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Jardine, Carla

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THE USE OF NASAL CPAP AT THE CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Carla Jardine

Student Number: 0201754G

This research report is submitted in partial fulfilment of the requirements for the degree of Master of Medicine in the Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Witwatersrand, Johannesburg

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Declaration:

I declare that this research report is my own original work as the primary author. This report is being submitted for the degree of Master of Medicine at the University of the Witwatersrand. It has not been previously submitted for any other degree or at any other University. This work has been accepted for publication in the South African Journal of Child Health (SAJCH) (see Appendix A).

Carla Jardine

On day of 20

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A special thanks to my family for their support during the process of writing this research report.

Abstract

Inroduction: Nasal continuous positive airway pressure (NCPAP) is well established as a treatment for hyaline membrane disease (HMD) and other respiratory diagnoses in neonates. NCPAP is an affordable intervention which results in a reduction in the number of neonatal admissions to the intensive care unit (ICU) for ventilation. At the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) we have been using NCPAP since April 2006.

Objectives: The aim of this study was to review the use of early NCPAP in our hospital setting.

Methods: This was a retrospective descriptive study of all neonates ≥ 750g admitted to CMJAH between 1st January 2013 and 31st July 2014 who received NCPAP within 72 hrs of birth. The characteristics and the survival of all infants who received NCPAP was described using univariate analysis.

Results: The NCPAP group (481) of neonates <1500g was significantly associated with surfactant use (p<0.0005), bronchopulmonary dysplasia (BPD) (p<0.0005) and late sepsis (p<0.0005). The survival to day 7 and to discharge of infants treated with NCPAP was significantly decreased (p<0.0005). NCPAP alone (without ventilation), improved the survival to discharge (p=0.001). The survival was 95.4% in the ≥1500g infants, compared to 87.6% in the very low birth weight (VLBW) infants (1000-1499g) and 55.2% in the extremely low birth weight (ELBW) infants (750-999g).

Conclusion: NCPAP is an effective intervention for HMD; it is both cost effective and easy to use in a resource limited setting and reduces the morbidity and mortality associated with ICU admission.

Abbreviations

NCPAP	Nasal Continuous Positive Airway Pressure
HMD	Hyaline Membrane Disease
GA	Gestational Age
CPAP	Continuous Positive Airway Pressure
BPD	Bronchopulmonary Dysplasia
NICU	Neonatal Intensive Care Unit
ELBW	Extremely Low Birth Weight
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CMV	Conventional Mechanical Ventilation
MOU	Midwife Obstetric Unit
BBA	Born Before Arrival
InSurE	Intubation, Surfactant, and Extubation
REDCap	Research Electronic Data Capture
NEC	Necrotising Enterocolitis
IVH	Intraventricular Haemorrhage
VLBW	Very Low Birth Weight
LBW	Low Birth Weight
TTN	Transient Tachypnoea of the newborn
MAS	Meconium Aspiration Syndrome
ICU	Intensive Care Unit
VON	Vermont Oxford Network

Chapter 1:

Introduction

Nasal continuous positive airway pressure (NCPAP) has become widely used and accepted as a treatment for hyaline membrane disease (HMD) since its first introduction in 1971[1,2]. HMD affects premature babies and causes considerable morbidity and mortality. The use of NCPAP on its own and also in combination with the use of surfactant has been shown to improve the outcomes of HMD in premature infants [3].

HMD [4] mainly occurs in neonates that are less than 34 weeks gestational age (GA). The primary cause of HMD is a surfactant deficiency. Surfactant is produced by the Type 2 pneumocytes in the epithelial lining of the lungs. Surfactant production begins at 24-28 weeks gestation but is usually only detectable in amniotic fluid from 28-32 weeks. Sufficient quantities of surfactant are usually only present from 34 weeks of gestation. It is composed mainly of phospholipids (75%) and protein (10-15%). The effect of surfactant is to reduce the surface tension of the alveoli and thus allow them to expand more easily and prevent alveolar collapse. Without surfactant, there is progressive collapse of the alveoli and the small airways resulting in lung injury and atelectasis. The cell damage causes the secretion of a proteinaceous exudate into the alveoli which characteristically stains as an eosinophilic hyaline membrane on pathology specimens [4]. In the premature neonate the respiratory distress is worsened by the presence of a compliant chest wall, as the large negative pressures needed to overcome the poor lung compliance cause chest retraction instead of lung inflation.

The incidence of HMD is related to the degree of prematurity of the lungs and therefore the incidence increases as the gestational age decreases. The use of antenatal steroids given to mothers where a premature delivery is expected has reduced the incidence and severity of

HMD [5]. The administration of surfactant for severe HMD has been shown to improve lung compliance, facilitate weaning off supplemental oxygen and results in fewer neonates needing ventilatory support. Surfactant replacement therapy also significantly reduces the mortality from HMD [6].

