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Original Article

Paediatrics Section

A Randomized Trial Comparing Efficacy of Bubble and Ventilator Derived Nasal CPAP in Very Low Birth Weight Neonates with Respiratory Distress

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ABSTRACT

Introduction: Continuous Positive Airway Pressure (CPAP) has an established role in the care of Very Low Birth Weight (VLBW) babies with respiratory distress. Bubble CPAP (BCPAP) is a cheap alternative for countries where resources are limited. However, data comparing efficacy of BCPAP with conventional ventilator derived (VCPAP) is limited.

Aim: To compare CPAP failure rates between BCPAP and VCPAP among VLBW, with moderate respiratory distress. Secondary objectives were to compare the rates of Intraventricular Haemorrhage (IVH), pulmonary air leaks and deaths between the two groups and determine the predictors of CPAP failure.

Materials and Methods: VLBW babies with moderate respiratory distress (Silverman Anderson score 4-7), born or admitted in Neonatal Intensive Care Unit (NICU) within 28 days of life were randomized to receive either BCPAP (n=34) or VCPAP (n=34). CPAP failure rate in both the groups was compared.

Results: The baseline characteristics were similar in both the groups. Five out of 34 (14.70%) babies in BCPAP group and 11 out of 34 (32.35%) in VCPAP failed CPAP (p=0.08). IVH (BCPAP group 24% and VCPAP group 9%, p= 0.10) and mortality (BCPAP group 6% and VCPAP group 9%, p=0.642) were comparable in both the groups. Factors such as gestational age <30 weeks, weight <1000 grams, Respiratory Distress Syndrome (RDS), shock, pulmonary haemorrhage, Disseminated Intravascular Coagulation (DIC) and multi-organ dysfunction were significantly associated with CPAP failure in our study.

Conclusion: The CPAP failure rates in VLBW babies with moderate respiratory distress were found to be similar whether bubble CPAP or ventilator CPAP was used. There was no difference in complication rates of IVH or mortality with either method of CPAP.

Keywords: Failure rate, Newborn, Pressure delivery system

INTRODUCTION

Nasal continuous Positive Airway Pressure (n CPAP) has revolutionized the care and outcomes of preterm Very Low Birth Weight (VLBW) babies. Ever since the discovery of bubble CPAP in 1971 [1], research in the field continues till date to find the most effective and safe method of pressure generation and delivery interface for optimizing short and long term outcomes of VLBW babies. An array of nasal interface devices and modes of pressure generation have been developed and investigated. Although review of trials has found that short binasal prongs are better than single prong CPAP, the optimal method of pressure delivery system is still unclear [2]. Techniques for CPAP generation include constant flow devices such as Ventilator derived CPAP (VCPAP) and underwater 'Bubble' CPAP, or variable flow devices such as Benveniste device and Infant Flow Driver (IFD) [3].

Ventilator-derived nasal CPAP (VCPAP) and underwater BCPAP are the commonly used methods for delivery of CPAP in our country. It has been shown that BCPAP is as effective as IFD in the post-extubation management of infants with Respiratory Distress Syndrome (RDS) [4]. Bhatti et al., in their study on jet CPAP (variable flow) vs BCPAP in preterm neonates with RDS observed similar CPAP failure rates with either of the devices [5]. Safety and cost effectiveness of bubble CPAP have popularized this method of CPAP delivery in peri-extubation period in developing countries [6,7]. However, only few randomized trials have compared the VCPAP with BCPAP in treatment of respiratory distress in preterm neonates [6-11].

The present randomized controlled trial was designed to compare BCPAP and VCPAP in terms of CPAP failure rate among VLBW with moderate respiratory distress. The secondary objectives were to compare the rates of IVH, pulmonary air leaks and deaths between the two groups and determine the predictors of CPAP failure.

MATERIALS AND METHODS

The present study was conducted at a tertiary level referral Neonatal Intensive Care Unit (NICU) of Northern India from September 2009 to July 2011. The study protocol was approved by institutional ethics committee. Written informed consent was taken from parents of all eligible babies.

Any baby with birth weight < 1500 g and moderate respiratory distress in the neonatal period was eligible for enrolment. Gestation was assessed by New Ballard score and in home deliveries where birth weight was not known, admission weight was taken as the baseline characteristic. Respiratory distress was considered moderate if Silverman score was ≥ 4. Babies with severe respiratory distress requiring mechanical ventilation (Silverman score ≥7) or who had received mechanical ventilation within previous one week or who had major congenital malformations (tracheo - oesophageal fistula/ congenital diaphragmatic hernia/ upper airway obstruction/ major cardiovascular/central nervous system/neuro-muscular abnormalities) or whose attendants refused for consent were excluded from the study.

