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Early CPAP (continuous positive airway pressure) versus surfactant in preterm neonates with RDS - a study of comparison of outcome

Dr. Boddu Praveen Kumar[1]*, Dr. RaginiMuthukulla[2], Dr. M. Alimelu[3]

[1]Department of pediatrics, Niloufer hospital for women and children, Hyderabad, India.
[2]Assistant professor of pediatrics, Osmania medical college, Hyderabad, India.
[3]Professor of pediatrics, Niloufer hospital, Osmania medical college, Hyderabad, India.

Corresponding author: *Dr.Boddu Praveen Kumar, Department of pediatrics, Niloufer hospital for women and children, Hyderabad, India.

Abstract

Introduction: Respiratory distress syndrome (RDS) is one of the most common causes of mortality and morbidity in preterm neonates. Surfactant and CPAP and mechanical ventilation have been the main stay management techniques in RDS. Surfactant is a costly intervention and most patients are transported and reach the treatment facility at a later time. This study aims at comparing the effects of CPAP alone to CPAP with surfactant.

Methods: The study was a randomized control clinical trial with 160 neonates born at Niloufer childrens hospital. Neonates born between 28 0/7 to 34 6/7 with evidence of RDS were randomized to receive either cpap alone or cpap with surfactant. Both the groups were compared fpr primary and secondary outcomes. The primary outcome measured was treatment success defined by the criteria. Secondary outcomes are mortality and other complications.

Results: During the study period of 12 months, 160 neonates were included in the study. The mean gestational age was 30.6 weeks. Cpap was started at a mean age of 35 minutes and surfactant was started at a mean age of 2.1 hours.

The rates of treatment success did not vary significantly in between the two groups(p=0.7). the rates of mortality did not differ between the groups (p=0.4).

The rates of secondary outcomes differed in terms of incidence of BPD, duration of hospital stay and duration of oxygen requirement. The incidence of BPD was more with surfactant group(p=0.15). The mean duration of hospital stay was longer in cpap group(p=0.00), the mean duration of oxygen requirement was longer with cpap group (p=0.00). In case of treatment failure, the average duration of mechanical ventilation was 3.3 days in CPAP group and 4.83 days in INSURE group. P=0.046.

Conclusions: CPAP is an effective alternative treatment to surfactant in selected neonates.

CPAP is a cost effective, less invasive, and requires less skill than surfactant for treatment of RDS. It is an ideal management option for RDS in a developing country.

Keywords: Respiratory distress syndrome (RDS), Continuous positive airway pressure (CPAP)

Introduction

Respiratory distress syndrome is one of the most common causes of morbidity and mortality in preterm neonates.[1] Pathologically and biochemically it is a condition due to surfactant deficiency.

Incidence of RDS is inversely proportional to gestational age. 95% to 98% of infants born at 22 to 24 weeks' gestation have RDS, decreasing to approximately 25% in infants with birth weights between 1251 and 1500 g.[2,3]

Most small premature neonates with respiratory distress syndrome (RDS) require some methods of respiratory support.[1]Surfactant administration, CPAP and mechanical ventilation are the most commonly available treatment strategies.

In spite of newer modes introduced in mechanical ventilation, the rate of chronic lung disease (CLD) has not reduced greatly,[4] and mechanical ventilation is still known as the major risk factor for the development of CLD.[4,5] Introduction of the continuous positive airway pressure (CPAP) as a respiratory support in an early stage of RDS[6,7] has been associated with lower rates of CLD.[4,8,9,10] Hence, it is considered as a popular mode of non-invasive ventilation.[11,12] If used early, CPAP could decrease the subsequent need for intubation and mechanical 10entilation.[4,5,9,13]Non-invasive ventilation (NIV) is increasingly being used in preterm infants with the purpose of reducing the risk of adverse pulmonary outcome associated with invasive mechanical ventilation. Physiologic data indicate advantages of NIV with regard to ventilation, gas exchange, breathing effort and thoraco-abdominal distortion. Data from clinicaltrials have consistently shown facilitation of weaning from mechanical ventilation and potential benefits in infants with RDS.[14]

