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Original Article

Neonatology Section

Outcome of Early CPAP in the Management of Respiratory Distress Syndrome (RDS) in Premature Babies with ≤32 Weeks of Gestation, A Prospective Observational Study

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ABSTRACT

Background: Controversies still exist in the management of Respiratory Distress Syndrome (RDS) in Premature infants. The standard treatment of Intermittent positive pressure ventilation (IPPV) with surfactant therapy may not be the ideal intervention in resource limited settings like India, considering the invasive nature, higher cost and high risk of chronic lung disease. Even though early CPAP therapy has been shown to be successful in many clinical trials in the management of RDS, studies documenting the outcome of early CPAP therapy are very scarce in India.

Aims: To assess the outcome and incidence of various adverse outcomes of early CPAP therapy in premature neonates with ≤ 32 weeks of gestation, in a tertiary care teaching hospital

Materials and Methods: The study was a prospective observational study, undertaken in neonatal care unit of a tertiary care teaching hospital, located in Kochi, Kerala, between January 2007 to December 2010. All the eligible children were included in the study, no sampling was done.

Statistical Analysis: Quantitative variables were presented is mean and standard deviation, categorical variables were presented as frequency and percentages. 95% CI for the primary outcome measures were assessed using Z-test.

Results: Seventy premature newborn with < 32 weeks of gestation were included in the final analysis. Majority of the cases received bubble CPAP. The incidence of CPAP failure was 30% (95% CI 19.3% to 40.7%) in study population. The proportion of neonates who required surfactant was 18.6% (9.5% to 27.7%), Who developed ROP was 37.1% (25.8% to 48.5%) and the proportion of children, who met with mortality was 7.1% (1.1% to 13.2%) Nasal Trauma, Hypotension, Intra Ventricular Hemorrhage and CPAP belly were the most common complications, occurring in 80% (70.6% to 89.4%), 11.4% (4% to 18.9%) and 10% (3 % to 17%) of neonates each respectively. No case of pulmonary hemorrhage was reported.

Conclusion: Early institution of CPAP in the management of RDS in premature neonates, can significantly reduce the need for mechanical ventilation (MV) and surfactant therapy, with minimum associated complications.

Keywords: Continuous positive Airway Pressure (CPAP), Outcome, Complications, Respiratory Distress Syndrome (RDS)

INTRODUCTION

RDS is the commonest cause of respiratory distress in preterm infants. Deficiency of pulmonary surfactant is one of the most important factors contributing to the development of respiratory RDS [1]. In immature lungs, the elevated surface tension resulting from surfactant deficiency leads to alveolar collapse at the end of expiration, atelectasis, uneven inflation and regional alveolar over distension. If untreated, this will result in epithelial injury and pulmonary edema which further interfere with surfactant function, producing the clinical picture of RDS [2]. Lower the gestation, higher is the incidence of RDS, accounting for nearly 80% incidence in preterm infants with gestation less than 28 wk.

IPPV with surfactant is the standard treatment for the condition. The major difficulty with IPPV is that it is invasive, resulting in airway and lung injury. Surfactant deficiency with superimposed lung injury from MV and high concentrations of inspired oxygen trigger the release of pro inflammatory cytokines, which further impair surfactant function and predispose to the development broncho pulmonary dysplasia (BPD) [2]. Continuous positive airway pressure (CPAP) is a noninvasive respiratory support option and a means to avoid harmful effects of positive pressure ventilation. Infants with mild RDS can often be managed on CPAP alone, without

exogenous surfactant treatment [3,4]. Many approaches to the initial respiratory management of preterm neonates with RDS have been assessed for their efficacy. These strategies included Prophylactic surfactant (PS) followed by a period of MV, prophylactic surfactant with rapid extubation to bubble nasal CPAP (intubate-surfactant-extubate [ISX]) or initial management with bubble CPAP and selective surfactant treatment (n CPAP) [4-8]. Out of all these strategies, The Scandinavian model, the so-called INSURE (Intubation SURfactant Extubation) procedure, has been in use for almost two decades [9-13].

All these trials have not documented the superiority of the CPAP over intubation and surfactant administration, but have clearly documented that CPAP can reduce the need for MV and need of surfactant, with lesser incidence of BPD and other complications.