A sample size of 34 babies for each of the study and control groups was arrived at an estimated failure rate of about 45% in VCPAP group and desiring an absolute reduction of about 30% failure rate in favour of BCPAP with 80% power and 5% type-I error [12].

Computer generated random number sequence was generated by a person not otherwise involved with the study, using STATA 9.0 version. Allocation concealment was achieved using sequentially numbered, opaque, sealed and stapled envelopes that were opened by the primary investigator and babies were randomized into bubble-CPAP or ventilator-CPAP. Given the nature of interventions, blinding in the study to the allocation status of baby was not possible.

CPAP Protocol

Ventilater derived Continuous Positive Airway Pressure (CPAP) was delivered by Newport (model-E100M, California, USA) ventilator. BCPAP was delivered by Fischer and Paykel (model-MR 850 AEU, Auckland, New Zealand). Disposable nasal CPAP prongs (Argyle, Hudson Binasal or Fisher & Paykel) were used based on internal diameter of nose in either group depending upon the availability. CPAP was initiated at a pressure of 4cm H_2O in babies <1000 g and at 5cm H_2O in those between 1000-1500g in both the groups. CPAP was optimized by stepwise increase of 1cm H_2O at a time until the respiratory distress ceased or a ceiling pressure of 7cm H_2O was reached. Starting with a FiO_2 of 0.30, and a flow of 6-8l/min, oxygen was adjusted appropriately to maintain oxygen saturation (SpO_2) between 90%-94%. CPAP was considered optimal if baby seemed comfortable with absent or minimal retractions, maintaining oxygen saturation, capillary refill <3 sec, normal vitals and urine output. A maximum CPAP of 7cm H_2O and FiO_2 of 0.60 was used. On improvement of the baby's underlying clinical condition FiO_2 was first decreased followed by weaning of pressure by 1 cm H_2O at a time to the minimum required. If the patient remained stable for 12 hours at CPAP of 4 and Fio_2 < 30%, an attempt was made to discontinue CPAP and place the neonate in air or ambient oxygen or on low flow nasal cannula at a flow of < 1L/min or in oxygen hood to maintain saturation between 90% to 94%.

CPAP failure was defined as inability of a baby to maintain SpO_2>90% or arterial partial pressure (PaO_2) > 50 mmHg at a maximum CPAP of >7cm of water at a FiO_2>0.6 or requiring mechanical ventilation. CPAP failure percent rate was calculated as the number of babies who failed CPAP/total of number of babies receiving that type of CPAP. CPAP therapy was considered successful if the baby did not require any respiratory support after weaning for at least seven days. If any baby required CPAP more than once after seven days of CPAP free period, he was allocated the same type of CPAP which he was initially allocated to and each episode was considered as a new episode.

Neonatologist trained in craniosonography performed bedside ultrasound, first within 24 hours of start of CPAP and then within two days after stopping of CPAP to look for IVH. Initial chest x-ray was performed in all babies not later than six hours of starting CPAP. Subsequently chest x-ray was repeated as considered clinically necessary. Demographic data and associated co-morbidities and outcomes were recorded.

Statistical analysis was conducted by using statistical software SPSS version 18.0 (Inc. Chicago, IL USA). Chi- square test was used to analyse categorical variables, while Mann-Whitney U test was applied for continuous variables.

RESULTS

A total of 96 VLBW babies with respiratory distress were screened for eligibility during the study period. Of the total 28 were excluded for reasons such as mechanically ventilated or congenital malformations. Remaining 68 neonates were randomized to receive VCPAP or BCPAP. Baseline characteristics were similarly distributed in both groups [Table/Fig-1].

Characteristics (Frequency,%)]/(mean ± SD)		Ventilator-CPAP (n=34). (Frequency, %)	Bubble-CPAP (n=34). (Frequency,%)
Sex	Male	24 (71)	11 (32)
Admission age	(<24 hrs)	18 (53)	17 (50)
	24hrs-7days	13 (38)	15 (44)
	>7 days	3 (9)	2 (6)
Gestational age	< 30 weeks	14 (41)	8 (23)
	> 30 weeks	20 (59)	26 (76)
Admission Weight.	(mean ± SD)	1.214±0.25	1.264±0.161
	<1000 gm	9(26)	2 (6)
	1000-<1500gm	25 (74)	32 (94)
Place of delivery	Home	10 (29)	3 (9)
	Hospital	24 (71)	31 (91)
Mode of delivery	Vaginal	29 (85)	32 (94)
	LSCS	5 (15)	2 (6)
Birth asphyxia	Moderate	3 (9)	9 (26)
Antenatal steroid (incomplete/complete)		15 (44)	16 (47)
Prior surfactant received		0	1 (3)
Vital parameters and blood sugar at admission time	Severe hypothermia	1 (3)	2 (6)
	Moderate hypothermia	14 (41)	10 (29)
	Cold stress	6 (18)	11 (32)
	Saturation <88%	10 (29)	9 (26)
	Delayed perfusion	9 (26)	6 (18)
	Hypoglycemia	3 (9)	0
Silverman score (mean ± SD)		4.647±0.774	4.529±0.507
	RDS	13 (38)	7 (20)
	Pneumonia	7 (21)	10 (29)

