RESEARCH PAPER

Bubble CPAP for Respiratory Distress Syndrome in Preterm Infants

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Objectives: To ascertain the immediate outcome of preterm infants with respiratory distress syndrome (RDS) on Bubble CPAP and identify risk factors associated with its failure.

Study design: Prospective analytical study.

Subjects: Inborn preterm infants (gestation 28 to 34 weeks) admitted to the NICU with respiratory distress and chest *X*- ray suggestive of RDS.

Intervention: Bubble CPAP with bi-nasal prongs.

Primary outcome: CPAP failures-infants requiring ventilation in the first one week.

Results: 56 neonates were enrolled in the study. 14 (25%) babies failed CPAP. The predictors of failure were; no or only partial exposure to antenatal steroids, white-out on the chest *X*-ray, patent ductus arteriosus, sepsis/pneumonia and Downe's score >7 or FiO_2 ≥50% after 15-20 minutes of CPAP. Other maternal and neonatal variables did not influence the need for ventilation. Rates of mortality and duration of oxygen requirement was significantly higher in babies who failed CPAP. Only two infants developed pneumothorax. No baby had chronic lung disease.

Conclusion: Infants with no or partial exposure to antenatal steroids, white-out chest *X*-ray, patent ductus arteriosus, sepsis/pneumonia and those with higher FiO_2 requirement after initial stabilization on CPAP are at high risk of CPAP failure (needing mechanical ventilation). Bubble CPAP is safe for preterm infants with RDS.

Key words: Bubble CPAP, CPAP failure, Management, Prematurity, Respiratory distress syndrome.

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Continuous positive airway pressure (CPAP), when applied to premature infants with Respiratory distress syndrome (RDS), re-expands collapsed alveoli, splints the airway, reduces work of breathing and improves the pattern and regularity of respiration(1). Atelecto-trauma (repeated opening and collapse of the alveoli), biotrauma (intubation of the airway) and volutrauma (overstretching of the alveoli), the key determinants of ventilator induced lung injury are minimal or absent in gentler modes of ventilation such as nasal CPAP(2,3). Bubble CPAP, when used appropriately, is more cost effective, less intensive, requires less training and has lower risk of complications. However, not all preterm infants with RDS respond to CPAP(4). We conducted this prospective analytical study to evaluate the immediate outcome of preterm infants (gestation 28 to 34 weeks) with RDS on Bubble CPAP, and to study the risk factors associated with failure of Bubble CPAP.

METHODS

The study was conducted at a level III neonatal unit between April 2007 to May 2008. Bubble CPAP for the treatment of RDS was available in the unit for 6 months before the start of the study.

Accompanying Editorial: Pages 129-130.

All consecutively born preterm infants with gestation between 28 to 34 weeks, admitted to the neonatal intensive care unit with respiratory distress and chest *X*-ray suggestive of respiratory distress syndrome (RDS) were included. Babies requiring intubation at birth and those with major malformation were excluded. If the parents opted for non-aggressive management in the antenatal counseling or refused consent, such babies were not included in the trial. Eligible babies were started on Bubble CPAP with bi-nasal prongs (Fisher and Paykel Healthcare, New Zealand). PEEP was started at 5 cm of water and adjusted to minimize chest retractions. FiO_2 was adjusted to maintain SpO_2 between 87% and 95%. Flow was titrated to the minimum to produce continuous bubbling in the bubble chamber. Surfactant was administered by INSURE technique (Intubate, Surfactant and Extubate after 3 to 5 minutes of intermittent positive pressure ventilation). Surfactant was given for babies with moderate or severe RDS on the chest *X*-ray and or FiO_2 requirement >30%.