NCPAP is not only used in HMD but is also used to treat apnoea of prematurity, respiratory distress due to other aetiologies, some types of upper airway obstruction and can sometimes be used as an alternative to endotracheal intubation or as a weaning mode of ventilation [1]. The continuous positive pressure provided by NCPAP helps to support and distend the alveoli, preventing their collapse. There is a reduction in proximal airway resistance with a decrease in physiological dead space and NCPAP also improves the disorganized breathing pattern seen in neonates by supporting the diaphragm. All of the above result in a reduction in the work of breathing in the neonate. This results in the recruitment of alveoli which improves the ventilation perfusion mismatch of the lungs, and increases the functional residual capacity and tidal volume thereby improving oxygenation in the neonate [1]. NCPAP also exerts a distending pressure on the larger airways thus stabilizing them and preventing upper airway collapse [1]. The early use of NCPAP in premature neonates reduces the need for surfactant and results in fewer neonates needing to be intubated and ventilated [3, 7, 8]. This is both cost saving and also decreases ventilator induced lung injury and results in fewer cases of bronchopulmonary dysplasia (BPD) [3, 8]. Adverse effects of NCPAP use such as "CPAP belly syndrome" [9], nasal septal necrosis and pneumothorax may sometimes occur.

NCPAP is an affordable intervention which is easy to use in a resource poor setting. The successful use of NCPAP could result in a considerable reduction in the costs of neonatal care as there would be a reduction in ventilation and neonatal intensive care unit (NICU)

admissions as well as a decrease in poor outcomes associated with prolonged ventilation. Recently there have been a number of studies reporting on the survival of extremely low birth weight (ELBW) infants. At Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) it was found that the use of NCPAP in ELBW infants was not associated with an improvement in survival [10]. This study was done using data from neonates ≤900g admitted between January 2006 and December 2010, a period during which fewer ELBW infants were receiving NCPAP than currently. A previous study at CMJAH which assessed the determinants of survival in very low birth weight (VLBW) neonates (birth weight <1500g) found that NCPAP was associated with improved survival [11]. Kirsten et al [12] at the Tygerburg Children's Hospital in the Western Cape found that NCPAP together with InSurE (where you intubate to give surfactant and then extubate) practiced in a neonatal high care ward with limited resources improved the survival of ELBW infants.

NCPAP was introduced into the neonatal unit at the CMJAH in April 2006. It is now used as the first line of ventilatory support in neonates with HMD. We currently have 9 Bubble CPAP (Fisher and Paykel™) machines in our neonatal unit and due to such limited resources we are only offering NCPAP to neonates that weigh more than 750g. The aim of this study was to review the use of early (within 72 hrs) NCPAP in neonates at CMJAH.

Chapter 2:

Methods

This was a retrospective descriptive study of all neonates with a birth weight ≥750g admitted to the neonatal unit at CMJAH between 1 January 2013 and 31 July 2014 who received NCPAP within 72hrs of birth. Neonates were excluded if there was insufficient information, if NCPAP was used post extubation from conventional mechanical ventilation (CMV) or if they had major congenital abnormalities. All in-born babies, babies born at midwife obstetric units (MOU), or born before arrival (BBA) were initially observed in the transitional care unit for assessment before being admitted to the neonatal unit and were included in our statistics. T-piece resuscitators were not available in the labour ward nursery and bag mask valve resuscitation was used for babies who required resuscitation at birth. The babies were observed for 1-2 hours in the transitional care unit and then a decision was made by the attending doctor on whether or not they required NCPAP and surfactant. NCPAP with early rescue surfactant was offered to neonates with respiratory failure due to HMD as per the neonatal unit's protocol. Respiratory failure was defined as an oxygen saturation below 88% in 60% supplemental oxygen, respiratory acidosis on arterial blood gas or clinical signs of severe respiratory distress including indrawing of the sternum and tachypnoea. Due to insufficient NCPAP machines, not all neonates who qualified for NCPAP could receive it. Neonates who required NCPAP were admitted to the high care neonatal ward where there were 9 Bubble NCPAP (Fisher and Paykel™) machines available; NCPAP was not initiated in NICU. If NCPAP was not available, babies were given surfactant and placed on nasal prong oxygen. The neonatal unit's policy at the time of the study was that neonates' ≥900g would qualify for ventilation in NICU if required.

2.1 Database:

The neonatal records at CMJAH are kept on the REDCap (Research Electronic Data Capture) electronic neonatal database [13]. REDCap is a secure, web-based programme that has been designed to aid data capture for the purpose of clinical audit and quality improvement. The data is collected upon discharge of patients and entered into the REDCap database. The information is verified at several different stages of collection. The following data were collected from the database: maternal data – antenatal steroids, place and mode of delivery, multiple gestation; infant data – gestational age, birth weight, gender, place of birth, 5 minute Apgar score, necrotising enterocolitis (NEC), intra-ventricular haemorrhage (IVH), NCPAP with or without surfactant or conventional mechanical ventilation (CMV), respiratory diagnosis, duration of NCPAP and ventilation, late sepsis (occurring after day 3), bronchopulmonary dysplasia (BPD) (defined by oxygen requirement at 28 days of age), nasal septal necrosis, pneumothorax, outcome (death or survival) at discharge.

2.2 Statistical analysis:

The data was entered into a MS Excel spreadsheet and imported into SPSS version 19, a statistical software package (http://www.spss.com). Categorical variables were described using frequencies and percentages while continuous variables were described using mean and standard deviation. The data were also stratified into birth weight categories (ELBW including 750-999g, VLBW including 1000-1499g, low birth weight (LBW) including 1500-2499g and weights ≥2500g) and the proportion of infants in each category receiving NCPAP determined. Neonates' <1500g who had not received NCPAP were compared with those who had received NCPAP both for characteristics and survival to discharge. Intraventricular haemorrhage (IVH) was graded according to the sonographic grading system described by Papile et al [14]. Grade 1 or 2 of IVH were considered together as "mild" and grade 3 or 4 as

"severe". The NEC category included grades 2 and 3 of NEC, according to the modified Bell's staging criteria [15]. Infants were regarded as having birth asphyxia if they had Apgar scores of ≤ 5 at 5 minutes. Babies on NCPAP who developed respiratory failure and required ventilation in NICU were regarded as having failed NCPAP. The babies that were transferred out and those that were discharged home directly were grouped together as survivors for the purposes of analysis. Univariate analysis was used to compare the characteristics of the two groups and survival was described. Categorical variables were compared using Chi-squared tests and continuous variables using unpaired t-tests (as the distribution was normal). A *p*-value of ≤0.05 was considered to be significant. In neonates' ≥1500g, the characteristics, respiratory diagnosis and survival of infants who received NCPAP were described.