Since the introduction of the combination of surfactant and mechanical ventilation in the treatment of RDS in 1980,[15]intratracheal surfactant administration has remained as the main treatment of RDS.[12] It has been shown that surfactant therapy reduces mortality and complications of RDS. Earlier treatment with surfactant (within 2 hours of birth) is much more effective than later treatment in decreasing mortality rate and complications of RDS.[16, 17]

Although both the CPAP or Intubation at Birth (COIN) and Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)[13] trials found that the rate of death or bronchopulmonary dysplasia (BPD) was not different between groups that received early CPAP or surfactant treatment, infants in the nasal CPAP group required less mechanical ventilation. The rate of ventilation was higher in the CPAP infants in the COIN trial[18], but not in SUPPORT trial.

CPAP and Surfactant are both used in the treatment of RDS in preterm neonates.

In spite of significant progress in understanding the etiology and pathophysiology of the RDS, the optimal treatment is still under debate. There are very few Indian studies comparing the outcome between CPAP and Surfactant. This study aims at comparing the outcome difference in neonates treated with Early CPAP alone and with Surfactant.

Aim and objectives

To compare the treatment success rate in preterm neonates receiving CPAP alone and CPAP with Surfactant.

To compare the incidence of complications in preterm neonates receiving CPAP alone and CPAP with Surfactant.

To find if CPAP alone can be used in treatment of RDS, especially in limited resource settings.

Patients and methods

Study design: This is a randomised controlled trial

Approval: This study received approval from college ethical committee

Setting: Niloufer hospital for women and children

Participants: 160 neonates born at Niloufer hospital

Study period: November 2016 to November 2017

Inclusion criteria:
Gestational age $28^{0/7}$ to $34^{6/7}$
Inborn neonates
Evidence of RDS: respiratory distress is defined as presence of any two of the following features[43]
Respiratory rate > 60/ minute
Subcostal / intercostals recessions
Expiratory grunt / groaning
Exclusion criteria:
Other gestational ages
Neonates requiring FiO2 > 50% after 1 hour
Major cardiac diseases
Asphyxiated newborns
Requiring intubation for resuscitation
Major congenital anomalies
History of PROM or Chorioamnionitis in mother.

Definitions used in this study
Treatment success: infant is stable on CPAP, had an acceptable arterial blood gas (P^h>7.20, PCO_2<60, PaO_2>50 with FiO_2<0.3), and had no respiratory distress for 48 hours.
Treatment failure: in surfactant group, failure to extubate with in 1 hour of INSURE, and in both groups when there was a need for mechanical ventilation within 72 hours.

CPAP failure[42]: CPAP is considered as a failure when FiO2 of 60% and PEEP of 7-8cm H2o is unable to relieve chest retractions or normalize arterial blood gases.

Broncho pulmonary dysplasia :[36]
Physiologic definition of BPD, based on SaO_2 during a room air challenge performed at 36 weeks (or 56 days for infants >32 weeks) or before hospital discharge, with persistent SaO_2<90, the cut off at which supplemental O_2 is required.
Treatment failure:
Failure to extubate within 1 hour of Surfactant administration.
Need for mechanical ventilation within 72 hours-
Prolonged, recurrent apnea
FiO2 requirement more than 0.7