In India, nearly 26 million infants are born every year. Assuming 10 % incidence of respiratory distress in newborn infants, nearly 2.6 million infants are at need of treatment for RDS.

As mentioned above, controversies still exist in the early respiratory management of RDS in Premature infants. Considering the invasive nature, higher cost and high risk of chronic lung disease, IPPV with surfactant therapy may not be the ideal intervention in resource limited settings like India. Even though early CPAP therapy has been shown to be successful in some clinical trials in the management of RDS, studies documenting the outcome of early CPAP therapy are very scarce India [14-17].

With this background, the current study has been undertaken to document the outcome early CPAP therapy in Indian premature infants treated in a tertiary care hospital.

OBJECTIVES

1. To assess the outcome of early CPAP therapy in premature neonates with ≤32 weeks of gestation, in a tertiary care teaching hospital

2. To assess the incidence of various adverse outcomes in neonates with ≤32 weeks of gestation undergoing CPAP therapy

MATERIALS AND METHODS

Study design: Prospective observational study.

Study setting: A tertiary care teaching hospital, located in Kochi, Kerala, South India.

Study population: Preterm babies with gestational age 32 weeks or less delivered in the study setting.

Study duration: The data was collected over a period of four years between January 2007 to December 2010

Inclusion criteria

- Babies born at or before 32 weeks of gestational age

Exclusion criteria

- Babies with congenital anomalies.
- Needed intubation at birth.
- Out born babies were excluded from the study.

Sample size: A total of 70 eligible babies were included in the study.

Study procedure: Preterm babies born <=32 wks were started on Early CPAP soon after birth (within 10 - 30 minutes) irrespective of the presence or absence of C/F of RDS and observed for the outcomes until discharge. Babies who failed were electively intubated and ventilated and given Surfactant. Ionotropes and Volume expansion were given if needed. ECHO was performed as per protocol and significant PDA were treated with Ibuprofen. Screening Neurosonogram was done as per protocol.

CPAP failure was defined as

- SpO2 <88% on FiO2 >60% for >30 minutes (with requirement of CPAP >8 cms of H_2O)
- Blood gases showing,
  a) PH <7.20
  b) PCO2 ≥ 65 mm Hg
  c) PO2 <50 mm Hg on FiO_2 >60%
- Pathologic apnoea
- Increasing Retractions

Primary outcome measures: The need for Intubation and MV, Use of Surfactant was considered as primary outcome measures.

Secondary outcome measures: Incidence of BPD (O_2 requirement at or >28 days of Post natal age). Incidence of IVH/PVL and Other Complications of CPAP were considered as secondary outcome measures.

Ethical considerations: The study was approved by institutional human ethics committee of the institute. Informed written consent from the parents or guardians of all he babies was taken after thoroughly explaining the objectives of the study, potential risks involved. All the information sought by the parents was provided. Confidentiality of the personal data was ensured throughout the study.

STATISTICAL PROCEDURES

Descriptive analysis of the neonatal parameters, predisposing factors for RDS, timing of development of RDS were done. The details of type of CPAP, and duration to achieve various treatment endpoints were described. The detailed descriptive analysis of outcome parameters (Need for MV, mortality and need for additional surfactant) and complications was done. Quantitative variables were presented is mean and standard deviation, categorical variables were presented as frequency and percentages. The p-value and 95% CI for the primary outcome measures were assessed using Z-test. IBM SPSS statistics, version 21 was used for statistical analysis.

RESULTS

A total of 70 eligible neonates were included in the final analysis. The number of neonates who were delivered by LSCS were 64 (91.4%) and 22 (31.4%) neonates were small for gestational age. Male children constituted 42 (60%) of the study subjects. The three most common predisposing factors for RDS seen in study population were Antenatal steroids, Premature rupture of membranes (PROM) and pregnancy induced Hypertension (PIH) seen in 52 (74.3%), 31 (44.3%) and 24 (34.3%) of the subjects respectively. The other predisposing factors were Chorioamnionitis, Gestational Diabetes Mellitus (GDM), Foul smelling liquor, Oligohydromnios, Abnormal Fetal Doppler with absent diastolic flow. Third trimester fever was reported in 2 (2.9%) of the participants [Table/Fig-1, 2].

