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Outcome of very low birth weight babies (800g-1499g) managed with nasal continuous positive airway pressure with or without surfactant in a high care nursery

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OUTCOME OF VERY LOW BIRTH WEIGHT BABIES (800g-1499g) MANAGED WITH NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE WITH OR WITHOUT SURFACTANT IN A HIGH CARE NURSERY

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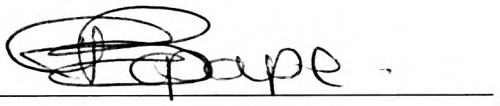
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A research report submitted to the faculty of Health Sciences, University of the Witwatersrand, in fulfillment of the requirements for the degree of Masters of Medicine, in the branch of Paediatrics

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DECLARATION

I, Thokozile Bopape-Chinyanga, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signed: 

On this: 6th day of February 2016

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ABSTRACT

Background: Very-low-birth-weight infants (VLBWI-800g-1499g) who require nasal continuous positive airway pressure (nCPAP) are managed in a neonatal intensive care unit (NICU) in developed countries but in low-resource settings this is not always possible. The failure-rate of nCPAP in a setting outside NICU is not well-known.

Objective: To determine the failure-rate [need for invasive mechanical ventilation (iMV) and mortality] of nCPAP in VLBWI (800g-1499g) managed outside NICU within the first 72 hours of life.

Methods: Medical records of VLBWI managed with nCPAP at Chris Hani Baragwanath Hospital in 2012 were reviewed for neonate characteristics, need for iMV and mortality on nCPAP. Clinical Risk Index for Babies (CRIB) was calculated for each neonate. Comparisons were made between those who needed iMV and those who did not; and between survivors and non-survivors on nCPAP.

Results: A total of 635 records of VLBWI were reviewed and of these, 325 (51%) were managed with nCPAP. The average birth-weight was 1120±184 grams and the gestational-age (GA) was <34 weeks in 98.5% of cases. Antenatal-steroids were recorded as being administered in 36%. Forty four (13%) demised while on nCPAP and 33% of survivors required iMV, an overall failure-rate of 43%. Factors associated with iMV were high CRIB score (34% vs 12%, $p<0.001$), lower PaO2 (137.3±67.3 vs 161±81, $p=0.022$) and high base-deficit (9.0±4.4 vs 7.8±4.1, $p=0.034$). Those who demised were more likely to have extreme-low-birth-weight (79.5 vs 21.4%, $p<0.001$), lower GA (27±2 vs 29±2 weeks, $p<0.001$), CRIB score >10 (51.2 vs 20.7%, $p<0.001$) and a high base-deficit (11.9±6.0 vs 8.2±4.2 mmols/l, $p<0.001$).

Conclusion: Although the failure-rate of nCPAP in VLBWI managed outside NICU is high at 43%, a proportion of VLBWI benefit from this intervention despite being managed outside NICU.

INTRODUCTION

Respiratory distress is a common clinical presentation in newborn infants shortly after birth. The respiratory distress in preterm infants or very low birth weight infants (VLBWI) is often due to respiratory distress syndrome (RDS) resulting from the insufficient production of surfactant leading to atelectasis. Many times it is also due to the weakness of the chest wall and immature alveoli. One of the management strategies for respiratory distress in VLBWI is non-invasive mechanical ventilation using continuous positive airway pressure (CPAP). Continuous positive airway pressure was first used as a method of providing respiratory support in infants with RDS in 1971.[1] It is still considered one of the interventions that have contributed significantly to the reduction of neonatal mortality globally.[2] The physiological effects of CPAP include increasing functional residual capacity, thereby improving oxygenation and maintaining lung volume, reducing the work of breathing, conserving surfactant and reducing obstructive apnoea.[3]

Nasal prongs are the commonly used nasal interface when applying CPAP because they are associated with less resistance and a reduced breathing workload than that of endotracheal tubes. Consequently nasal CPAP (nCPAP) is the most commonly used form of administering CPAP.[3] Nasal CPAP is widely used for a range of neonatal respiratory conditions and is considered the first line intervention in the management of preterm infants or VLBWI with respiratory distress.[4] In developed countries, this intervention is applied to infants admitted to NICU but in developing or low-resource settings, this is not always possible.

The proportion of preterm infants at a gestation of 25-28 weeks who are managed successfully with nCPAP soon after birth ranges from 45-68%, and the proportion of those at a gestation of 29-32 weeks have been reported to be 64-76%.[5-7] The use of nCPAP in preterm infants with respiratory distress is associated with a lower risk for death and a lower risk for the use of assisted ventilation.[8] One study in preterm infants reported that the use of nCPAP soon after birth with or without the prior administration of exogenous surfactant was associated with similar or better outcomes than invasive mechanical ventilation.[9] Although a large number of patients managed with nCPAP do well, a significant proportion of infants managed on nCPAP fail to improve sufficiently and need to be intubated for mechanical ventilation. The proportion of preterm or VLBWI who are initially managed with nCPAP only and subsequently require intubation for mechanical ventilation is reported to be 45-51%.[7] Even with the addition of exogenous surfactant to nCPAP, there is still a failure rate