2.3 Ethics:

Ethics approval for the study was granted by the Committee for Research on Human Subjects at the University of the Witwatersrand, Johannesburg; clearance certificate number M140403 (see Appendix B).

Chapter 3:

Results

3.1 Infants <1500g:

There were 748 VLBW infants admitted over the 19 month period. Information was not available on 9 infants, 18 infants had major birth defects, NCPAP was used as a weaning mode of ventilation in 3 infants and NCPAP was started after >72hrs in 7 infants. All of the above were excluded leaving a total of 711 infants in the study.

The majority were females at 378 (53.2%). The mean birth weight was 1158grams (SD 220) and GA was 29.5 weeks (SD 2.6). The majority of infants (380 (53.4%)) were born by emergency caesarean section. Most of the infants (591 (83.1%)) were inborn. Antenatal steroids were given in 275 (38.7%) cases. NCPAP was provided to 481 (67.7%) of the infants in total. Most babies (397 (82.5%)) coped on NCPAP alone; in 84 (17.5%) infants NCPAP failed. Overall there were 560 (78.8%) survivors. The mean duration of NCPAP was 2.58 days (SD 3.52) with a maximum duration of 35 days. Nasal septal necrosis occurred in 27/481 (5.6%) and pneumothorax occurred in 5/481 (1%) of the infants who received NCPAP. Surfactant was given to 507 (71.3%) infants in total; 43 (8.4%) of these infants received surfactant without NCPAP. Birth asphyxia occurred in 79 (11.1%) infants.

3.1.1 VLBW 1000-1499g:

In this category there were 517 infants, of whom 453 (87.6%) survived. 308 (59.6%) infants received NCPAP and surfactant was given to 329 (63.6%) infants. There were 41 (8%) infants with birth asphyxia. The use of NCPAP was significantly associated with death (p=0.001, OR 0.41, 95% CI 0.23-0.73). 252 (81.8%) infants coped on NCPAP alone, while 56 (18.2%) infants failed NCPAP.

3.1.2 ELBW 750-999g:

In this category there were 194 infants, of whom 107 (55.2%) survived. 173 (89.2%) infants received NCPAP and surfactant was given to 178 (91.8%) infants. There were 38 (19.6%) infants with birth asphyxia. NCPAP was not significantly associated with survival (p=0.261, OR 0.72, 95% CI 0.39-1.35). 145 (83.8%) infants coped on NCPAP alone, while 28 (16.1%) infants failed NCPAP (these were all >900g and thus were offered ventilation).

3.1.3 NCPAP versus no NCPAP Group:

The entire group of neonates 750g-1499g was divided into two: those who had received NCPAP and those who had not. The characteristics of the two groups were compared and significant differences are shown in Table 1. There was no significant difference in the babies with regards to CMV, pneumothorax, antenatal steroids, IVH or NEC. Mild IVH occurred in 69 (14.4%) infants in the NCPAP group compared to 18 (7.8%) infants not receiving NCPAP and severe IVH occurred in 20 (4.2%) infants receiving NCPAP compared to 7 (3%) infants not receiving NCPAP. These differences were not significant. The survival of the infants in the two groups was compared in Table 2. The use of NCPAP was associated with an increased risk of death by day 7 and at discharge. There were 43 infants who demised between day 3 and day 7. Within this group, 26 (60%) were under 1000g, 10 (23%) failed CPAP and needed CMV, 5 (2%) had NEC, 5 (2%) had sepsis and 4 (2%) had a severe grade of IVH. When the successful use of NCPAP alone was compared to those who failed NCPAP, there was a significantly higher rate of survival to discharge. This is shown in Table 3.

Table 1: Characteristics of the NCPAP group and no NCPAP group in neonates <1500g

Variable	NCPAP (481)	No NCPAP (230)	*p*-value
Surfactant:	464 (96.4%)	43 (18.7%)	<0.0005
BPD:	108 (22.4%)	18 (7.8%)	<0.0005
Late Sepsis:	125 (25.9%)	30 (15%)	<0.0005

Table 2:

The survival of infants who were treated with NCPAP compared to those without NCPAP in neonates <1500g

	NCPAP (481)	No NCPAP (230)	*p*-value
Survival to day 3	450 (93.5%)	222 (96.5%)	0.104
Survival to day 7	407 (84.6%)	218 (94.7%)	<0.0005
Survival to discharge	351 (72.8%)	209 (90.8%)	<0.0005

Table 3: The survival of infants who were treated with NCPAP alone in neonates <1500g

	NCPAP Alone (397)	Failed NCPAP (84)	*p*-value
Survival to day 3	370 (93.2%)	80 (95.2%)	0.489
Survival to day 7	336 (84.6%)	71 (84.5%)	0.980
Survival to discharge	302 (76%)	49 (58.3%)	0.001

3.2 ≥1500g Group:

There was a total of 1997 neonates weighing ≥ 1500g; 1570 infants did not receive NCPAP, 154 had a major birth defect, 7 had insufficient information and 5 had NCPAP as a weaning mode from CMV. There were thus 261 infants in the NCPAP group.