Bubble CPAP was considered to be successful if the respiratory distress improved and the baby could be successfully weaned off from CPAP. The criteria for weaning was absence of respiratory distress (minimal or no retractions and respiratory rate between 30 and 60 per minute) and, SpO_2>90% on FiO_2 <30% and PEEP <5 cm of water. Infants were diagnosed to have failed CPAP and were started on mechanical ventilation when they: (*a*) remained hypoxic, i.e. SpO_2<87% despite FiO_2>70% and PEEP >7cm of water; (*b*) had severe retractions on PEEP >7cm of water; (*c*) had prolonged (>20 seconds) or recurrent apneas (>2 episodes within 24 hours associated with bradycardia) requiring bag and mask ventilation; and, (*d*) had severe metabolic acidosis or shock requiring inotropic support (dopamine and or dobutamine) >20µg/kg/min. Infants failing CPAP in the first 1 week of life were considered to be CPAP failures.

Data collection of maternal variables included multiple births, pregnancy induced hypertension, preterm premature rupture of membrane, cesarean section and antenatal steroids. Gestational age was calculated based on mothers last menstrual period and or early pregnancy ultrasound scan or New Ballard score. Infant variables evaluated included birth weight, gestational age, presence of IUGR (weight <10th on Lubchenko percentile), Apgar score at 1minute, delivery room management (oxygen, bag and mask, intubation), *X*-ray chest, arterial blood gas, FiO_2 requirement and Downe's score at 15 to 20 minutes of starting CPAP. Based on radiological findings, the severity of RDS was graded as mild (mild granularity of lungs), moderate (generalized granularity of lungs with air bronchogram with preserved cardiac borders) and severe (white out lungs with loss of cardiac borders). The other clinical data recorded are patent ductus arteriosus (PDA) (clinical and Echo proven), pneumothorax, culture positive sepsis, pneumonia, necrotizing enterocolitis (NEC) (modified Bells criteria), chronic lung disease (oxygen requirement at 36 weeks PMA), germinal matrix - intraventricular hemorrhage (IVH), periventricular leucomalacia (PVL) (neurosonogram before day 7, at discharge and at 40 weeks PMA), retinopathy of prematurity (ROP) of any grade, duration of hospital stay among the survivors, and mortality.

The study assessed the following outcomes: CPAP failure, mortality, incidence of pneumothorax, IVH, PVL, ROP, CLD, duration of hospital stay and predictors of CPAP failure. Variables distributed normally are represented as mean ± SD and the others as medians (range). Maternal, infant and clinical data was compared between infants who succeeded CPAP with CPAP failures. P value <0.05 was considered to be significant. The study was approved by the institute ethics committee and informed consent was obtained from either the father or a guardian.

RESULTS

We enrolled 56 neonates in the study. The mean gestation was 30.98±2 weeks and mean birthweight was 1387 ± 402 grams. 51 mothers received either 1 (*n*=7, 12.5%) or 2 doses (*n*=44, 78.6%) of antenatal steroids (***Table* 1**). The median age of starting CPAP was 1.7 hours of life. 30 (53.6%), 10 (17.9%) and 16 (28.6%) babies had chest *X*-ray findings suggestive of mild, moderate and severe RDS, respectively. INSURE was done in 55.4% (31 babies) and the median age of surfactant administration was 3 hrs

TABLE I BASELINE CHARACTERISTICS OF PARTICIPANTS

Characterstic	*n* (%)
Males	31 (55.4)
IUGR	06 (10.7)
Multiple pregnancies	10 (18)
Gestation ≤30 weeks	22 (39.3)
VLBW (weight ≤1500g)	31 (55.3)
ELBW (weight ≤1000g)	10 (17.9)
Maternal hypertension	17 (30.4)
Premature rupture of membranes	12 (21.4)
Preterm labor	04 (7.1)
Cesarean section	45 (80.4)
Fetal distress	21 (37.5)
Antenatal steroids	51 (91.1)
1 minute Apgar ≤3	4 (7.1)
5 minute Apgar ≤3	1 (1.8)
Bag and mask at birth	7 (12.5)

(range 1 hr to 15 hrs of life). The median duration of CPAP was 23.5 hours (range 2 -144 h). In infants surviving till discharge, the median duration of oxygen requirement was 102 (range 13-504 h) and median duration of hospital stay was 11 days (range 3-37 days). No baby had chronic lung disease. 3 (5%) developed retinopathy of prematurity but none required laser therapy.