of 25-38%.[10] The criteria used to define the failure of nCPAP varies from study to study and this most likely explains the variation in the proportion of infants reported to have failed on CPAP. Studies have used different parameters and values to define criteria for nCPAP failure. The criteria have included FiO2 ranging from 0.3 to >0.6, PaCO2 >60 or 65 mmHg, pH <7.20 or 7.25, pressure on nCPAP and persistent apneas.[10, 11] Factors that have been found to be associated with nCPAP failure have included lower gestational age and birth weight, amount of supplemental oxygen, male gender, FiO2/PaO2 ratio, PaCO2, pH and presence of apnoeas.[11, 12] These factors indirectly reflect on the maturity of the infant and severity of the lung disease. A composite parameter that has been used to assess severity of illness in neonates is the CRIB (Clinical Risk Index for Babies) score.[13] A number of the factors that have been associated with nCPAP failure are part of the CRIB score. It is therefore one of the parameters that can be used in predicting nCPAP failure in hospitals. The CRIB score assists in assessing the severity of illness during the early neonatal period. The variables used in calculating it are gestational age, weight, maximum base excess, congenital abnormalities, and minimum and maximum FiO2 requirements. These variables are assessed in the first 12 hours of life, making them less susceptible to treatment effects. A score of <5 has a smaller risk for mortality when compared to a score of >10.[13] CRIB is a tool that is objective and can possibly be used by junior and professional nursing staff to identify those babies that will need intensive care management before they deteriorate or demise, though it is not widely used.

Most of the studies that researched the nCPAP failure rate were conducted in developed countries. None of the babies were reported to have demised on nCPAP as everyone who failed nCPAP were subsequently intubated and placed on mechanical ventilation.[6] In developing countries, or settings where intensive care resources, professional nurses and doctors are limited, a number of preterm infants may demise while receiving nCPAP because of a shortage of these resources. A study in a developing country where NICU facilities are limited examined the outcomes of extreme low birth weight infants (ELBWI) managed with nCPAP. It reported a mortality rate of 8% on nCPAP.[10] Factors associated with deaths in VLBWI managed with nCPAP in a setting with limited resources are not known. In this study we sought to determine the success rate of VLBWI managed with nCPAP outside NICU and used the need for intubation for ventilation or death as the determining criteria. We also sought to determine factors associated with poor outcomes Outcome was measured at the first 72hrs of life. This study was conducted after gaining approval from the University of the Witwatersrand Human Research Ethics Committee (M130744 02/08/2013).

METHODS

Study Design: This was a retrospective descriptive study.

Study Population: VLBWI weighing 800g-1499g admitted to the high-care nursery at Chris Hani Baragwanath Academic Hospital (CHBAH) between January and December 2012 and managed with nCPAP within first 72 hours of life, with or without surfactant.

Inclusion criteria

a. Infants weighing 800g-1499g
b. Infants who received nCPAP either from the labour ward nursery, ward 66 or while in the high care nursery within the first 72 hours of life

Exclusion criteria

a. VLBWI (800g-1499g) extubated to nCPAP after conventional mechanical ventilation
b. Neonates who were started on nCPAP in NICU

Study Procedures: Medical records of VLBWI weighing 800g-1499g were retrieved and reviewed for maternal and infant data. A data collection sheet was compiled to capture all the information required. The CRIB score was then calculated by the researcher for each infant. Of the 325 files examined, 1 had an 'outcome page' missing from the records.

Study Setting: CHBAH is the referral hospital for all clinics in Soweto and its surrounding areas. Very low birth weight infants (800g-1499g) are all offered nCPAP if they have respiratory distress. Junior staff (Interns, Medical Officers, and Registrars) identifies the babies that may need this intervention, and a decision is made by the consultant as to which management to proceed with. Exogenous surfactant is administered if a patient requires $FiO_2 \geq 0.4$ to maintain pulse oximeter saturations between 88-94%. This is given within 2 hours of initiating nCPAP. Most patients with respiratory distress have an arterial blood gas taken before nCPAP. These neonates admitted with respiratory distress have a full blood count (FBC) and blood cultures taken on admission. A c-reactive protein (CRP) is obtained 24-48 hours after birth. Patients who weigh more than 900g and have severe RDS, are offered mechanical ventilation and transferred straight to NICU: if they fail to maintain saturations

between 88-94% despite nCPAP and surfactant; have a FiO2 >0.60, a PaO2 <50 mmHg on an FiO_2 >0.60; a $PaCO_2$ >55 mmHg with pH<7.25; or a $PaCO_2$ >60 mmHg.

Data collection: Data collected included maternal and infant characteristics, antenatal management, clinical diagnosis, laboratory findings, the use of exogenous surfactant and outcomes on nCPAP. Outcomes were defined as weaning off nCPAP in high care, the need for mechanical ventilation, or demise on nCPAP. Data was captured in an Excel spreadsheet.

Data analysis: The Excel spreadsheet was imported into *Statistica Version 12.0* for statistical analysis. Means with standard deviations and medians with interquartile ranges were used to describe the parametric and non-parametric data respectively. Frequencies and percentages were used to describe categorical variables. In comparing those who failed on nCPAP and those who were weaned off nCPAP, Chi-square and Fisher exact tests were used to assess for statistically significant differences between categorical variables; and Student t-test and Mann-Whitney U-test were used for parametric and non-parametric continuous variables. Comparisons were also made between survivors and those that demised, and those that received surfactant and those that did not. Differences with p-values <0.05 were considered to be statistically significant. The outcomes of those admitted to NICU were not measured.

RESULTS

There were 21601 live births conducted at CHBAH in 2012 and 806 of them were VLBWI accounting for 3.7% of all live births. Among these 806 VLBWI, medical records of 635 (78.8%) were retrieved and of these 325 (51.2%) patients were managed with nCPAP in high care nursery. There was one missing page in one of the records; therefore the outcomes table has a total of 324 patients.