Fifty nine (84.3%) neonates developed RDS soon after birth and in the remaining children the onset was delayed. Only 7 (10%) children required bag and mask ventilation. Nasal CPAP was used in 60 (85.7%) participants and the remaining 10 neonates received bubble CPAP [Table/Fig-3]. The average time taken for improvement in Arterial Blood Gas (ABG) values was 5.66 hours. The average duration of CPAP was 8.63 hours and time taken for clinical disappearance of RDS was 8.73 hours and it took an average of 11.73 hours to reach Fio_2 21 [Table/Fig-4].

Parameter	Frequency	Percentage
I. Mode of delivery		
LSCS	64	91.4
NVD	6	8.6
Ii. Weight for gestational age		
AGA	48	68.6
SGA	22	31.4
I. Gender		
Male	42	60.0
Female	26	37.1
Ambiguous	2	2.9

[Table/Fig-1]: Descriptive analysis of neonatal parameters (N=70)

Parameter	Frequency	Percentage
Antenatal Steroids	52	74.3
PROM at 12 hours	31	44.3
Pregnancy Induced Hypertension (PIH)	24	34.3
Chorioamniotis	13	18.6
Gestational Diabetes Mellitus (GDM)	12	17.1
Foul smelling liquor	8	11.4
Oligohydromnios	4	5.7
Abnormal Fetal Doppler with absent diastolic flow	4	5.7
Third trimester fever	2	2.9

[Table/Fig-2]: Descriptive analysis of Factors predisposing to Respiratory Distribution Syndrome (N=70)

Parameter	Frequency	Percent
I. RDS soon after birth		
Yes	59	84.3
No	11	15.7
II. Resuscitation		
Routine	63	90.0
Bag and mask ventilation	7	10.0
III. Mode of CPAP		
Nasal CPAP	60	85.7
Bubble	10	14.3

[Table/Fig-3]: Descriptive analysis of Details of resuscitation & Mode of CPAP (N=70)

Parameter	Mean ± STD	Median
Hours taken for improvement in ABG	5.66±3.47	4
Duration of CPAP till pull off	8.63±2.54	8
Hours taken for Disappearance of RDS Clinically	8.73±7.43	6
Hours to reach FiO2 (21)	11.73±10.77	8

[Table/Fig-4]: Analysis of time taken for various events during and after CPAP (N=70)

The incidence of CPAP failure was 30% (95% CI 19.3% to 40.7%) in study population. The proportion of neonates who required surfactant was 18.6% (9.5% to 27.7%), Who developed ROP was 37.1% (25.8% to 48.5%) and the proportion of children, who met with mortality was 7.1% (1.1% to 13.2%) [Table/Fig-5].

Nasal Trauma, Hypotension, Intra Ventricular Hemorrhage and CPAP belly were the most common complications, occurring in 80% (70.6% to 89.4%), 11.4% (4% to 18.9%) and 10% (3% to 17%) of neonates each respectively. The other complications observed were CPAP belly, oliguria, septal injury, metabolic acidosis etc. No case of pulmonary hemorrhage was reported in the study. The corresponding standard error of the proportion and 95% CI are presented in the table [Table/Fig-6].

DISCUSSION

Since the first successful reporting of use of CPAP in treating RDS by Gregory et al., [18] many studies have been published evaluating the effectiveness of CPAP. Many approaches with different combinations of all the available modalities, including CPAP, surfactant and MV have been assessed for their efficacy. These approaches included Prophylactic surfactant followed by a period of MV, prophylactic surfactant followed by bubble nasal CPAP or initial management with bubble CPAP and selective surfactant treatment [4-8]. Out of all these strategies, The Scandinavian model, the so-called INSURE procedure, has been in use for almost two decades.[9-13].