Written parental consent was obtained before randomisation. Gestational age is estimated from the mother's first trimester ultra sonogram.
All premature infants received the initial steps of resuscitation. At the time of admission to NICU, all eligible infants were placed on NCPAP with 5 cm of H_2O PEEP and 0.5 FiO_2 with binasal appropriate sized prongs. And a chest X ray was taken 30 minutes after starting CPAP. Those who had RDS continued in study, and those without RDS are excluded from the study.
A random number table was used to assign each eligible neonate into one of the two groups, in 1:1 ratio. These assignments were enclosed in sealed envelopes, consecutively numbered and opened after eligibility was determined. The randomization envelope was opened and allocated treatment was started if inclusion criteria were met.
Neonates assigned to the control group remained on NCPAP of 5 cm H_2O with adjusted FiO_2 to SPO2 88% to 95%. Neonates assigned to INSURE group were intubated and the correct position of ET tube was determined by the evaluation of breath sounds, chest rising and tip-tip length of the ET tube.We have used the SURVANTA and each dose of this Surfactant, 4ml per Kg , was divided in to four equal aliquots and administered. After each aliquot, manual ventilation was given. Then if stable, they are extubated and connected to NCPAP with PEEP of 5cm H_2O and 0.5 FiO_2. All cases are followed till discharge or death.
Treatment success: In both groups, if the infant was stable on NCPAP, had an acceptable ABG, and no respiratory distress. Then CPAP was discontinued.
Treatment failure:

- Failure to extubate within 1 hour of Surfactant administration.
- Need for mechanical ventilation within 72 hours-

- Prolonged, recurrent apnea
- FiO2 requirement more than 0.7

All treatment failure cases would receive treatment according to institutional guidelines.

Primary outcome studied was: treatment success or failure

Secondary outcomes studied were:

Death, Incidence of Pneumothorax, BPD, PVL, IVH, ROP,

Duration of NCPAP, O_2 requirement, duration of hospital stay and duration of mechanical ventilation.

Statistical analysis

The data were analysed with SPSS 21 software.

Student t test was used for continuous data. Categorical data were analysed with Pearson chi square test and Fisher's extraction test.

P value <0.05 was considered as existence of statistically significant difference.

Observations and results

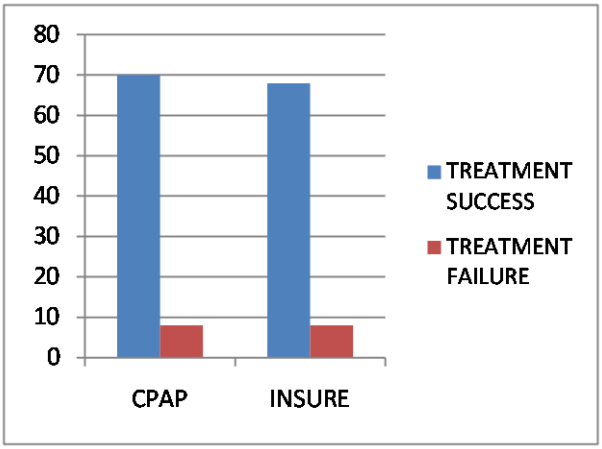
During the study period, 260 neonates were attended. 160 neonates were included in the study after meeting the inclusion criteria and excluding when they met exclusion criteria.

In this study the mean gestational age of the neonates was 30.6 (SD 2.0) weeks.

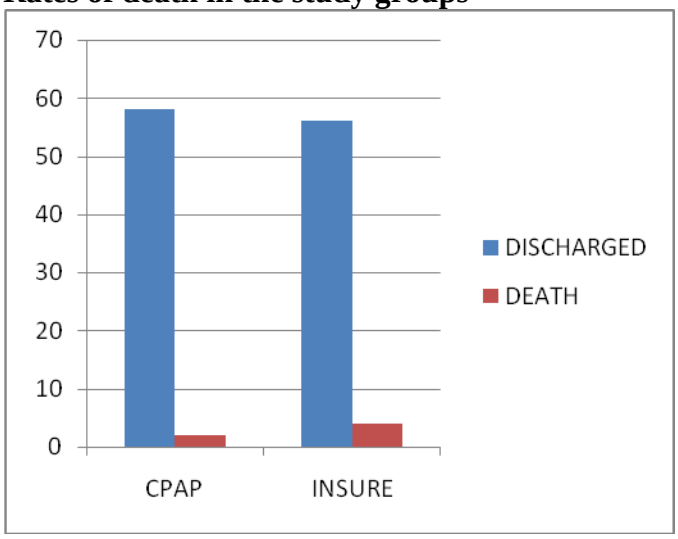
Baseline characteristics in both the groups were similar. CPAP was started at the mean age of 35 minutes. In the INSURE group Surfactant was given at a mean age of 2.1 hours. In CPAP group 8 neonates had treatment failure. INSURE group also had 8 treatment failures. Out of which, in 3 neonates we were not able to extubate after Surfactant administration and 5 neonates had CPAP failure. P=0.706.