The majority of mothers (75.2%) were in the age group of 20-35 years and 11% were teenagers; a third (33.4%) of VLBWI were born to mothers with positive human immunodeficiency virus (HIV) status and only 78.5% of mothers attended antenatal care (Table 1). Most deliveries (94.1%) took place in a health care facility and 58% were born through a caesarean section. Antenatal steroids during labour were recorded as being given in only 36.3% of patients, and not given in 12.9%; there were no records of whether or not antenatal steroids were given in 50.8% of cases. Only 29% weighed between 800g-1000g. Neonates less than 900g were 13.5% of the population. The gestational age of most (98.5%) neonates was <34 weeks. Numbers of male and female babies were equally distributed. Forty seven percent required resuscitation, with most of them only requiring bag mask ventilation. An APGAR score <7 at 5 minutes was recorded in 16.3% of the babies.

The common diagnosis on admission was RDS. About two third of patients (66.2%) had a CRIB score of 4-10 and 23.7% had a CRIB score of >10. Arterial blood gases done before the administration of nCPAP showed a mean pH of 7.24±0.12, PaCO2 of 46±26 mmHg, PaO2 of 149±76 mmHg and a base deficit of 8.70±4.7 mmol/l (Table 2). FBC on admission showed that 22.8% had an abnormal white cell count (18.3% with leukopenia and 4.5% with leukocytosis), 5% had anaemia (haemoglobin <12 g/dl) and 35% had thrombocytopaenia (platelet count <150 x 10^9/l). Only 12.9% had C-reactive protein >10 mg/l and 6% had positive blood cultures. The median age when nCPAP was started was 3.6 hours (IQR 2.0; 6.4).

Table 1. Baseline characteristics of very low birth weight infants managed with nCPAP

Characteristic	Number n=325 (%)
Maternal age (years)*	28 ± 7†
- <20	35 (11.3)
- 20-35	233 (75.2)
- >35	42 (13.5)
Place of birth	
- CHBAH‡	283 (87.1)
- Clinic	22 (6.8)
- Born outside healthcare facility	20 (6.1)
Mode of delivery	
- Vaginal delivery	136 (41.8)
- Caesarean section	189 (58.2)
HIV status*	
- Positive	107 (33.4)
- Negative	213 (66.6)
Booked	
- Yes	255 (78.5)
- No	70 (21.5)
Antenatal steroids	
- Yes	118 (36.3)
- No	42 (12.9)
- Not recorded	165 (50.8)
Gestation (weeks)	29 ± 2†
- <28	76 (23.4)
- ≥28 to <30	128 (39.4)
- ≥30 to <34	116 (35.7)
- >34	5 (1.5)
Weight (grams)	1120 ± 184†
- 800-999	95 (29.2)
- ≥1000	230 (70.8)
Gender	
- Male	161 (49.5)
- Female	164 (50.5)
APGAR Score at 5 minutes <7	53 (16.3)
Resuscitation required	
- No	168 (51.7)
- Yes	157 (48.3)
Extent of resuscitation required	
- Bag mask ventilation (BMV) only	153 (97.4)
- BMV and Adrenalin	4 (2.6)

* Missing data = 15 for maternal age, 5 for HIV (Human Immunodeficiency Virus) status
† Data presented as mean ± standard deviation
‡ CHBAH (Chris Hani Baragwanath Academic Hospital)
§ BMV (Bag Mask Ventilation)

Table 2. Clinical diagnosis, severity of illness (CRIB score) and laboratory findings

Characteristics	Number n=325 (%)
Clinical Diagnosis	
– Respiratory distress syndrome	307 (94.5)
– Asphyxia	11 (3.4)
– Congenital pneumonia	5 (0.5)
– Apnoea	2 (0.6)
CRIB† Score*	
– <4	18 (5.5)
– 4-10	215 (66.2)
– >10	77 (23.7)
Postnatal age (hours)*	3.6 (2.0; 6.4)‡
– ≤2 hours	65 (23.0)
– 2-6	143 (50.5)
– 6.1-12	48 (17.0)
– >12	27 (9.5)
Blood gases	
– pH	7.24 ± 0.12§
– $paCO_2$	46 ± 26
– paO_2	149 ± 76
– Base excess	8.7 ± 4.7
White cell count (Wcc) ($x10^9$/l)*	
– <5	57 (18.3)
– 5-25	241 (77.2)
– >25	14 (4.5)
Haemoglobin (Hb) (g/dL)*	
– <12	16 (5.1)
– 12-18	267 (85.6)
– >18	29 (9.3)
Platelets ($x10^9$/l)*	
– <100	42 (13.5)
– 100-150	67 (21.5)
– >150	203 (65.0)
C-reactive protein (CRP) (mg/dL)*	
– ≤10	256 (87.1)
– >10	38 (12.9)
Blood culture*	
– Positive	18 (5.8)
– Negative	295 (94.2)

* Missing data: 15 for CRIB score; 42 for postnatal age; 13 for Wcc, Hb and Platelets; 31 for CRP; 12 for blood culture

† CRIB (Clinical Risk Index for Babies)

‡ Values are median postnatal age (25^{th}; 75^{th} percentile)

§ Values are mean ± standard deviation

Out of the 325 VLBWI who received nCPAP, 156 (48%) required surfactant in addition to nCPAP, 44 (13.5%) demised while on nCPAP and the 96 (34.2%) who survived required intubation for mechanical ventilation (Table 3). Overall, 56.6% of VLBWI managed with nCPAP in the high care nursery were weaned off nCPAP, and 43.4% either required intubation for mechanical ventilation or demised whilst on nCPAP.