The majority were males (164 (62.8%)). Most of the infants were inborn (217 (83.1%)). In 129 (49.4%) infants the mode of delivery was by emergency caesarean section. In the LBW (1501-2500g) category there were 220 (84.3%) infants and in the >2500g category there were 41 (15.7%) infants. The mean birth weight was 2044 grams (SD 528) with a maximum of 5250 grams and the mean GA was 33.5 weeks (SD 2.9) with a minimum of 28 weeks. 249 (95.4%) infants survived. Surfactant was given to 210 (80.5%) of infants. The mean duration of NCPAP was 1.62 days (SD 1.7) with a minimum of <1 day and a maximum of 31 days. There were 33 (12.6%) infants who failed NCPAP. This group of larger infants represented 35.1% (261/742) of all the babies that received NCPAP over the study period. The respiratory diagnosis in the majority of cases was HMD (213 infants, 81.6%) but also included transient tachypnoea of the newborn (TTN), congenital pneumonia, meconium aspiration syndrome (MAS) and apnoea as shown in Table 4.

Table 4: Respiratory Diagnosis in ≥1500g group who received NCPAP

Respiratory Diagnosis	LBW <2500g	>2500g
TTN	8 (3.6%)	5 (12.2%)
Congenital Pneumonia	9 (4.1%)	5 (12.2%)
MAS	2 (0.9%)	10 (24.4%)
HMD	200 (90.9%)	13 (31.7%)
Apnoea	8 (3.6%)	1 (2.4%)

Chapter 4:

Discussion

This was the first study from our unit to study how we are using NCPAP in all our neonates from 750g to 5250g. Previously we had investigated the use of NCPAP as it relates to the survival of both ELBW and VLBW infants in our unit but we have not determined the characteristics of the infants who are receiving NCPAP across all weight categories.

The majority of the babies in the ELBW category (750-999g) received NCPAP (89.2%). It is expected that all the babies in this weight category would have had HMD requiring NCPAP and surfactant replacement and it is encouraging that we managed to provide NCPAP to most patients. However, NCPAP was not significantly associated with an improvement in survival in this group (p=0.261). A previous study at our hospital which looked at the survival of ELBW infants also found that NCPAP was not associated with improved survival and that the most important determinants of survival were birth weight and gestational age [10]. Only 16.1% of the ELBW infants and 18.2% of the VLBW infants (1000-1499g) failed NCPAP and were given ventilation. However, in the ELBW category only infants >900g would have been offered CMV. These figures are appropriate for a limited resources setting in a high care nursery such as ours. We have only 9 Bubble NCPAP machines available but most of our babies were able to receive NCPAP. This may be attributed to the fact that babies were able to wean off of the NCPAP relatively quickly allowing a high turnover of these machines. With the successful use of NCPAP far fewer premature babies are requiring NICU admission for ventilation. This is both cost saving and prevents a large amount of morbidity and mortality that is associated with NICU. Our ICU is shared between neonates, paediatrics and paediatric surgery patients. There was a concern that lowering our ICU admission weight category to 900g would inundate the ICU with premature babies, but largely due to NCPAP

this has not been the case. However, it is important to note that although babies that require NCPAP do not need NICU admission, they do require adequate high-care facilities with well-trained nursing staff as they need close monitoring and active weaning of the NCPAP.

In the larger ≥1500g babies, only 12.6% failed NCPAP. In these babies we are using NCPAP for other indications such as TTN, congenital pneumonia, MAS and apnoea but in the majority of cases it is used for HMD in larger premature babies.

It is disappointing to note that in this study there has been no improvement in the use of antenatal steroids since the study that was done at CMJAH in 2010 [11] (38.7% in this study vs 36% in the 2010 study). This is largely due to missed opportunities and late presentation once already in preterm labour [16].

The use of NCPAP was significantly associated with a higher mortality to day 7 ($p<0.0005$) and discharge ($p<0.0005$). The increased mortality with NCPAP use may be due to other factors affecting survival such as late sepsis and NEC, which VLBW infants are prone to. There is also a selection bias as NCPAP is given to babies with more severe respiratory illness and not routinely offered to all premature babies. Within the NCPAP group, NCPAP alone (without CMV) improved survival to discharge ($p=0.001$). Prolonged ventilation is associated with increased morbidity and infants who fail NCPAP have a more severe degree of HMD with higher mortality.

Surfactant, BPD and late sepsis were shown to be significantly associated with the use of NCPAP. The overall incidence of 22.4% BPD is higher than the 8.8% reported in our hospital in 2010 [11]. More babies are now offered NCPAP and surviving long enough to develop BPD than in 2010 where over a one year period only 96/474 (20.3%) VLBW infants

received NCPAP. VLBW infants are prone to late onset sepsis [17] and the use of NCPAP has also been associated with late onset sepsis [18]. Limited nursing staff and overcrowding in the neonatal nursery further compound this problem.