Base line charecteristics	NCPAP group N=80	INSURE N=80	Significance
Gestational age	30.84	30.48	P=0.7
Sex (females)	42	38	P=0.5
Birth weight	1763gms	1845gms	P=1
APGAR	7.93	7.85	P=0.6
LSCS	40	32	P=0.2
Steroids received	24	22	P=0.7

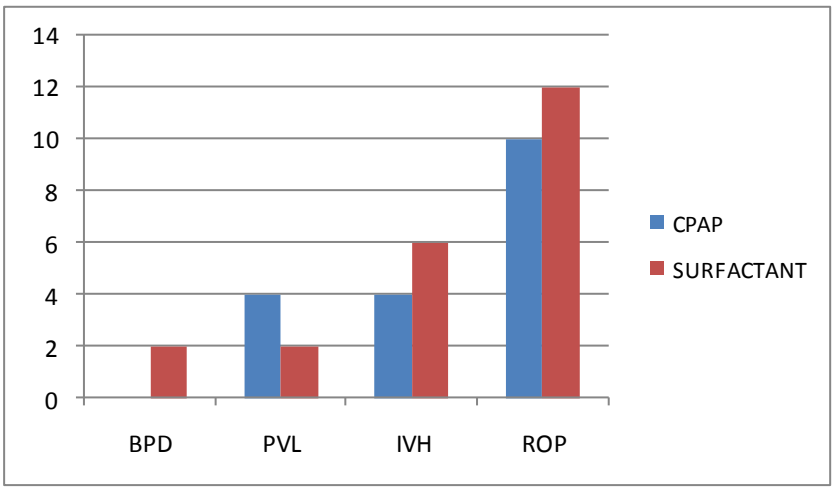
Primary outcome in study groups



Rates of death in the study groups

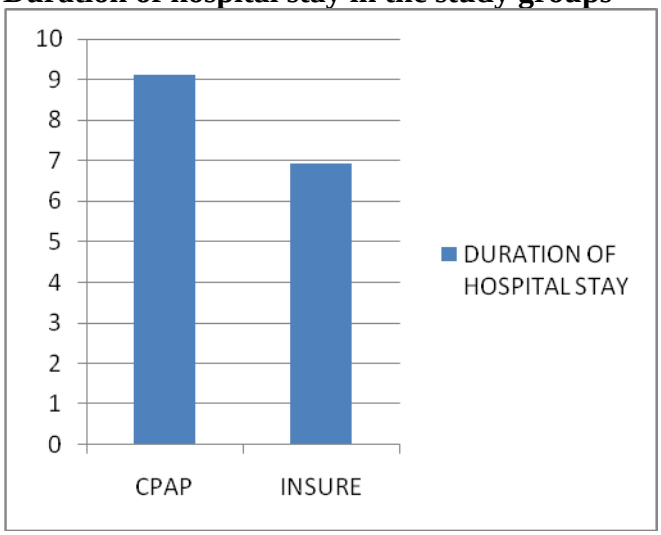


The number of deaths in CPAP group was 2 (2.5%) and in INSURE group 4 (5%). But this difference was not statistically significant. P=0.4 Secondary outcomes:



