To study the Effectiveness of Early CPAP in the management of respiratory distress syndrome (RDS) in premature babies with ⩽ 34 weeks of gestation.

*Dr. Sachin Vahadane, **Dr.Shashank Mohole ***Dr.Sunil Mhaske, ****Dr. Bipin Rathod, ****Dr. Thaslima K.

*Asst Prof (Paediatrics) , **Asso. Prof, (Anaesthesia), ***Prof & Head, (Paediatrics), ****Resident (Paediatrics)

Corresponding Author : Dr. Shashank Mohole

Mail id : shashankmohole43@gmail.com

Mobile No.: 9767705059

Corresponding Address : Department of Anaesthesia, Dr. VVPF's Medical College, Ahmednagar, Maharashtra.

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 ≤ 34 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, between January 2014 to December 2016. 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 < 34 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% (9.5% to 27.7%), Who developed ROP was 37% (25.8% to 48.5%) and the proportion of children, who met with mortality was 7% (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 signifiantly reduce the need for mechanical ventilation (MV) and surfactant therapy, with minimum associated complications.

Introduction : RDS is the commonest cause of respiratory distress in preterm infants. Defiiency 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 inflmmatory 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 PS, 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).[4,5] Out of all these strategies, The Scandinavian model, the so-called INSURE (Intubation SURfactant Extubation) procedure, has been in use for almost two decades .[6,7] 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.[8,9]

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.

Study population: Preterm babies with gestational age 34 weeks or less delivered in the study setting.

Study duration: The data was collected over a period of 3 years between January 2014 to December 2016

Inclusion criteria

- Babies born at or before 34 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 30 eligible babies were included in the study.

Study procedure : Preterm babies born <=34wks 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 & 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 H2O)
- Blood gases showing,

a) PH <7.20

b) PCO2 ≥65 mm Hg

c) PO2 <50 mm Hg on FiO2 >60%

- Pathologic apnea
- 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 (O2 requirement at or >28 days of Post natal age). Incidence of IVH/PVL & 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. Confientiality 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 30 eligible neonates were included in the final analysis. The number of neonates who were delivered by LSCS were 27(91%) and 10 (32%) neonates were small for gestational age. Male children constituted 18 (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 22(74%), 13(44%) and 10 (34%) 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 1(2%) of the participants [Table/ Fig-1, 2]. Twenty five(84%) neonates developed RDS soon after birth and in the remaining children the onset was delayed.

Only 3 (10%) children required bag and mask ventilation. Nasal CPAP was used in 25(85%) 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 Fio2 21 [Table/Fig-4].

Table 1: Neonatal Parameters

Parameters	Frequency	Percentage
I. Modes of delivery		
LSCS	27	91
NVD	3	9
II. Weight for gestational age		
AGA	20	68
SGA	10	32
III. Gender		
Male	18	60
Female	11	37
Ambiguous	1	3

Table 2: Factors disposing Respiratory distress syndrome

Parameters	Frequency	Percentage
Antenatal steroids	22	74
PROM at 12hours	13	44
Pregnanacy induced hypertension(PIH)	10	34
Chorioamionitis	5	18
Gestational diabetismellitis(GDM)	5	17
Foul smelling liquor	4	11
Oligohydromious	2	5
Abnormal fetal Doppler with absent diastolic flow	2	5
Third trimester fever	1	2

Table 3- Details of Resuscitation & mode of CPAP used

Parameters	Frequency	Percentage
I. RDS soon after birth		
Yes	25	84
No	5	16
II. Resuscitated		
Routine	27	90
Bag & mask ventilation	3	10
III. Modes of CPAP		
Nasal CPAP	25	85
Bubble CPAP	5	15

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% (9.5% to 27.7%), Who developed ROP was 37% (25.8% to 48.5%) and the proportion of children, who met with mortality was 7% (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.