There was a very low rate of complications of NCPAP in our study with only 5/481 infants developing a pneumothorax, and 27/481 infants developing nasal septal necrosis, while IVH was not found to be significantly associated with NCPAP. When compared to the Vermont Oxford Network (VON), our rate of pneumothoraces is lower (1% vs 4%) and our NCPAP use (67.7% vs 73.5%) is also lower than theirs.

Chapter 5:

Conclusion

NCPAP is cost effective and easy to use in a resource limited environment with a small number of Bubble NCPAP machines being able to treat a large number of neonates with HMD. This effectively releases ICU beds thereby increasing the number of beds that are available for ventilatory support for our neonatal and general paediatric patients. NCPAP can be administered to neonates with HMD in a high-care nursery environment with adequately trained nurses such as in a level 2 hospital. This would decrease the burden on tertiary level hospitals both for NCPAP administration and for NICU admissions for babies with HMD who have respiratory failure. More resources need to be dedicated to patient education and access to sufficient antenatal care in order to decrease the number of premature deliveries. More could be done to improve our rates of antenatal steroid administration but for this to be effective our patients need to access our healthcare facilities timeously and this depends on improved patient education and transport to our hospitals.

Chapter 6:

Limitations and Recommendations

The retrospective design of this study was a limitation as a number of the neonatal records in the database were incomplete. Due to this some of the records had to be excluded based on inadequate available information. Human error also plays a role, as on entering the records into the database certain dates were sometimes entered incorrectly. This resulted in inaccurate lengths of stay or inaccurate estimates of the amount of time that the neonates' spent on NCPAP or on ventilation. The date of starting NCPAP was very important as we only wanted to look at babies where NCPAP was started within 72 hours of birth. Some cases were difficult to identify due to a lack of information in the neonatal record as well as an inability to verify the diagnosis where information was incomplete.

A considerable number of studies have shown that NCPAP administered to premature infants with HMD results in a significant improvement in survival. It is recommended that further prospective studies be done on NCPAP outcomes in our local hospitals.

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Appendix A

ARTICLE

The use of nasal CPAP at the Charlotte Maxeke Johannesburg Academic Hospital

C Jardine, MB BCh; **D E Ballot**, MB BCh, FCPaed (SA), PhD

Department of Paediatrics and Child Health, University of the Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

Corresponding author: *C Jardine (carlsjardine@gmail.com)*

Background. Nasal continuous positive airway pressure (NCPAP) is well established as a treatment for hyaline membrane disease (HMD) and other respiratory diagnoses in neonates. NCPAP is an affordable intervention that reduces the number of neonatal admissions to the intensive care unit (ICU) for ventilation. At the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) we have been using NCPAP since April 2006.
Objectives. To review the use of early NCPAP in our hospital setting.
Methods. This was a retrospective, descriptive study of all neonates ≥750 g admitted to CMJAH between 1 January 2013 and 31 July 2014, who received NCPAP within 72 hours of birth. The characteristics and the survival of all infants who received NCPAP were described using univariate analysis.
Results. The NCPAP group (n=481) of neonates <1 500 g was significantly associated with surfactant use (p<0.0005), bronchopulmonary dysplasia (p<0.0005) and late sepsis (p<0.0005). The survival to day 7 and to discharge of infants treated with NCPAP was significantly decreased (p<0.0005). NCPAP alone (without ventilation) improved the survival to discharge (p=0.001). The survival was 95.4% in the ≥1 500 g infants, compared with 87.6% in the very low birth weight infants and 55.2% in the extremely low birth weight infants.
Conclusion. NCPAP is an effective intervention for HMD; it is both cost-effective and easy to use in a resource-limited setting, and reduces the morbidity and mortality associated with ICU admission.

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Nasal continuous positive airway pressure (NCPAP) has become widely used and accepted as a treatment for hyaline membrane disease (HMD) since its first introduction in 1971.[1,2] HMD affects premature babies and causes considerable morbidity and mortality. The use of NCPAP on its own and in combination with the use of surfactant has been shown to improve the outcomes of HMD in premature infants.[3]

The incidence of HMD is related to the degree of prematurity of the lungs, and therefore the incidence increases as the gestational age (GA) decreases. The use of antenatal steroids given to mothers where a premature delivery is expected has reduced the incidence and severity of HMD.[4] The administration of surfactant for severe HMD has been shown to improve lung compliance, facilitate weaning off supplemental oxygen and result in fewer neonates needing ventilatory support. Surfactant replacement therapy also significantly reduces the mortality from HMD.[5]

NCPAP is not only used in HMD but is also used to treat apnoea of prematurity, respiratory distress due to other aetiologies, some types of upper airway obstruction, and can sometimes be used as an alternative to endotracheal intubation or as a weaning mode of ventilation.[1] The continuous positive pressure provided by NCPAP helps to support and distend the alveoli, preventing their collapse. This results in the recruitment of alveoli, which improves the ventilation perfusion mismatch of the lungs and increases the functional residual capacity and tidal volume, thereby improving oxygenation in the neonate.[1] NCPAP also exerts a distending pressure on the larger airways, thus stabilising them and preventing upper airway collapse.[1] The early use of NCPAP in premature neonates reduces the need for surfactant and results in fewer neonates needing to be intubated and ventilated.[3,6,7] This decreases ventilator-induced lung injury and results in fewer cases of bronchopulmonary dysplasia (BPD).[3,7] Adverse effects of NCPAP use, including 'CPAP belly syndrome',[8] nasal septal necrosis and pneumothorax, may sometimes occur.