Table 3. Outcome of patients of very low birth weight infants managed with nCPAP in high care

Management and Outcome	**Numbers (%)**
Number requiring Surfactant on nCPAP*	156 (48.0)
Type of Surfactant†	
- Survanta	91 (61.5)
- Curosurf	57 (38.5)
Demise on nCPAP* (n=324)‡	
- Yes	44 (13.6)
- No	280 (86.3)
Number who required intubation for mechanical ventilation among survivors	
- Yes	96 (34.2)
- No	184 (65.8)
Weaned off nCPAP* in high care nursery (n=324)	
- No	140 (43.2)
- Yes	184 (56.6)

† Missing data – 8 for type of surfactant
* nCPAP (nasal Continuous Positive Airway Pressure)
‡ Patient outcome not recorded as last page was missing

There were more patients who needed resuscitation (64.9% vs 52.7%, p=0.003), and who had a CRIB score >10 (28.9% vs 20.2%, p=0.001) in the VLBWI who required surfactant in addition to nCPAP when compared to those who did not require surfactant (Table 4). There were no statistically significant differences in other variables.

There were more patients with a CRIB score >10 (37.4% vs 12.0%, p<0.001) amongst those who needed mechanical ventilation. They also had a lower PaO2 (137±67 vs 161±81 mmHg, p=0.022) and higher base deficit (9.0±4.4 vs 7.8±4.0 mmol/l, p=0.034) when compared to those who did not need ventilation (Table 5). There were no statistically significant differences in other variables between those who required mechanical ventilation and those who did not require ventilation amongst the survivors.

Table 4. Comparison between those who needed surfactant and those who required nCPAP only

	nCPAP and Surfactant N=156	**nCPAP only** N=169	**p-value**
Mode of delivery	n = 156	n = 169	0.587
– Vaginal delivery	63 (40.4)	73 (43.2)	
– Caesarean Section	93 (59.6)	96 (56.8)	
Maternal Steroids	n = 82	n = 78	0.142
– Yes	56 (68.3)	62 (79.4)	
– No	26 (31.7)	16 (20.6)	
Gestation (weeks) (mean ± SD)	29.0 ± 2.1	28.9 ± 2.3	0.754
Birth weight (grams) (mean ± SD)	1112 ± 185	1124 ± 184	0.554
Sex	n = 156	n = 169	0.265
– Male	83 (53.2)	78 (46.2)	
– Female	73 (46.8)	91 (53.8)	
APGAR score at 5 minutes*	8 (7; 9)	9 (7; 10)	0.777
Resuscitation required	n = 131	n = 151	0.003
– None	46 (35.1)	71 (47.0)	
– Yes	85 (64.9)	80 (53.0)	
Postnatal age at starting nCPAP†	n = 138	n = 145	0.959
– <2 hours	39 (28.3)	36 (24.8)	
– 2-6 hours	64 (46.4)	70 (48.3)	
– 6-12 hours	23 (16.7)	25 (17.2)	
– >12 hours	12 (8.70)	14 (9.7)	
CRIB‡ Score	n = 149	n = 161	0.001
– <4	6 (4.03)	12 (7.5)	
– 4-10	100 (67.1)	115 (71.4)	
– >10	43 (28.9)	34 (21.1)	
Blood gases (mean ± SD)	n = 134	n = 148	
– pH	7.24 ± 0.10	7.23 ± 0.13	0.360
– paCO2 (mmHg)	45.0 ± 32.8	45.6 ± 14.5	0.437
– paO2 (mmHg)	145 ± 72.8	154 ± 79.4	0.896
– Base deficit (mmol/l)	8.79 ± 3.89	8.51 ± 5.17	0.610
C-reactive protein (mg/l)	n = 142	n = 152	0.469
– ≤10	126 (88.7)	130 (85.5)	
– >10	16 (11.3)	22 (14.5)	
Blood culture on admission	n = 147	n = 155	0.804
– Positive	17 (11.6)	20 (12.9)	
– Negative	130 (88.4)	134 (87.1)	

* Median (IQR)
† nCPAP (nasal Continuous Airway Pressure)
‡ CRIB (Clinical Risk Index for Babies)

Table 5. Comparison of those who needed intubation and those who did not amongst survivors