Discussion : Since the first successful reporting of use of CPAP in treating RDS by Gregory et al., [10] 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] Out of all these strategies, The Scandinavian model, the socalled INSURE procedure, has been in use for almost two decades.[6]

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 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% (9.5% to 27.7%), Who developed ROP was 37% (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% 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.[11] Bassiouny et al.,[12] 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 haemorrhage and retinopathy of prematurity with CPAP. No pneumothorax was reported in the study .[12]

Sai Sunil Kishore et al [13] in their stratifid open-label randomized controlled trial, neonates (28-34 weeks gestation) with respiratory distress within six h of birthwere randomly allocated to 'early-NIPPV' or 'earlyCPAP' after stratifying for gestation (28-30 weeks, 31- 34 weeks) and surfactant use. Failure rate was less withh'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.,[14] 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 et al .[15] In a multicentre 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.,[16] have compared the effiacy of early routine versus late selective surfactant treatment in reducing the need for MV during the fist 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 signifiantly 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 fidings.[16] Zaharie G et al.[17] 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 fist 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).[18] 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 MV by day seven of life (p = 0.01).[14] 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.[6]

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 FiO2 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 infantsand that early identification of those infants that will need surfactant remains elusive .[17] In a recent review Bohlin[19] 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[20].

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 .[20]

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.

References

1. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. AMA journalof diseases of children. 1959;97(5, Part 1):517-23.
2. Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. American journal ofrespiratory and critical care medicine. 1998;157(1):294-323.
3. Kamper J, Wulff K, Larsen C, Lindequist S. Early treatment with nasal continuous positive airway pressure in very low-birth-weight infants. Actapaediatrica(Oslo, Norway : 1992). 1993;82(2):193-97.
4. Sandri F, Ancora G, Lanzoni A, Tagliabue P, Colnaghi M, Ventura ML, et al. Prophylactic nasal continuous positive airways pressure in newborns of 28-31 weeks gestation: multicentre randomised controlled clinical trial. Archivesof disease in childhood Fetal and neonatal edition. 2004;89(5):F394-98.
5. Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D, et al. Randomized trial comparing three approaches to the initial respiratory management of preterm neonates. Pediatrics. 2011;128(5):e1069-76.
6. Verder H, Robertson B, Greisen G, Ebbesen F, Albertsen P, Lundstrom K, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. The New England journal of medicine. 1994;331(16):1051-15.
7. Bohlin K, Gudmundsdottir T, Katz-Salamon M, Jonsson B, Blennow M. Implementation of surfactant treatment during continuous positive airway pressure. Journal of perinatology :offiial journal of the California Perinatal Association. 2007;27(7):422-27.
8. Diblasi RM. Nasal continuous positive airway pressure(CPAP) for the respiratory care of the newborn infant.

Respiratory care. 2009;54(9):1209-35.

9. Sekar K. The role of continuous positive airway pressure therapy in the management of respiratory distress in extremely premature infants. The journal of pediatric pharmacology and therapeutics : JPPT : the offiial journal of PPAG. 2006;11(3):145-52.
10. Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. The New England journal of medicine. 1971;284(24):1333-40.
11. Dunn PM, Thearle MJ, Parsons AC, Watts JL. Use of the 'Gregory box' (CPAP) in treatment of RDS of the newborn: preliminary report. Archives of disease in childhood. 1972;47(254):674-75.
12. Bassiouny MR, Gupta A, el Bualy M. Nasal continuous positive airway pressure in the treatment of respiratory distress syndrome: an experience from a developing country. Journal of tropical pediatrics. 1994;40(6):341-44.
13. Sai Sunil Kishore M, Dutta S, Kumar P. Early nasal intermittent positive pressure ventilation versus continuous positive airway pressure for respiratory distress syndrome. Act apaediatrica (Oslo, Norway : 1992). 2009;98(9):1412-15.
14. Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Early CPAP versus surfactant in extremely preterm infants. The New England journal ofmedicine. 2010;362(21):1970-79.
15. Tapia JL, Urzua S, Bancalari A, Meritano J, Torres G, Fabres J, et al. Randomized trial of early bubble continuous positive airway pressure for very low birth weight infants. The Journal of pediatrics. 2012;161(1):75-80.e1.
16. Kandraju H, Murki S, Subramanian S, Gaddam P, Deorari A, Kumar P. Early routine versus late selective surfactant in preterm neonates with respiratory distress syndrome on nasal continuous positive airway pressure: a randomized controlled trial. Neonatology. 2013;103(2):148-54.
17. Zaharie G, Ion DA, Schmidt N, Popa M, Kudor-Szabadi L, Zaharie T. [Prophylactic CPAP versus therapeutic CPAP in preterm newborns of 28-32 gestational weeks]. Pneumologia (Bucharest, Romania). 2008;57(1):34-37.
18. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. The New England journal of medicine. 2008;358(7):700-08.
19. Bohlin K. RDS--CPAP or surfactant or both. Actapaediatrica (Oslo, Norway : 1992) Supplement. 2012;101(464):24-28.
20. Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ (Clinical research ed).2013;347:f5980.