Fourteen (25%) babies failed CPAP. Of the 14 infants, in 4 (7%) ventilation was started after an initial recovery from CPAP. Six (11%) babies died during the hospital stay. The variables associated with failure of CPAP were: no or only partial exposure to antenatal steroids (RR 3, 95% CI 1.2 - 7.8), whiteout on the chest *X*-ray (RR 3.9, 95% CI 1.8-8.4), patent ductus arteriosus (RR 3, 95% CI 1.02-8.8), sepsis/pneumonia (RR 7.5, 95% CI 1.6-34) and Downe's score >7 or FiO_2 ≥50% after 15 to 20 minutes of CPAP (RR 1.6, 95% CI 1.1-2.6). Other maternal and neonatal variables did not influence the need for ventilation (***Table* II**). Mortality was higher in the babies who required ventilation. In infants surviving till discharge, duration of hospital stay was longer in babies who failed CPAP (***Table* III**).

DISCUSSION

This is one of the few prospective studies on the role of Bubble CPAP for RDS in preterm neonates (gestation 28 to 34 weeks). In our study 25% of babies started on Bubble CPAP required ventilation. No baby required oxygen for more than 28 days. Only two babies had pneumothorax but both these babies were stabilized on Bubble CPAP and required neither ventilation nor chest tube drainage. No exposure to antenatal steroids, severe RDS as suggested by white out *X*-ray, presence of PDA, sepsis/pneumonia, higher FiO_2 and persisting distress after stabilization on CPAP, are the early predictors of CPAP failure.

In a retrospective study by Ammari, *et al.*(5), the failure rate of Bubble CPAP was 24% in babies' ≤1250g and 50% in babies ≤750g. None of the babies with gestation >30 weeks failed CPAP. In their study nearly 65% of the babies were ELBW and 85.5% of babies had gestation less than 30 weeks as against 17.9% and 39.3% respectively in our study. The main difference between our study and that by Ammari, *et al.*(5) are, (*a*) ours is a unit which is doing Bubble CPAP for RDS for 6 months before the onset of the study, (*b*) we used Fisher and Paykel nasal prongs while it was Hudson prongs in their study, (*c*) definition of CPAP failure included FiO_2 >70% and PEEP >7cm for the first 7 days of life as against FiO_2 >60% for the first 72 hours of life. No PEEP criteria were set in their study. These major differences might explain the differences in failure rates in the two studies. Since most events in the early neonatal period are reflections of the care and support in the first couple of days, we choose 7 days as the cut off for CPAP failures.

In other uncontrolled studies and in the studies comparing INSURE with ventilation, CPAP failure rate ranged from 14% to 40%(4). The difference may be attributed to birthweight and gestation of infants enrolled, type of nasal interface, the CPAP device, age of starting CPAP, and use of antenatal steroids and surfactant. In the study by Ammari, *et al.*(5), the predictors of CPAP failure were (*i*) need for positive pressure ventilation at birth; (*ii*) alveolar to arterial oxygen difference (A-a DO_2) >180mm of Hg on the first blood gas; and (*iii*) severe RDS on the initial chest *X*-ray. Similar to their study, parameters of severe lung disease such as white out chest *X*-ray, higher FiO_2 requirement and higher Downe's score