	Needed mechanical ventilation despite nCPAP N=96 n (%)	**Mechanical ventilation not required** N=184 n (%)	**p-value**
Mode of delivery	n = 96	n = 184	0.780
- Vaginal delivery	38 (39.6)	76 (41.3)	
- Caesarean Section	58 (60.4)	108 (58.7)	
Maternal Steroids	n = 55	n = 81	0.698
- Yes	43 (79.2)	61 (75.3)	
- No	12 (21.8)	20 (24.7)	
Gestation (weeks) (mean±SD)	29 ± 2.2	29 ± 2.1	0.678
Weight (grams) (mean±SD)	1143 ± 151	1149 ± 187	0.778
Female infants	43 (44.8)	96 (52.2)	0.241
Median APGAR at 5 minutes	8 (6; 9)	9 (7; 10)	0.013
Resuscitation required	n = 84	n = 161	0.056
- None	52 (61.9)	79 (49.1)	
- Yes	32 (38.1)	82 (50.9)	
Postnatal age at initiation of nCPAP*	n = 85	n = 159	0.789
- <2 hours	23 (27.1)	46 (28.9)	
- 2-6 hours	38 (44.7)	77 (48.4)	
- 6-12 hours	15 (17.6)	24 (15.1)	
- >12 hours	9 (10.6)	12 (7.55)	
Crib Score	n = 91	n = 175	<0.001
- ≤10	57 (62.6)	154 (88.0)	
- >10	34 (37.4)	21 (12.0)	
Blood gases†	n = 81	n = 159	
- pH	7.233±0.115	7.256±0.099	0.119
- paCO2 (mmHg)	44.3±18.9	46.0±29.3	0.658
- paO2 (mmHg)	137.3±67.3	161±81	0.022
- Base deficit (mmol/l)	9.0±4.4	7.8±4.1	0.034
C-reactive protein (mg/l)	n = 87	n = 178	0.644
- ≤10	75 (86.2)	157 (88.2)	
- >10	12 (13.8)	21 (11.8)	
Blood culture	n = 97	n = 183	0.601
- Positive	9 (10.1)	15 (8.2)	
- Negative	88 (89.9)	168 (91.8)	

* nCPAP (nasal Continuous Airway Pressure)
† Blood gases (± 2SD)

Amongst all the patients who were managed with nCPAP within the first 72 hours of life, 44 demised whilst on nCPAP and 280 survived either weaning off nCPAP or required intubation for mechanical ventilation. There were more patients with a CRIB score >10 in those who demised than in those who survived (51.2% vs 20.9%, $p<0.001$). Patients who demised had a lower birth weight (944±142g vs 1147±175g, $p<0.001$), were of lower gestation (27±2 vs 29±2 weeks, $p<0.001$), had a lower pH (7.165±0.16 vs 7.25±0.11), a lower PaO2 (120±62 vs 153±77, $p=0.011$), higher base deficit (11.9±6.0 vs 8.2±4.2, $p<0.001$), and a lower median APGAR at 5min (8 [6;9] vs 9 [7;10], $p=0.013$) than those who survived (Table 6). There were no statistically significant differences in other variables between those who demised and those who survived.

Table 6. Comparison of deaths and survivors on nCPAP with or without need for surfactant or intubation*

	Demised on nCPAP (N=44) n (%)	**Did not demise on nCPAP** (N=280) n (%)	**p-value**
Mode of delivery	n = 44	n = 277	0.338
– Vaginal delivery	21 (47.7)	111 (40.1)	
– Caesarean Section	23 (52.3)	166 (59.9)	
Maternal Steroids	n = 24	n = 136	0.063
– Yes	14 (58.3)	104 (76.5)	
– No	10 (41.7)	32 (23.5)	
Gestation (weeks)†	27 ± 2	29 ± 2	<0.001
Weight (grams)†	944±142	1147±175	<0.001
Females	25 (56.8)	139 (49.6)	0.376
Resuscitation required	n = 38	n = 245	0.055
– None	11 (29.7)	114 (46.5)	
– Yes	26 (70.7)	131 (53.5)	
Postnatal age	n = 44	n = 225	0.501
– <2 hours	11 (25.0)	77 (27.5)	
– 2-6	19 (43.2)	143 (51.1)	
– 6-12	9 (20.4)	3 (13.9)	
– >12	5 (11.4)	21 (7.50)	
CRIB Score	n = 41	n = 250	<0.001
– ≤10	19 (48.8)	195 (79.3)	
– >10	22 (51.2)	55 (20.7)	
Blood gases†	n = 41	n = 240	
– pH	7.165±0.163	7.248±0.105	<0.001
– $PaCO_2$	49.9±21.4	45.4±26.2	0.305
– PaO_2	120±62	153±77	0.011
– Base deficit	11.9±6.0	8.2±4.2	<0.001
CRP	n = 28	n = 267	0.418
– ≤10	23 (82.1)	234 (87.5)	
– >10	5 (17.9)	33 (12.4)	
Blood culture	n = 29	n = 272	0.733
– Positive	3 (10.3)	33 (12.1)	
– Negative	26 (89.7)	239 (87.9)	

* One patient outcome not recorded as the last page in her file was missing
† Mean ± SD

DISCUSSION

Very low birth weight infants account for a significant number of infants who require respiratory support soon after delivery. Providing nCPAP has been reported to reduce mortality and the need for intubation for mechanical ventilation in this group of infants.[14] Success or failure rates of nCPAP are often reported in developed countries where it is often initiated soon after delivery and offered in a setting where resources are not restricted; it is usually administered in an NICU setting. In developing countries where resources are limited, nCPAP is often offered outside the NICU setting. Some of the infants may not qualify for NICU and therefore demise on nCPAP in high care. It is therefore important to assess the success or failure rate of nCPAP in a setting where intubation for mechanical ventilation may not always be accessible to those who fail on nCPAP. This study examined the short-term outcomes of babies who were treated with nCPAP, with or without surfactant, outside NICU setting. The short-term outcomes assessed in this report were demise on nCPAP or the need for intubation for mechanical ventilation. This group of patients was labelled as those that failed nCPAP.