NCPAP is an affordable intervention that is easy to use in a resource-poor setting. The successful use of NCPAP could result in a considerable reduction in the costs of neonatal care, as there would be a reduction in ventilation and neonatal intensive care unit (NICU) admissions, as well as a decrease in poor outcomes associated with prolonged ventilation. Recently, there have been a number of studies reporting on the survival of extremely low birth weight (ELBW) infants (birth weight <1 000 g). At Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), it was found that the use of NCPAP in ELBW infants was not associated with an improvement in survival.[9] This study was done using data from neonates ≤900 g admitted between January 2006 and December 2010, a period during which fewer ELBW infants were receiving NCPAP than currently. A previous study at CMJAH, which assessed the determinants of survival in very low birth weight (VLBW) neonates (birth weight <1 500 g) found that NCPAP was associated with improved survival.[10] Kirsten *et al.*[11] at the Tygerberg Children's Hospital in the Western Cape found that NCPAP practised together with InSurE (intubating to give surfactant and then extubating) in a neonatal high-care ward with limited resources improved the survival of ELBW infants.

NCPAP was introduced into the neonatal unit at the CMJAH in April 2006. It is now used as the first line of ventilatory support in neonates with HMD. The objective of this study was to review the use of early NCPAP in neonates at CMJAH.

Methods

This was a retrospective, descriptive study of all neonates with a birth weight ≥750 g admitted to the neonatal unit at CMJAH

between 1 January 2013 and 31 July 2014, who received NCPAP within 72 hours of birth. Neonates were excluded if there was insufficient information, if NCPAP was used post extubation from conventional mechanical ventilation (CMV) or if they had major congenital abnormalities. All in-born babies, babies born at maternity outpatient units, or babies born before arrival (BBA) were initially observed in the transitional care unit for assessment before being admitted to the neonatal unit, and were included in our statistics. T-piece resuscitators were not available in the labour ward nursery, and bag mask valve resuscitation was used for babies who required resuscitation at birth. The babies were observed for 1 - 2 hours in the transitional care unit and then a decision was made by the attending doctor on whether or not they required NCPAP and surfactant. NCPAP with early rescue surfactant was offered to neonates with respiratory failure due to HMD as per the neonatal unit's protocol. Respiratory failure was defined as an oxygen saturation <88% in 60% supplemental oxygen, respiratory acidosis on arterial blood gas or clinical signs of severe respiratory distress, including indrawing of the sternum and tachypnoea. Due to insufficient NCPAP machines, not all neonates who qualified for NCPAP could receive it. Neonates who required NCPAP were admitted to the high-care neonatal ward where there were nine Bubble NCPAP (Fisher and Paykel, New Zealand) machines available; NCPAP was not initiated in the NICU. If NCPAP was not available, babies were given surfactant and placed on nasal prong oxygen. The neonatal unit's policy at the time of the study was that neonates ≥900 g would qualify for ventilation in the NICU if required.

Database

The neonatal records at CMJAH are kept on the REDCap (Research Electronic Data Capture) electronic neonatal database.[12] REDCap is a secure, web-based program that has been designed to aid data capture for the purposes of clinical audit and quality improvement. Data are collected upon discharge of patients and entered into the REDCap database. The information is verified at several different stages of collection. The following data were collected from the database: (*i*) maternal data – antenatal steroids, place and mode of delivery, multiple gestation; and (*ii*) infant data – gestational age, birth weight, gender, place of birth, 5-minute Apgar score, necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), NCPAP with or without surfactant or CMV, respiratory diagnosis, duration of NCPAP and ventilation, late sepsis (occurring after day 3), BPD (defined by oxygen requirement at 28 days of age), nasal septal necrosis, pneumothorax, and outcome (death or survival) at discharge.

Statistical analysis

The data were entered into an MS Excel (Microsoft, USA) spreadsheet and imported into statistical software package SPSS version 19 (IBM, USA). Categorical variables were described using frequencies and percentages, while continuous variables were described using means and standard deviations (SDs). The data were also stratified into birth weight categories (ELBW <1 000 g, VLBW <1 500 g, low birth weight (LBW) <2 500 g and weight ≥2 500 g), and the proportion of infants in each category receiving NCPAP was determined. Neonates <1 500 g who had not received NCPAP were compared with those who had received NCPAP, with regard to characteristics and survival to discharge. IVH was graded according to the sonographic grading system described by Papile *et al.*[13] Grades 1 and 2 of IVH were considered together as 'mild' and grades 3 and 4 as 'severe'. The NEC category included grades 2 and 3 of NEC, according to modified Bell's staging criteria.[14] Infants were regarded as having birth asphyxia if they had Apgar scores of ≤5 at 5 minutes. Babies on NCPAP who developed respiratory failure and required ventilation in the NICU were regarded as having failed NCPAP. Babies who were transferred out and those who were discharged home directly were grouped together as survivors for the purpose of analysis. Univariate analysis was used to compare the characteristics of the two groups, and survival was described. Categorical variables were compared using χ^2 tests, and continuous variables using unpaired *t*-tests (as the distribution was normal). A *p*-value of <0.05 was considered to be significant. In neonates ≥1 500 g, the characteristics, respiratory diagnosis and survival of those who received NCPAP were described.

Ethics

Ethics approval for the study was granted by the Human Research Ethics Committee at the University of the Witwatersrand, Johannesburg (clearance certificate number M140403).