The current study reported the short term outcome of the early CPAP therapy with selective administration of surfactant in 70 premature newborn with <32 weeks of gestation. Majority of the cases received bubble

Primary outcome	Frequency	Percentage	SE	95% CI	
				Lower	Higher
Mechanical ventilation	21	30.0%	5.47	19.3%	40.7%
Surfactant given	13	18.6%	4.64	9.5%	27.7%
Retinopathy of prematurity (ROP)	26	37.1%	5.77	25.8%	48.5%
Mortality	5	7.1%	3.07	1.1%	13.2%

[Table/Fig-5]: Descriptive analysis of Primary outcome measures in study (N=70)

Primary outcome	Frequency	Proportion	SE of Proportion	95% CI of proportion	
				Lower	Upper
Nasal Trauma	56	80.0%	4.78	70.6%	89.4%
Hypotension	8	11.4%	3.80	4.0%	18.9%
Intra Ventricular Hemorrhage	7	10.0%	3.59	3.0%	17.0%
CPAP belly	7	10.0%	3.59	3.0%	17.0%
Oliguria	5	7.1%	3.08	1.1%	13.2%
Septal injury	4	5.7%	2.77	0.3%	11.2%
Metabolic Acidosis	4	5.7%	2.77	0.3%	11.2%
NEC	3	4.3%	2.42	-0.5%	9.0%
Occurrence BPD	2	2.9%	1.99	-1.0%	6.8%
Pneumothorax	1	1.4%	1.42	-1.4%	4.2%
Pulmonary Hemorrhage	0	0.0%	0	0.0%	0.0%

[Table/Fig-6]: Descriptive analysis of the complications (N=70)

CPAP. The incidence of CPAP failure was 30% (95% CI 19.3% to 40.7%) in study population. The proportion of neonates who required surfactant was 18.6% (9.5% to 27.7%), Who developed ROP was 37.1% (25.8% to 48.5%) and the proportion of children, who met with mortality was 7.1% (1.1% to 13.2%) Nasal Trauma, Hypotension, Intra Ventricular Hemorrhage and CPAP belly were the most common complications, occurring in 80% (70.6% to 89.4%), 11.4% (4% to 18.9%) and 10% (3% to 17%) of neonates each respectively. The other complications observed were CPAP belly, oliguria, septal injury, metabolic acidosis etc. No case of pulmonary hemorrhage was reported in the study.

Dunn et al., in one of the very early preliminary report on Use of the 'Gregory box' (CPAP) in treatment of RDS of the newborn have reported lesser mortality with CPAP compared to existing methods [19]. Bassiouny et al., [20] in their study of Forty-four premature infants with RDS, treated with binasal, have reported the incidence of CPAP failure as 39% and significant improvement of RDS with a mild to moderate degree of severity on CPAP. They have also reported significantly lower incidence of infection, apnea, intraventricular hemorrhage and retinopathy of prematurity with CPAP. No pneumothorax was reported in the study [20].

Sai Sunil Kishore et al., [21] in their stratified open-label randomized controlled trial, neonates (28-34 weeks gestation) with respiratory distress within six hours of birth were randomly allocated to 'early-NIPPV' or 'early-CPAP' after stratifying for gestation (28-30 weeks, 31-34 weeks) and surfactant use. Failure rate was less with 'early-NIPPV' versus 'early-CPAP' [13.5% vs. 35.9%, respectively, RR 0.38 (95% CI 0.15-0.89), p = 0.024]. Similarly, need for intubation and MV by seven days (18.9% vs. 41%, p-0.036) was less with NIPPV. The authors concluded early use of NIPPV reduces the need for intubation and MV compared to CPAP.

Finer NN et al., [22] in a randomized, multicenter trial of 1316 infants reported that, Infants who received CPAP treatment, as compared with infants who received surfactant treatment, less frequently required intubation or postnatal corticosteroids for bronchopulmonary dysplasia (p<0.001), required fewer days of MV (p=0.03), and were more likely to be alive and free from the need for MV by day 7 (p=0.01). They supported consideration of CPAP as an alternative to intubation and surfactant in preterm infants. Tapia JL et al., [23] In a multicenter randomized controlled trial of spontaneously breathing VLBWIs weighing 800-1500 g were allocated to either CPAP/INSURE or Oxygen/MV group. In this study, need for MV was lower in the CPAP/INSURE group (29.8% vs 50.4%; P -001), as was the use of surfactant (27.5% vs 46.4%; P -002). There were no differences in death, pneumothorax, bronchopulmonary dysplasia, and other complications of prematurity between the two groups. The authors have concluded that, CPAP and early selective INSURE reduced the need for MV and surfactant in VLBWIs without increasing morbidity and death and these results may be particularly relevant for resource-limited regions.