TABLE II MATERNAL AND NEONATAL VARIABLES AMONG NEONATES WITH CPAP SOURSES AND CPAP FAILURE

Variable	CPAP Success *n*=42 (%)	CPAP failures *n*=14 (%)	*P* value
Birthweight (g) (mean±SD)	1360±357	1467±520	0.39
Gestation (wk) (mean±SD)	30.9±1.9	31.1±2.5	0.73
Male	21 (50)	10 (71)	0.22
Twins/triplets	8 (19)	2 (14)	0.50
Birthweight ≤1500 g	23 (54.8)	8 (57)	0.92
Birthweight ≤1000 g	7 (16.7)	3 (21)	0.90
Gestation≤30 wk	16 (38)	6 (43)	0.76
Partial/no antenatal steroids	6 (14)	6 (43)	0.02
PROM	9 (21)	3 (21)	1.0
Maternal hypertension	12 (29)	5 (36)	0.74
Cesarean delivery	34 (81)	11 (79)	0.79
Apgar 1min ≤3	4 (9)	0 (0)	0.56
Chest X-ray Severe RDS	7 (17)	9 (64)	0.001
Age at CPAP (hours) (mean±SD)	2.07±1.6	2.34±1.5	0.58
FiO_2 at 15-20min of CPAP (mean±SD)	46.2±20	64.1±24	0.008
PEEP at 15-20min of CPAP (mean±SD)	4.9±0.6	5.2±0.4	0.10
Downe's >7 at 15-20min of CPAP	0 (0)	4 (29)	0.003
FiO_2 ≥50% at 15-20min of CPAP	20 (48)	11 (79)	0.04
Surfactant	21 (50)	10 (71)	0.22
Age at surfactant (hrs) (mean±SD)	3.5±1.9	4.8±4.1	0.23
Patent ductus arteriosus	5 (12)	5 (36)	0.04
Sepsis/pneumonia	2 (4.8)	5 (36)	0.007

were associated with CPAP failure in our study. In comparison with A-a DO_2, we feel FiO_2 requirement and Downe's scoring are more clinically relevant and easily assessable variables.

In a case-control study by Boo, *et al*.(6), of the 97 preterm babies (gestation <37 weeks) with RDS on ventilator CPAP or Bubble CPAP, 38% failed CPAP and required ventilator support. Babies were given ventilator support for hypoxia (SpO_2 <90%) on FiO_2 ≥90%. Only 34% of the infants in their study received antenatal steroids and the authors did not report the usage of surfactant in their study. Similar to our study and that by Ammari, *et al*.(5) severe RDS on the chest *X*-ray was an important predictor of CPAP failure. Pneumothorax and septicemia was higher in the CPAP failures. Although septicemia predicted CPAP failure in our study too, pneumothorax was seen in 2 babies in the success group. The higher failure rates in the study by Boo, *et al*.(6) may be attributed to inadequate usage of antenatal steroids and may be due to lesser use of surfactant.

We conclude that Bubble CPAP for RDS in moderately preterm babies is safe and associated with lesser lung injury (no CLD or prolonged

TABLE III IMMEDIATE OUTCOMES

Outcome	CPAP Success *n*=42 (%)	CPAP failures *n*=14 (%)	*P* value
Pneumothorax	2 (4.7)	0	1.00
Apnea	6 (14.3)	4 (28.6)	0.25
IVH/PVL	0	2 (14)	0.06
Shock	0	2 (14)	0.06
Duration of oxygen (h)*	104±103	196±105	0.02
Hospital stay (d)*	12±7.5	16.8±8	0.11
Mortality	1 (2.4)	5 (35.7)	0.002

**Mean ± SD*

WHAT IS ALREADY KNOWN?

- CPAP is a safe and effective treatment modality for preterm infants with RDS.

WHAT THIS STUDY ADDS?

- The probability of Bubble CPAP failure in preterm neonate is higher in those with no or partial exposure to antenatal steroids, whiteout on the chest X-ray, patent ductus arteriosus, sepsis/pneumonia, FiO_2 requirement ≥50% or Downe's score >7 after 15 to 20 minutes of CPAP.

oxygen requirement). Nearly 25% of these infants fail CPAP and the predictors for failure are no exposure to antenatal steroids, severe RDS, presence of PDA or sepsis, persisting FiO_2 ≥50% or persisting distress even after stabilization on CPAP.

Contributors: SM and DRR designed the study. JK recruited the subjects and collected the data. SM, PG and AR monitored the patient recruitment and data collection. JK and SM analyzed data and wrote the manuscript with inputs from DRR, AR, PG. All authors approved the final manuscript.

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