[Table/Fig-1]: Baseline characteristics of study population.
CPAP = Continuous positive airway pressure; SD = Standard deviation; LSCS = Lower segment caesarian section; RDS = Respiratory distress syndrome.

The failure rate with BCPAP was 14.70% (5 out of 34) as compared to 32.35% (11 out of 34) with VCPAP. However, this difference of 17.65% was not statistically significant (p= 0.08). IVH as a complication occurred more frequently in the BCPAP group-24% (8), compared to 9% (3) in VCPAP Group (p= 0.10). No babies developed pulmonary air leak in either of the group. Mortality in both groups was similar 6% (2) in BCPAP and 9% (3) in VCPAP, p=0.642).

We observed a trend towards lower CPAP requirement in BCPAP group than in the VCPAP group. Babies in the VCPAP group required prolonged duration of CPAP as compared to BCPAP (mean= 62.56 hours and 48.74 hours respectively, p=0.07). There was no statistical difference in the number of babies who required more than 0.50 FiO_2 in either group. Maximum CPAP requirement, surfactant administration and mean duration of hospitalization were also similar in both the groups. Frequency of nasal septal necrosis and feed intolerance was not different between the groups [Table/Fig-2].

There was no statistically significant difference in associated morbidities like sepsis, shock, meningitis, DIC, Necrotizing Enterocolitis (NEC), acute renal failure, Patent Ductus Arteriosus (PDA), pulmonary haemorrhage and duration of hospitalization in between the groups.

We tried to find the factors associated with CPAP failure in both groups collectively. These factors were assessed for up to 72 hours after removal of CPAP. CPAP failure was found to be significantly more in babies with gestational age <30 weeks, birth weight <1000 g, shock, administration of surfactant, pulmonary haemorrhage and multi-organ dysfunction syndrome as compared to the CPAP success group [Table/Fig-3].

Characteristics (mean ± SD)/[Frequency,%]	VCPAP (n=34)	BCPAP (n=34)	p-value
Maximum CPAP (in cm of H_2O) (mean ± SD)	5.68±1.00	5.21±0.77	0.033
CPAP duration (in hours) (mean ± SD)	62.56±45.91	48.74±27.00	0.07
Maximum FiO_2 [Frequency,%] <40% 41-50% >50%	 16 (47) 6 (18) 12 (35)	 23 (68) 6 (18) 5 (15)	0.126
Surfactant	13 (38)	6 (18)	0.055
Septal necrosis	3 (9)	2 (6)	0.65
Feed intolerance	2(6)	1 (3)	0.62

[Table/Fig-2]: CPAP requirement and hospital course.

Characteristics [Frequency,%] / (mean ± SD)	CPAP Success (n=52) [Frequency,%]	CPAP failure (n=16) [Frequency,%]	p-value
Gestational age <30 weeks >30 weeks	 13 (25) 39 (75)	 9 (56) 7(44)	0.019
Admission weight (mean ± SD) <1000 gm >1000 gm	1.27±0.19 4 (8) 48 (92)	1.14±0.25 7(44) 9 (56)	0.035 <0.001
Antenatal steroid received	22 (42)	9 (56)	0.33
Respiratory distress syndrome	10 (19)	10(62)	<0.001
Pneumonia	13 (25)	4 (25)	1
Surfactant therapy	10 (19)	10(62)	0.008
Culture positive sepsis	7 (13)	3(19)	0.60
Shock	12 (23)	15(94)	<0.001
Pulmonary haemorrhage	0	5 (31)	<0.001
DIC	1 (2)	6(38)	<0.001
MODS	1 (2)	3(19)	0.012

[Table/Fig-3]: Risk factors for CPAP failure.
CPAP = Continuous positive airway pressure; SD = Standard deviation; DIC = Disseminated intravascular coagulation; MODS = Multi organ dysfunction syndrome.