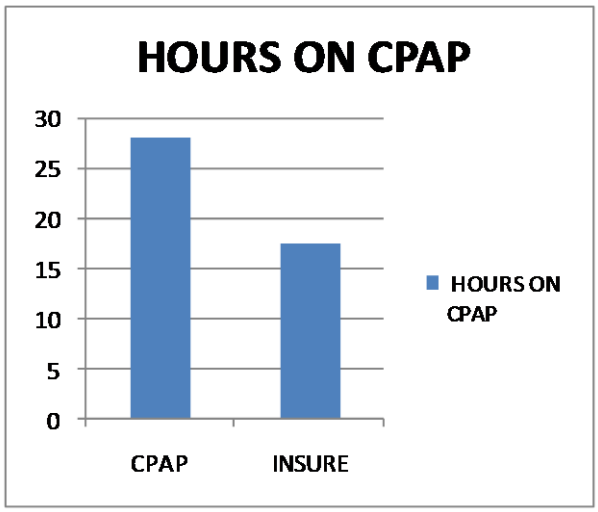
There were no neonates effected with BPD in CPAP group, while there were 2 (2.5%) neonates with BPD in Surfavtant group. This difference was not statistically significant. P=0.15
4 neonates (5%) in CPAP group developed Peri ventricular 13entilation13 and in INSURE group 2 neonates (2.5%) developed PVL. This difference was not statistically significant. P=0.4
4 (5%)neonates in CPAP group and 6 (7.5 %) neonates in INSURE group had developed Intra ventricular haemorrhage. P= 0.5
10 neonates in CPAP group and 12 neonates in INSURE group developed ROP. P=0.6

Duration of hospital stay in the study groups



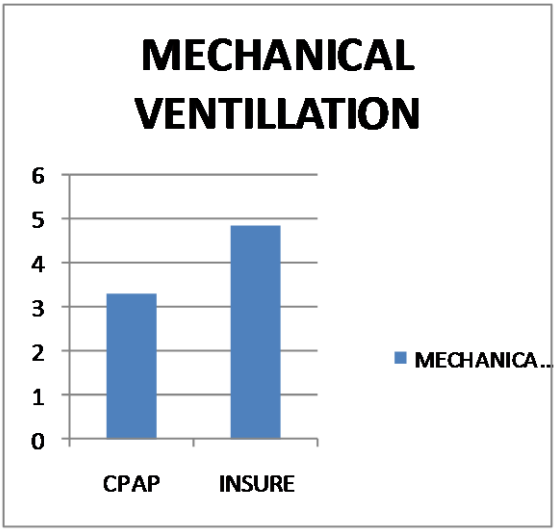
There was a significant difference in the average duration (days) of hospital stay. In CPAP group it was 9.1 days and in INSURE group it was 6.9 days.
P=0.006

Hours of cpap requirement in the study groups



The average duration of neonates requiring CPAP in CPAP group was 27.92 hours and in INSURE group it was 17.40 hours. P=0.00

Duration of mechanical ventilation in study groups



In case of treatment failure, the average duration of mechanical ventilation was 3.3 days in CPAP group and 4.83 days in INSURE group. P=0.046.

Discussion

In the present study done on 28 to 34 weeks gestational age neonates, Surfactant in comparison with CPAP alone bears no significant advantage in terms of

- Need for mechanical ventilation
- Incidence of BPD, ROP, PVL and IVH.

CPAP is recognised as an effective and non-invasive method in the treatment of RDS[37]. The use of early CPAP will prevent the progression of RDS, and it will decrease the need of excess Surfactant[11].

In the present study, treatment failure occurred in 10% (n=80) of neonates given CPAP and 10% (n=80) who received Surfactant.

In agreement with the present study, Maryam Nakshab[32]study shows treatment failure has occurred in 26.7% (n=40) in CPAP group and 16.7% (n=40) in INSURE group. And the p value was 0.53.