The main findings in this study were that 51% of VLBWI (800g-1499g) required nCPAP within the first 72 hours of life and were managed in a high-care nursery. The median age of starting nCPAP was about 3.5 hours of life. Forty eight percent of VLBWI required exogenous surfactant despite receiving nCPAP. Thirteen percent of VLBWI managed with nCPAP demised while receiving nCPAP and 34% of the survivors required invasive mechanical ventilation. The overall nCPAP failure rate was 43%. This report included both deaths and those requiring invasive mechanical ventilation as having failed nCPAP, whereas the other studies have reported the two outcomes separately. This explains why the failure rate in this study appears disparately high. The patients who required invasive mechanical ventilation had a lower median Apgar score at 5 minutes, a higher CRIB score, lower PaO_2 and higher base deficit. Those who demised on nCPAP had a CRIB score more than 10, were of extreme low birth weight, had a lower gestation period, lower pH and PaO_2 and a higher base deficit than the survivors.

Among the VLBWI managed with nCPAP in whom use of antenatal steroids was recorded, less than 50% had received antenatal steroids. This most likely contributed to these infants presenting with severe disease (shown by high CRIB scores), requiring nCPAP and having poor outcomes, because it has been shown that the use of antenatal steroids reduces the

incidence of RDS and mortality in preterm infants.[15] A study conducted in the same institution (CHBAH) in 2005 also reported a low percentage (30%) of mothers being given antenatal steroids.[16]

In settings where NICU facilities are limited, the management of VLBWI outside NICU is feasible. While 13% demised on nCPAP, 66% of survivors were weaned off nCPAP without the need for intubation for mechanical ventilation. Not many studies have reported on the use of nCPAP in VLBWI outside the NICU setting. One study from a developing country reported on the use of nCPAP outside NICU and showed that 92% of ELBW were managed with nCPAP outside the NICU setup with good outcomes.[10] Recently a report from a district hospital showed that managing patients outside NICU is possible and that it improves outcomes and gives an opportunity to offer support while waiting for transport for transfer to a facility with a NICU.[17] This suggests that nCPAP can be safely used in resource-limited settings as a first line of therapy with great benefits.

Forty eight percent of patients who were managed with nCPAP in this report also required exogenous surfactant. This is similar to the 46% reported by Dunn et al.[9] Patients who required exogenous surfactant were smaller and sicker as reflected by higher CRIB scores and had factors that might have inhibited the production or function of surfactant, namely acidosis, resulting in the greater need for surfactant. Randomised trials point towards using early nCPAP as an alternative to surfactant administration in preterm infants with RDS,[18] but in smaller VLBWI the elective administration of surfactant may decrease the need for mechanical ventilation.

A third of patients required intubation for mechanical ventilation despite nCPAP. Other studies have reported higher numbers (40-48%) of patients managed with nCPAP, requiring intubation for mechanical ventilation.[19, 20] The reasons for the lower rates needing mechanical ventilation in this study is most likely due to those neonates weighing <1000g not being considered for ventilation because of limited NICU beds. Other factors associated with a need for intubation for mechanical ventilation in infants managed with nCPAP have been reported to be a high FiO2 ($\geq$0.3) requirement in the first hours of life, and moderate to severe respiratory distress syndrome.[21] The severity of respiratory distress syndrome could be abated by the improved administration of maternal antenatal steroids. This is similar to the findings in this study which showed that a need for invasive mechanical ventilation was associated with high CRIB scores which represents the severity of illness.

Thirteen percent of patients demised on nCPAP. Most of these deaths were babies who were of lower gestation and birth weight. In areas where resources are limited, infants at borders of viability are often not offered invasive mechanical ventilation in NICU. For example, in the setting where this study was conducted, neonates <900g are generally not offered invasive mechanical ventilation and the highest ventilatory support they can get is nCPAP. In this study, that amounted to 13.5% (44) of patients. The mortality rate of 13% on nCPAP reported in this study is higher than that reported by Kirsten et al.[10] who state a mortality rate of 8%. The explanation for this difference could be due to differences in the severity of illness and gestational age which are reflected in the CRIB score. The study included neonates with birth weight from 500g. This study by Kirsten did not report on the CRIB score of babies studied. At Tygerberg hospital, the cut-off weight for neonates receiving surfactant, and admission into NICU is lower (750g) but it is stated that this is only applicable under exceptional circumstances and if there is an availability of NICU beds. That in itself could decrease their mortality rates when compared to CHBAH, where the admission to NICU is at best 900g, and the administration of surfactant is reserved for those >800g. Use of antenatal maternal steroids has been shown, in the study mentioned, to contribute significantly to the survival of neonates ≥750g or ≤25weeks' gestation, whereas in this study, it was found not to be significant. Outcomes were defined differently in the Tygerberg study. Kirsten et al defined nCPAP failure as the need for mechanical ventilation, and excluded death. This study included death on nCPAP as well as intubation for mechanical ventilation as nCPAP failure.

There are some limitations in the data collection in this study. The retrospective design of the study led to one being unable to retrieve all the files. Some files were missing from the filing room and others had data missing or were incomplete. This is, however, unlikely to have affected the results of this report as a significant number (79%) of files of VLBWI were retrieved. The missing data was <20% for most variables except for antenatal steroids.

CONCLUSION

The use of nCPAP in VLBWI can be applied outside NICU setting with reasonable short term outcomes. It is effective in the management of respiratory distress as about 87% of patients survive on nCPAP; about a third of those who survived on nCPAP ended up requiring invasive mechanical ventilation. The patients who demised on nCPAP were those of lower gestation and who presented with severe illness. The ones who demised with lower gestation were most likely not offered invasive mechanical ventilation because of limited NICU beds. The high failure rate on nCPAP which included deaths is therefore partly related to inadequate resources. There is therefore a need to improve access to invasive mechanical ventilation to fully appreciate the impact of providing nCPAP, especially to those who are of lower gestation and are critically ill.