Results

Infants <1 500g

There were 748 VLBW infants admitted over the 19-month period. Information was not available on 9 infants, 18 infants had major birth defects, NCPAP was used as a weaning mode of ventilation in 3 infants and NCPAP was started after 72 hours in 7 infants. All of the above were excluded, leaving a total of 711 infants in the study.

The majority were female (*n*=378, 53.2%). The mean birth weight was 1 158 (SD 220) g and GA was 29.5 (2.6) weeks. The majority (*n*=380, 53.4%) were born by emergency caesarean section, and most (*n*=591, 83.1%) were inborn. Antenatal steroids were given in 275 (38.7%) cases. NCPAP was provided to 481 (67.7%) of the infants in total. Most babies (*n*=397, 82.5%) coped on NCPAP alone; in 84 (17.5%), NCPAP failed. Overall, there were 560 (78.8%) survivors. The mean duration of NCPAP was 2.58 (3.52) days with a maximum duration of 35 days. Nasal septal necrosis occurred in 27/481 (5.6%) and pneumothorax occurred in 5/481 (1%) of the infants who received NCPAP. Surfactant was given to 507 (71.3%) infants in total; 43 (8.4%) of these received surfactant without NCPAP. Birth asphyxia occurred in 79 (11.1%) infants.

VLBW 1 000 - 1 499 g

In this category, there were 517 infants, of whom 453 (87.6%) survived. A total of 308 (59.6%) infants received NCPAP, and surfactant was given to 329 (63.6%) infants. There were 41 (8%) infants with birth asphyxia. The use of NCPAP was significantly associated with death (p=0.001, odds ratio (OR) 0.41, 95% confidence interval (CI) 0.23 - 0.73). Overall, 252 (81.8%) infants coped on NCPAP alone, while 56 (18.2%) infants failed NCPAP.

ELBW 750 - 999 g

In this category, there were 194 infants, of whom 107 (55.2%) survived. A total of 173 (89.2%) infants received NCPAP, and surfactant was given to 178 (91.8%) infants. There were 38 (19.6%) infants with birth asphyxia. NCPAP was not significantly associated with survival (p=0.261, OR 0.72, 95% CI 0.39 - 1.35). Overall, 145 (83.8%) infants coped on NCPAP alone, while 28 (16.1%) infants failed NCPAP (these were all >900 g and thus were offered ventilation).

NCPAP v. no NCPAP

The entire group of neonates between 750 and 1 500 g was divided into two groups: those who had received NCPAP and those who

Table 1. Characteristics of the NCPAP group and no NCPAP group in neonates <1 500 g

Variable	NCPAP (*n*=481), *n* (%)	No NCPAP (*n*=230), *n* (%)	*p*-value
Surfactant	464 (96.4)	43 (18.7)	<0.0005
BPD	108 (22.4)	18 (7.8)	<0.0005
Late sepsis	125 (25.9)	30 (15.0)	<0.0005

Table 2. Survival of infants who were treated with NCPAP compared with those who were not

	NCPAP (n=481), n (%)	No NCPAP (n=230), n (%)	p-value
Survival to day 3	450 (93.5)	222 (96.5)	0.104
Survival to day 7	407 (84.6)	218 (94.7)	<0.0005
Survival to discharge	351 (72.8)	209 (90.8)	<0.0005

Table 3. Survival of infants who were treated with NCPAP alone

	NCPAP alone (n=397), n (%)	Failed NCPAP (n=84), n (%)	p-value
Survival to day 3	370 (93.2)	80 (95.2)	0.489
Survival to day 7	336 (84.6)	71 (84.5)	0.980
Survival to discharge	302 (76.0)	49 (58.3)	0.001

Table 4. Respiratory diagnosis in the ≥1 500 g group who received NCPAP

Respiratory diagnosis	LBW <2 500 g, n (%)	≥2 500 g, n (%)
TTN	8 (3.6)	5 (12.2)
Congenital pneumonia	9 (4.1)	5 (12.2)
MAS	2 (0.9)	10 (24.4)
HMD	200 (90.9)	13 (31.7)
Apnoea	8 (3.6)	1 (2.4)

had not. The characteristics of the two groups were compared and significant differences are shown in Table 1. There was no significant difference in the babies with regards to CMV, pneumothorax, antenatal steroids, IVH or NEC. Mild IVH occurred in 69 (14.4%) infants in the NCPAP group compared with 18 (7.8%) infants not receiving NCPAP, and severe IVH occurred in 20 (4.2%) infants receiving NCPAP compared with 7 (3%) infants not receiving NCPAP. These differences were not significant. The survival of the infants in the two groups was compared in Table 2. The use of NCPAP was associated with an increased risk of death by day 7 and at discharge. When the successful use of NCPAP alone was compared with those who failed NCPAP, there was a significantly higher rate of survival to discharge (Table 3).

Infants ≥1 500 g

A total of 1 997 neonates weighed ≥1 500 g; 1 570 infants did not receive NCPAP, 154 had a major birth defect, 7 had insufficient information and 5 had NCPAP as a weaning mode from CMV. There were thus 261 infants in the NCPAP group.