In Mahmoud Imani[33] study, 15% (n=30) neonates who received CPAP and 10% (n=30) neonates who received Surfactant needed mechanical ventilation. And the p value was 0.737.

The present study, in agreement with these two studies has shown that there is no significant difference in the need for mechanical ventilation between neonates receiving CPAP and Surfactant. In the present study need for mechanical ventilation by the end 72 hours was taken as treatment failure.

In the present study the number of deaths in neonates receiving CPAP alone was 2 (2.5%) and in neonates receiving Surfactant and CPAP were 4 (5%). And the p value was 0.706.

In Maryam Nakshab[32]study percentages of deaths in neonates receiving CPAP alone and Surfactant with Surfactant group were equal (3.3%).P>0.99

In Mahmoud Imani[33] study, the death percentage in CPAP group was17.5% and in Surfactant group was 10%. P=0.517.

In SUPPORT trial, 14.2% death occurred in CPAP group and 17.5% deaths occurred in surfactant group.

There was no difference in the rates of death in either of the treatment groups.P=0.09. Relative risk 0.81 (95% CI; 0.63 – 1.03).

The present study also shows that there is no significant difference in the rates ofBPD between CPAP alone and INSURE

techniques. There were no neonates effected with BPD in CPAP group, while there were 2 neonates (2.5%)with BPD in INSURE group. P=0.15.

In Maryam study[32], the rate of BPD in CPAP group was 10% and INSURE group was also 10%. P>0.99

In SUPPORT[13] trial, there was no difference in the rates of BPD in either of the treatment groups.P=0.84

In COIN trial[18], early NCPAP did not significantly reduce the rate of BPD,as compared to intubation.

SUPPORT[13] trial and Maryam Nakshab[32] study has shown, in agreement with the present study, that Surfactant has no added benefit of reducing the incidence of BPD.

In support to the present study, Dunn MS[8]study, a large study on the comparison between three groups of prophylactic surfactant, INSURE, and CPAP alone, no difference was found in the rate of death or BPD between groups.

In the study of Colombian Neonatal Research Network[4] on the comparison of NCPAP with INSURE in infants with a gestational age of 27-31 weeks, in their lower gestational age stratum (27-29 weeks), the rate of BPD or mechanical ventilation (treatment failure in the present study) was not different between the two groups.

In the present study, IVH occurred in 2.5% of neonates given CPAP and 7.5% who received Surfactant. P=0.6. In agreement with the present study, Maryam Nakshab[32]study shows IVH has occurred in 3.3% in CPAP group and 10% in INSURE group. And the p value was 0.6.

In Mahmoud Imani[33] study, 2.5% neonates who received CPAPdeveloped IVH and none of the neonates who received Surfactant developed IVH. But this difference was statistically not significant.The p value was 1.000.The present study, in agreement with these two studies has shown that there is no significant difference in the rates of IVH between neonates receiving CPAP and Surfactant.

In SUPPORT[13] study, 14.3% in CPAP group and 11.5% in Surfactant group have had developed IVH. P=0.12.

The present study also shows that there is no significant difference in the rates of PVL between CPAP alone and INSURE techniques.

5% neonates in CPAP group were effected with PVL in CPAP group, while 2.5% neonates in INSURE group developed PVL. P=0.4.

In Maryam study[32], the rate of PVL in CPAP group was 3.3% and in INSURE group was also 3.3%.P>0.99.

In the present study, ROP occurred in 12.5% of neonates given CPAP and 15% who received Surfactant. P=0.6

In agreement with the present study, Maryam Nakshab[32]study shows ROP has occurred in 10% in CPAP group and 6.1% in INSURE group. And the p value was >0.99.

In SUPPORT[13] study, 13.1% in CPAP group and 13.7% in Surfactant group have had developed ROP. P=0.71.