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APPENDIX A: SAJCH SUBMISSION GUIDELINES



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APPENDIX B: PROTOCOL

BACKGROUND

Respiratory distress is a common clinical presentation of premature babies that manifests shortly after birth. Some of the causes of distress are respiratory distress syndrome (RDS) or hyaline membrane disease (HMD), transient tachypnea of the newborn (TTN) and congenital pneumonia. RDS develops when the infant attempts to take their first breath to ventilate an immature lung. There are several factors that worsen this condition, which include; an insufficient production of surfactant to cover the entire surface area of the lung, the weakness of the chest wall, immature alveoli and few alveolar ducts (2). Surfactant is produced by the type II pneumocytes, which are airway epithelial cells in the lung, stored in lamellar bodies and secreted as tubular myelin. Surfactant forms a monolayer at the air-water interface which serves to decrease the surface tension upon inspiration and prevent the collapse of open alveoli during expiration.

Lack of or insufficient production of surfactant predisposes the alveolus to collapse and increases the pressure needed to inflate the airways. The work of breathing is increased & the lung becomes stiff. The Laplace relationship explains this. It states that the pressure difference (P) across a curved surface, needed to maintain a given radius (r), is inversely proportional to the radius and directly related to twice the surface tension (P=2ST/r) (2, 3). The infant then presents with respiratory distress and failure.

Surfactant is composed of phospholipids (75% to 80%), proteins (10%) and lipids (10%). The phospholipid component of surfactant dipalmitoylphosphatidylcholine (mainly DPPC) is responsible for forming surface active films, and providing the scaffolding needed for other components of surfactant to assemble at the air-liquid interface of the alveolus. There are four surfactant apoproteins, SP-A, SP-B, SP-C, SP-D. SP-B & SP-C are hydrophobic membrane proteins that are responsible for the rate of surfactant spread over the surface area of the alveoli. They are required for proper biophysical function of the lung. SP-A & SP-D have an immunological function and are able to bind to the surface of multiple pathogens, bacteria, viruses, fungi, contributing to their elimination from the airways(4).

Exogenous surfactant preparations available in South Africa are Beractant, a bovine derivative & Poractant, a porcine derivative. Both are natural surfactants. They are derived from minced animal lungs (5). The classic way to administer the surfactant is via a

nasogastric tube fed through an endotracheal tube. This is followed by either continued mechanical ventilation or extubation, and connection to nasal continuous positive airway pressure (nCPAP). Among infants with early RDS (those with an inspired oxygen requirement of >40%), surfactant administration via transient intubation with rapid extubation to nCPAP (INSURE) reduces the need for mechanical ventilation by up to 40% (6). Exogenous surfactant therapy is effective in reducing RDS mortality and morbidity in preterm infants (7). The risk of RDS increases with decreasing gestational age. Factors such as maternal diabetes, white race, male sex, asphyxia, and sepsis increase the risk of RDS, while antenatal steroids and prolonged rupture of membranes decrease the risk(2).

Continuous positive airway pressure (CPAP) was first used as a form of supporting the respiration of preterm infants in 1971(8). Several routes of administration have been attempted but the nasal route is largely used, because it allows for better access to the infant. The physiological effects of nasal CPAP (nCPAP) include increasing functional residual capacity, hence improving oxygenation and maintaining lung volume, lowering upper airway resistance, and reducing obstructive apnea(9). Nasal CPAP is used widely for a range of neonatal respiratory conditions. Increasingly nCPAP is being used as a non-invasive form of ventilation and it has been shown to be an alternative to intubation and mechanical ventilation for the management of respiratory distress syndrome. These studies have reported a survival rate of approximately 90% in infants of gestation of 25-28 weeks managed with nCPAP (10). There are no clear definitions of NC PAP failure in the literature, when it is used for supporting babies with RDS or preventing re-intubation after extubation. Typical 'failure' criteria for those infants treated with nCPAP for early RDS include; persistent apneic episodes, PaCO2 of >=60mmHg, FiO2 of >=0.6 to maintain adequate oxygen saturation.

Most of the studies reporting on outcomes of very low birth weight infants managed with nCPAP with or without surfactant have been conducted in developed countries, where these infants are managed in an intensive care unit with adequate resources.

JUSTIFICATION FOR THE STUDY

The current protocol of managing VLBW infants with respiratory distress at CHBAH is to offer nCPAP to all VLBW babies weighing 800g or above who are breathing spontaneously with signs of respiratory distress. Exogenous surfactant is administered to these babies if they fail to wean to less than 40% supplemental oxygen to maintain oxygen saturations >88% in the first 2 hours of life. Babies are referred for mechanical ventilation if the paCO2 is more

than 55 mmHg and pH <7.25 or paCO2 >60, requires >60% supplemental oxygen to maintain saturations >88%, or requires a second dose of surfactant. Conventional mechanical ventilation is only offered to those weighing >900 grams due to limited intensive care beds.
There are a significant number of premature infants born at Chris Hani Baragwanath Academic Hospital (CHBAH), especially those that are in need of respiratory support. The current bed status of the neonatal ICU at CHBAH is incapable of catering for all the neonates that require respiratory support. Patients who are admitted in NICU are nursed with a staff ratio of 1 professional nurse to 2 patients irrespective of whether they are on CPAP or conventional mechanical ventilation, whereas those who are nursed in high care nursery are nursed by any category of nurse including nursing assistants and enrolled nurses.