The majority were males (n=164, 62.8%). Most of the infants were inborn (n=217, 83.1%). In 129 (49.4%) infants, the mode of delivery was by emergency caesarean section. In the LBW (1 500 - 2 499 g) category, there were 220 (84.3%) infants, and in the ≥2 500 g category, there were 41 (15.7%) infants. The mean birth weight was 2 044 (528) g, with a maximum of 5 250 g, and the mean GA was 33.5 (2.9) weeks with a minimum of 28 weeks. Overall, 249 (95.4%) infants survived. Surfactant was given to 210 (80.5%) infants. The mean duration of NCPAP was 1.62 (1.7) days, with a minimum of <1 day and a maximum of 31 days. There were 33 (12.6%) infants who failed NCPAP. This group of larger infants (≥1 500 g) represented 35.1% (261/742) of all the babies who received NCPAP over the study period. The respiratory diagnosis in the majority of cases was HMD (n=213, 81.6%) but also included transient tachypnoea of the newborn (TTN), congenital pneumonia, meconium aspiration syndrome (MAS) and apnoea (Table 4).

Discussion

This was the first study from our unit on how we are using NCPAP in all our neonates from 750 g to 5 250 g. Previously, we had investigated the use of NCPAP as it relates to the survival of both ELBW and VLBW infants in our unit, but we had not determined the characteristics of the infants receiving NCPAP across all weight categories.

The majority of the babies in the ELBW category received NCPAP (89.2%). It was expected that all the babies in this weight category would have had HMD, requiring NCPAP and surfactant replacement, and it is encouraging that we managed to provide NCPAP to most patients. Only 16.1% of the ELBW infants and 18.2% of the VLBW infants failed NCPAP and were given ventilation. However, in the ELBW category, only infants ≥900 g would have been offered CMV. These figures are appropriate for a resource-poor setting in a high-care nursery such as ours. We have only nine Bubble NCPAP machines available, but most of our babies were able to receive NCPAP. This may be attributed to the fact that babies were able to wean off of the NCPAP relatively quickly, allowing a high turnover of these machines. With the successful use of NCPAP, far fewer premature babies are requiring NICU admission for ventilation. This is both cost-saving and greatly reduces morbidity and mortality associated with the NICU. Our ICU is shared between neonates, paediatrics and paediatric surgery patients. There was a concern that lowering our ICU admission weight category to 900 g would inundate the ICU with premature babies, but – largely due to NCPAP – this has not been the case. However, it is important to note that although babies who require NCPAP do not need NICU admission, they do require adequate high-care facilities with well-trained nursing staff, as they need close monitoring and active weaning off the NCPAP.

In the larger (≥1 500 g) babies, only 12.6% failed NCPAP. In these babies, we were using NCPAP for other indications such as TTN, congenital pneumonia, MAS and apnoea, but in the majority of cases it was used for HMD in larger premature babies.

It is disappointing to note that in this study there was no improvement in the use of antenatal steroids since the study done in 2010[10] (38.7% in this study v. 36% in the 2010 study). This is largely due to missed opportunities and late presentation once the mother was already in preterm labour.[15]

The use of NCPAP was significantly associated with a higher mortality to day 7 (p<0.0005) and discharge (p<0.0005). The increased mortality with NCPAP use may be due to other factors affecting survival, such as late sepsis and NEC, which VLBW infants are prone to. There is also a selection bias, as NCPAP is given to babies with more severe respiratory illness and not routinely offered to all premature babies. Within the NCPAP group, NCPAP alone (without CMV) improved survival to discharge (p=0.001). Prolonged ventilation is associated with increased morbidity, and infants who fail NCPAP have a more severe degree of HMD with higher mortality.

Surfactant, BPD and late sepsis were shown to be significantly associated with the use of NCPAP. The overall incidence of

22.4% BPD was higher than the 8.8% reported in our hospital in 2010.[10] More babies are now offered NCPAP and are surviving long enough to develop BPD than in 2010, where over a 1-year period only 96/474 (20.3%) VLBW infants received NCPAP. VLBW infants are prone to late-onset sepsis[16] and the use of NCPAP has also been associated with this.[17] Limited nursing staff and overcrowding in the neonatal nursery further compound this problem.

There was a very low rate of complications of NCPAP in our study, with only five infants developing a pneumothorax, and 27/481 infants developing nasal septal necrosis, while IVH was not found to be significantly associated with NCPAP. When compared with the Vermont Oxford Network, our rate of pneumothoraces was lower (1% v. 4%) and our NCPAP use (67.7% v. 73.5%) was also lower.

Conclusion

NCPAP is cost-effective and easy to use in a resource-poor environment with a small number of Bubble NCPAP machines being able to treat a large number of neonates with HMD. This effectively releases ICU beds, thereby increasing the number of beds that are available for ventilatory support for neonatal and general paediatric patients.

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Appendix B

M140403

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140403

NAME: (Principal Investigator)	Dr Carla Jardine
DEPARTMENT:	Paediatrics Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	The Use of Continous Positive Airway Pressure (CPAP) at the Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	25/04/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Daynia Ballot
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 28/05/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature M140403Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C



Carla Jardine <carlsjardine@gmail.com>

[SAJCH] Editor Decision

2 messages

John M Pettifor <sajch.editor@hmpg.co.za> Mon, Oct 20, 2014 at 8:00 PM
To: Carla Jardine <carlsjardine@gmail.com>

Dear Dr Jardine:

I am happy to inform you that your revised manuscript, "The use of nasal CPAP at the Charlotte Maxeke Johannesburg Academic Hospital", has been accepted by the South African Journal of Child Health for publication.

Prior to publication you should receive a final proof for checking.

Congratulations,
regards
John Pettifor

John M Pettifor
sajch.editor@hmpg.co.za
Emeritus Professor and Editor: South African Journal of Child Health

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