The duration of hospitalisation in the present study was less in the neonates who received Surfactant compared to those who received CPAP. The mean duration of hospital stay in Surfactant group was6.9 days and in CPAP group it was 9.1 days. P=0.006.

In contrast, in Maryam Nakshab[32] study, there was no significant difference between neonates receiving CPAP and Surfactant in terms of duration of hospitalisation.

This difference could be attributed to the significant difference in birthweights between two groups in Maryam Nakshab[32] study. The mean birthweight of neonates in INSURE group was 1515 GMs while in CPAP group was 1709 gms. P=0.03.

As low birth weight neonates require more days of hospitalisation in view of weight gain and associated complications, the comparatively lower weight in surfactant group in Maryam Nakshab[32] study must have not resulted in significant difference.

The duration of oxygen therapy was significantly lower with Surfactant compared to CPAP alone. The mean duration of oxygen requirement in Surfactant group was 1.82 days and in CPAP group it was 2.92 days. P=0.00

In agreement with the present study, in Maryam Nakshab[32] study, the duration of oxygen requirement was significantly lower in Surfactant group than CPAP group.

The duration of oxygen requirement was lower in INSURE, in other studies.[9,11,38]

In the present study, the average duration of CPAP requirement was also less in Surfactant group (1.82 days) compared to CPAP group (2.92 days). P=0.00

But in Maryam Nakshab[32] study, there was no significant difference in duration of CPAP requirement.

The duration of mechanical ventilation was also significantly lower with Surfactant compared to CPAP in treatment failure cases

The mean duration of mechanical ventilation with Surfactant was 4.83 days and with CPAP alone was 3.3 days. P=0.046. The results are similar with Rojas MA et al study[4], Verder H study[30] and Reininger A et al study[38].

There were no significant differences in the primary outcomes and most secondary outcomes between CPAP alone and Surfactant. This is supported by other studies including Maryam Nakshab[32] study and Mahmoud Imani study[33].

In one study by Levesque et al in 2011,[39]five strategies were introduced as superior practices for the treatment of respiratory problems in neonates to reduce the need for mechanical ventilation, the use of Surfactant, and costs. This study emphasised the application of CPAP in three of these five strategies, without the use of Surfactant, for better outcome of neonates.

Ammari et al. (2005)[40] reported that 78% of spontaneously breathing preterm babies with RDS and birth weight <1240 g could be managed with CPAP alone.

There is growing evidence that indicates early CPAP from birth is feasible and safe in preterm infants. NCPAP improves oxygenation in the few hours of the life.The use of CPAP was able to help in the establishment and maintenance of functional residual capacity (Gregory etal.1971)[7]. Although, many infants will develop RDS and require surfactant treatment (Bohlin, 2012)[11].

In Dunn et al's[8] study, 48% of patients on NCPAP did not need any intubation, and 54% managed without the administration of surfactant. In the study of Escobedo et al[41] only 29 of 67 infants in the control group needed intubation.

In addition, in the study of Rojas et al,[4]only 26% of infants in the NCPAP group needed surfactant administration. Therefore, it seems that more than half of the patients on NCPAP will not require intubation and surfactant treatment. The increasing tendency to use antenatal steroids can also lead to a reduced need for surfactant administration in mild and moderate RDS.[8]

Conclusions and summary

Mortality due to RDS in preterm neonates and need for mechanical ventilation is not statistically different between neonates treated with either nasal CPAP alone or surfactant and CPAP. In this study surfactant was not superior to CPAP in terms of incidence of BPD. Surfactant administration has decreased the duration of hospital stay. Surfactant administration required lesser duration of oxygen therapy than CPAP. Duration of mechanical ventilation is lesser with surfactant compared to CPAP. In conclusion, CPAP is an effective alternative treatment to surfactant in selected neonates. CPAP is a cost effective, less invasive, and requires less skill than surfactant for treatment of RDS. It is an ideal management option for RDS in a developing country.

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