Study done at CHBAH looking at survival of infants weighing between 500g – 1499g (10) reported that the high mortality rate in the extremely low birth weight category was attributed mainly to the fact that ventilation was not offered to these babies. At that time nCPAP was not offered to babies below 1000g. We would like to retrospectively analyse the outcomes of VLBW infants following the increase in the use of nCPAP and surfactant in babies weighing below 1500 grams and to determine the factors associated with outcomes so that one can use these limited resources appropriately.

AIM

To determine the characteristics and outcomes of very low birth weight (VLBW) babies weighing between 800g and 1499 grams managed with nasal continuous positive airway pressure (nCPAP) with or without surfactant in a high care nursery at Chris Hani Baragwanath Academic Hospital.

OBJECTIVES

1. To determine the proportion of VLBW babies (800g -1499 grams) who were managed with nCPAP in high care nursery.
2. To determine the proportion of VLBW (800g- 1499g) babies who were given surfactant while receiving nCPAP in high care nursery. To compare characteristics and outcomes of those that received surfactant to those that did not.
3. To determine demographic and clinical characteristics of VLBW (800g- 1499g) babies managed with nCPAP in high care nursery.
4. To determine the proportion of VLBW (800g- 1499g) babies who were weaned off nCPAP while in the high care nursery.

5. To determine the proportion of VLBW (800g- 1499g) babies who were managed with nCPAP in high care nursery and were subsequently transferred to NICU (CHBAH or other health care centres) for conventional mechanical ventilation (failed nCPAP).
6. To determine the proportion of VLBW (800g- 1499g) babies who demised in high care nursery while receiving nCPAP.
7. To compare demographic and clinical characteristics (including gestational age) of those VLBW (800g- 1499g) babies who weaned off nCPAP while in high care nursery and those who either demised or failed nCPAP.

METHODS

Study design

Retrospective descriptive study, through conducting a review of hospital records of VLBW (800g-1499g) infants admitted to the high care nursery at Chris Hani Baragwanath who were managed with nCPAP with or without surfactant during the period 01 January 2012 to 31 December 2012.

Patient population

All babies who were admitted to Chris Hani Baragwanath Hospital neonatal unit with a birth weight 800g - 1499g, who were managed with nCPAP with or without surfactant.

Inclusion criteria

a. Infants weighing (800g- 1499g)
b. Infant who received nCPAP either from labour ward nursery, ward 66 or while in high care nursery within the first 72 hours of life.

Exclusion criteria

a. Absent or incomplete patient records where final outcome is not recorded
b. VLBW (800g- 1499g) babies extubated to nCPAP after conventional mechanical ventilation

Study procedures and data collection

Records of all VLBW (800g-1499g) infants will be retrieved. Data will be collected from records of VLBW (800g-1499g) who were admitted between 01 January and 31 December 2012. Patients' details will be sourced from the records department. A data collection capture sheet will be used (appendix). Patient will be identified by study numbers, to uphold confidentiality. The data sheet will capture demographic information, antenatal management, maternal demographic information, clinical diagnosis, investigations (blood gases, full blood counts, CRPs, blood cultures), admission to either ICU or transitional unit, what interventions

were given, and the outcome of the patient (weaned off CPAP in high care, transferred for mechanical ventilation while on nCPAP, demised or survived to hospital discharge).

Data analysis

Data will be entered into a Microsoft Excel spreadsheet and basic statistical analysis will be performed using Microsoft Excel. Appropriate descriptive statistical analysis using percentages, means and standard deviations and medians and ranges will be used for demographic data. For comparisons the Student t-test, Mann-Whitney and Chi squared tests will be used using STATA. A statistician will be consulted for further assistance if needed.

ETHICS APPROVAL

The proposal for this study will be submitted to the Postgraduate Committee of the University of the Witwatersrand and the hospital protocol review committee. It will also be submitted to the Human Research Ethical Committee (HREC) of the University of the Witwatersrand for ethics approval. As this is a retrospective audit, no consent will need to be obtained from individual patients. Data sheets will only contain a study number. The patient's name and file numbers will be stored in a separate database at a different, secure location so that only the investigator and the supervisor will have access to this information.

COST/FUNDING

The cost for the study includes the use of stationary e.g. paper for photocopying/printing, binding. This cost will be the investigators responsibility as there is no external funding.

TIMELINE

	Feb 2013	Mar 2013	April 2013	May 2013	June 2013	July 2013	Aug 2013	Sept 2013
Literature Review								
Protocol Preparation								
Protocol Assessment								
Ethics Application								
Response to Committee								

	Oct 2013	Nov 2013	Dec 2013	Jan 2014	Feb 2014	Mar/Apr 2014	May/Jun 2014	Jul/Aug 2014
Data Collection								
Data Analysis								
Write up Paper								

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APPENDIX C: ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Thokozile Bopape-Chinyanga

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130744

NAME: (Principal Investigator)	Dr Thokozile Bopape-Chinyanga
DEPARTMENT:	Paediatrics and Child Health University of Witwatersrand Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Outcome of Very Low Birth Weight Babies managed with Nasal Continous Positive Airway Pressure with or without Surfactant in a High Care Nursery
DATE CONSIDERED:	26/07/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof S Velaphi
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	02/08/2013

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 _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES