicting clinical failure

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Sex(1)	-8.558	3.975	4.635	1	.031	.000	.000	.464
	RBS	.538	.470	1.309	1	.253	1.712	.682	4.299
	BweightCat(1)	2.800	2.775	1.018	1	.313	16.443	.071	3784.649
	Apgar1min	-.853	1.702	.251	1	.616	.426	.015	11.982
	Apgar5min	-2.719	1.767	2.368	1	.124	.066	.002	2.105
	Days_CPAP	-2.866	1.509	3.608	1	.057	.057	.003	1.096
	Constant	32.788	17.414	3.545	1	.060	1.737E+14		
Step 3[a]	Sex(1)	-6.546	2.560	6.536	1	.011	.001	.000	.217
	RBS	.659	.333	3.925	1	.048	1.933	1.007	3.709
	Apgar5min	-2.720	.964	7.968	1	.005	.066	.010	.435
	Days_CPAP	-2.357	.997	5.589	1	.018	.095	.013	.668
	Constant	26.135	9.729	7.217	1	.007	2.239E+11		

a. Variable(s) entered on step 1: Sex, RBS, BweightCat, Apgar1min, Apgar5min, Days_CPAP.

CHAPTER FIVE: DISCUSSION

5.1. Discussion

The standard of care for all preterm neonates with respiratory distress is CPAP. Evidence from high-quality studies suggests significant survival advantage in preterm neonates with severe respiratory distress and managed with CPAP as compared with those managed with only oxygen.[9] This study's results suggest that implementation of CPAP therapy is feasible in level 2 to 3 NICUs of LMICs. Only 25 to 40% of preterm neonates receiving CPAP therapy required mechanical ventilation. The results are similar to a recent systematic review by A Thukral et al, which suggested a reduction in mechanical ventilation by 30 to 50% of neonates managed with only bCPAP.[19, 27] . In this study, 17.6% did not improve on bCPAP and required invasive mechanical ventilation. In the course of review of literature, no randomized trial that had compared the effect of CPAP with other methods such as oxygen by prongs or head box on neonatal mortality was identified. However, a total of 13 observational studies had reported the effect of CPAP therapy on in-hospital or neonatal mortality in preterm neonates (see results above) with the general conclusion that clinical success is more pronounced in the very low birth weight preterms with a significant lower mortality (40% vs 22% OR 0.22, 0.08 to 0.63). I also found a significant reduction in the risk of in-hospital mortality following introduction of CPAP therapy. Using respiratory rate as a proxy (neonatal distress) the mean RR at initial assessment was 71.3 (SD = 8.11) and mean RR at follow-up assessment 48.9 (SD = 12.44), and this drop in mean RR between the assessment points was statistically significant (P<0.001) [Figure 1.4].This cohort showed marked increase in oxygen saturations with a shorter stay on CPAP (mean 2.1 days). The near term (LBW) also had improvements (decreased RR from above 60 to mean 55, oxygen saturations above 94.5%) but had significantly more mortalities (37% for weight band). This could be explained by the inherent risk a near term faces with delay in recognition of danger signs and consequent delay in placement on bCPAP. The pooled effect size (OR 0.34, 95% CI 0.14 to 0.82) suggested similar, if not better, beneficial effect when compared with that reported from high-income countries (relative risk 0.52, 95% CI 0.32 to 0.87). [9]There is a need to generate more evidence on the efficacy of CPAP in preterm neonates from LMICs. It may not be ethical to do randomized studies on the effects of CPAP now but it is definitely possible to have large high-quality observational studies from these settings. A low baseline temperature would be associated with a symmetrically low RBS (positive predictive value 83.4%) and markedly raised respiratory rate. An explanation is the resultant vicious cycle that arises in this vulnerable population (hypothermia, hypoglycemia and consequent respiratory distress). A correction of ALL parameters resulted in clinical success and reduced time on CPAP (mean duration on CPAP 2.1 days), with no correction or singular correction resulting in clinical failure. Nurses can institute CPAP easily after 1 to 2 months of training and institution of CPAP has the potential to bring down the requirement and the cost of surfactant therapy.[15] Nurses are also ideally placed to recognise the aforementioned danger signs of the cycle. The reduction in cost, the reduced hospital stay has huge financial implications for LMIC.

The studies on safety of CPAP therapy suggested a very-low risk of pneumothorax (0 to 7.2%). When considering the lack of skilled manpower and the sub-optimal equipment available in most LMIC settings, the low risk is definitely reassuring. The recent systematic review on the efficacy and safety of bCPAP in LMIC settings also reported similar results.[39] I found a high risk of nasal trauma in neonates managed with CPAP in similar studies (up to 20% neonates developed nasal bleeding in one study.[34]) but no records on files reviewed of adverse events. This reinforces the need for good nursing care and monitoring.[15, 23, 25] With improving survival of very preterm neonates and need for longer duration of CPAP administration, nasal mucosal injury attains importance, given that it predisposes to immediate as well as long-term functional and cosmetic sequelae.[40]

CHAPTER SIX CONCLUSION AND RECOMMENDATIONS

6.1. Conclusion

BCPAP can be safely and successfully administered to neonates in Zambia. A greater majority of the neonates had improved respiratory distress compared to who did not and ended up on the ventilator. Since most health care facilities do not have the capabilities to ventilate, this is an optimal alternative. BCPAP can be safely and successfully administered to neonates in Zambia. BCPAP is optimal for respiratory support ESPECIALLY for VLBW and this study has shown that early initiation of bCPAP, results in quicker resolution of respiratory distress and shorter hospital stay. For our local setting with minimal mechanical ventilatory capabilities, bCPAP is better than mechanical ventilation. A significant number of babies with culture positive sepsis-pneumonia had quicker recovery time of respiratory distress compared to RDS as primary cause.

6.2. Recommendations

i. CPAP should be rolled out in Zambia for use in respiratory distress in Neonates.
ii. Early initiation of all Neonates in respiratory distress.
iii. Special care and focus of premature babies especially for the late preterm.
iv. KMC can be provided while baby receives CPAP.
v. CPAP can be applied by all health care providers so long as they are proficient at monitoring and interpreting vitals.

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7.1 APPENDICES

DATA EXTRACTION SHEET