Kandraju H et al., have compared the efficacy of early routine versus late selective surfactant treatment in reducing the need for MV during the first week of life among moderate-sized preterm infants with RDS being

supported by nCPAP. Among 153 infants randomized to early (n -74) or late surfactant (n - 79) groups, the need for MV was significantly lower in the early surfactant group (16.2 vs. 31.6%; relative risk 0.41, 95% confidence interval 0.19-0.91). The authors advocated the use of early surfactant basing on this study findings [24].

Zaharie G et al., [25] have compared prophylactic (A) and curative CPAP (B) in a prospective study on 90 newborns. In this study, Surfactant was necessary in 40% of group A, over 23% in group B (p–0,269). Mechanical ventilation in first 72 hours of life was necessary in 72% of cases in A and in 84% of cases in group B. The authors have concluded that, using early CPAP may reduce: necessity for surfactant, MV.

The CPAP or Intubation at Birth (COIN) trial on 610 preterm infants born at 25 and 0⁄7 to 28 and 6⁄7 weeks has reported 46% in the CPAP group required intubation. The study also reported fewer infants in the CPAP group receiving surfactant (38% vs. 77%, p –0.001), but significantly higher rate of pneumothorax (9.1% vs.3.0%. p < 0.001) [26].

The Surfactant Positive Pressure and Oxygen Randomized Trial (SUPPORT) on 1316 infants , reported CPAP infants had fewer days on MV, had less use of postnatal corticosteroids for BPD and were more likely to be alive and off MVby day seven of life (p = 0.01) [22].

The CURPAP trial aimed to evaluate the efficacy of combining prophylactic surfactant and early nasal CPAP in very preterm infants have reported similar need for MV in both groups (31.4% vs. 33.0%). Mortality, BPD and the incidence of air leaks did not differ [7].

The Vermont Oxford Network reports that in comparing DR intubation with prophylactic surfactant and continued MV to DR intubation with rapid extubation to CPAP and early CPAP with rescue surfactant when FiO_2 exceeded 0.6, the outcome was similar, but approximately half of the early CPAP infants required MV and received late rescue surfactant treatment, suggesting both that with early CPAP intubation can be avoided in many infants and that early identification of those infants that will need surfactant remains elusive [25].

In a recent review Bohlin [27] have concluded that "current evidence indicates that a strategy of early CPAP in very preterm infants is as safe as routine intubation in the delivery room. There appears to be no serious side effects and a tendency towards improved outcome, at least in the short term. Prophylactic surfactant no longer gives any clear benefits over selective treatment." In a recent cochrane data base review, the authors have observed significant benefit for the combined outcome of death or bronchopulmonary dysplasia, or both, at 36 weeks corrected gestation for babies treated with nasal CPAP (relative risk 0.90 (95% confidence interval 0.83 to 0.98, risk difference -0.04 (95% confidence interval -0.08 to -0.00), NNT [corrected] of 25). And concluded that, one additional infant could survive to 36 weeks without bronchopulmonary dysplasia for every 25 babies treated with nasal CPAP in the delivery room rather than being intubated [28].

The current study findings and bulk of the evidence from across the globe suggest, the early CPAP can have a favorable impact on the outcome of premature infants with RDS, but the final consensus about clear superiority of the early CPAP or other available interventions is yet to be reached.

CONCLUSION

- Early institution of CPAP in the management of RDS in premature neonates, can significantly reduce the need for MV & surfactant therapy.
- Early institution of CPAP can also reduce the incidence of BPD, with minimum associated complications.

RECOMMENDATION

- This study suggests that a trial of ECPAP at birth is not detrimental and may be justified in case of RDS, providing Early Surfactant rescue is given if the infant needs to be intubated and ventilated.
- Early use of CPAP will be a low-cost, simple and non-invasive option for a country like India, where most places cannot provide invasive ventilation and Surfactant.
- Large scale Randomized controlled trials (RCTS) are warranted for further analysis of immediate and long term outcomes of CPAP and factors influencing those outcomes in neonates with RDS.

LIMITATIONS OF STUDY

- No Control group was taken for comparative analysis of the efficacy
- Proportion of babies below 28 wks of GA is low, which limits the generalizability of the results.
- The role of many confounding factors could not be evaluated because of the limited sample size.

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