DISCUSSION

CPAP is an established modality for management of respiratory distress in VLBW neonates. BCPAP and VCPAP are commonly used methods, both of which are acceptable and widely used for delivery of CPAP. In developing countries where resources fall short widely of demand, BCPAP is a cost-effective alternative to decrease RDS-specific neonatal mortality [11-15]. However, till date it is not clear which of the pressure generation mode is better. We thought it was pertinent to demonstrate whether the efficacy of BCPAP is comparable to that of VCPAP as it may spare the ventilator for use of other sick neonates.

Our findings showed that there was no difference between the failure rates with BCPAP or VCPAP. This was consistent with the results of a pilot trial by Tagare et al., McEvoy CT et al., and Colaizy TT et al., [8,10,16] but in contrast to the results of studies by Lee et al., Bahman- Bijari et al., and Tagare et al., who reported a higher success rate with BCPAP than VCPAP in preterm neonates with respiratory distress [6,9,11]. This variation in the success rate in between the groups may be attributed to, variation in the subject population, disease severity, co-existence of morbidities, insufficient sample size of our study and also the fact that ours is a referral unit and we included all VLBW neonates irrespective of gestational age, post-natal age and underlying lung pathology.

The failure rates with BCPAP among preterm and LBW babies with RDS have been reported to be in between 20% and 25% [12,17,18]. These rates are higher compared to failure rate of BCPAP in our study (14.70%). This could again be due to difference in study population (gestational age, birth weight) and difference in definition of CPAP failure in various studies. Failure rate with VCPAP in our study (32.3%) was comparable to that of Bahman-Bijari et al., (28%) and Tagare et al., (36.8%) [9,11]. McEvoy CT et al., have reported a higher failure rate of 48% in their study which could possibly be due to the fact that babies enrolled in their study were of rather lower gestational age between 25 to 32 weeks as compared to others [10].

We observed that no babies on CPAP developed pulmonary air leak. This was similar to a controlled trial by Narendran et al., [19] but in contrast to other studies where the rate of air leak was between 2% -10% [11,18,20,21]. This could be because we used a maximum CPAP of 7 cm of water against CPAP of > 7 cm of H_2O in other studies. In our study, although mortality was not significantly different between VCPAP or BCPAP groups, it occurred only in the babies who failed CPAP. Koti et al., also observed a higher mortality in CPAP failure group (35.7%) as compared to CPAP success group (2.4%) [12].

A lower gestation (<30 weeks) and presence of RDS have been reported by others as well as us to be associated with CPAP failure [11,12,17,18]. Some other factors reported to be associated with CPAP failure are presence of PDA and sepsis, need for positive pressure ventilation at birth; alveolar to arterial oxygen difference ($A\text{-}aDO_2$) >180mmHg on the first blood gas analysis [17,18]; higher Silverman–Anderson score, lower arterial to alveolar oxygenation ratio and need of surfactant [6]. In addition, we found factors such as weight <1000g, shock, pulmonary haemorrhage, DIC and multi organ dysfunction syndrome to be significantly associated with CPAP failure, thus highlighting the impact of gestational age, birth weight and haemodynamic stability in success of CPAP.

The present study has shown that there was no difference between the failure rates of BCPAP and VCPAP even for babies who were admitted at later ages and suffered from pneumonias or RDS with comparable safety as against other studies in which babies were inborn with RDS and started on CPAP early [6-9,11].

LIMITATION

It is possible that the results may not have reached statistical significance as the sample size in our study may have been inadequate to demonstrate a higher success rate of BCPAP that we desired. This was the major limitation of our study. However, it still addresses a pertinent research question on comparative efficacy of bubble and ventilator derived CPAP among VLBW babies through a robust study design. Stand-alone B-CPAP machines are less costly and technologically simpler than mechanical ventilators used for providing CPAP [15]. Outcomes or complications with B-CPAP being similar to those of ventilator delivered CPAP; this strategy has implications for practice in resource limited developing countries like ours where it may be feasible to offer B-CPAP to more number of babies with respiratory distress requiring CPAP.

CONCLUSION

Nasal CPAP has an established role in the care of VLBW babies with respiratory distress: however, the optimal method of pressure delivery system is still unclear. In the present study there was no difference in the CPAP failure rate with BCPAP or VCPAP among VLBW babies with moderate respiratory distress. The complications like IVH and mortality were also similar in both the groups. Gestational age <30 weeks, weight <1000g, RDS, shock, pulmonary haemorrhage, DIC and multi organ dysfunction syndrome were associated with CPAP failure in our study.

As per the present study results, BCPAP may offer a safe and effective alternative to ventilators for delivery of CPAP to VLBW neonates with moderate respiratory distress especially in resource limited countries. However, controlled trials with larger sample size are required to demonstrate the superiority of BCPAP.

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