P-ISSN: 2664-3685
E-ISSN: 2664-3693
www.paediatricjournal.com
IJPG 2019; 2(2): 52-57
Received: 25-05-2019
Accepted: 28-06-2019

Debasish Nanda
Assistant Professor, Department of Neonatology, IMS and SUM hospital, Siksha "O" Anusandhan University Deemed to be, K8, Kalinga Nagar, Bhubaneswar, Odisha, India

Sandeep Jhajra
Department of Neonatology, Postgraduate institute of Medical education and Research, Rohtak, Haryana, India

Sristi Goel
Department of Neonatology, Lady Hardinge Medical College, Kalawati Saran Children's Hospital and Smt. Sucheta Kriplani Hospital, New Delhi, India

Sushma Nangia
Department of Neonatology, Lady Hardinge Medical College, Kalawati Saran Children's Hospital and Smt. Sucheta Kriplani Hospital, New Delhi, India

Jatindra Nath Mohanty
Medical Research Laboratory, IMS and SUM hospital, Siksha "O" Anusandhan University Deemed to be, K8, Kalinga Nagar, Bhubaneswar, Odisha, India

Corresponding Author:
Debasish Nanda
Assistant Professor, Department of Neonatology, IMS and SUM hospital, Siksha "O" Anusandhan University Deemed to be, K8, Kalinga Nagar, Bhubaneswar, Odisha, India

Clinical profile and outcome of premature neonates with respiratory distress syndrome: An experience from a tertiary care neonatal unit in Delhi

Debasish Nanda, Sandeep Jhajra, Sristi Goel, Sushma Nangia and Jatindra Nath Mohanty

DOI: https://doi.org/10.33545/26643685.2019.v2.i2a.36

Abstract
Background: Respiratory distress continues to be a significant cause of admission to the NICU. It also contributes significantly to morbidity and adverse outcome during the clinical course of the disease. Advances in the field of neonatal care like the use of antenatal corticosteroids, CPAP and noninvasive Ventilation, surfactant, gentle mechanical ventilation, a better understanding of the disease process and early enteral nutrition have resulted in improved survival of premature neonates.
Methods: This was a prospective observational study done between January 2015 and September 2016 in a tertiary care NICU which included 209 preterm neonates between 26 weeks to 34 weeks of gestation with respiratory distress. The demographic, clinical, treatment profile and outcome were documented till discharge or death.
Result: Out of 209, nearly 61% of the admitted neonates received any course of antenatal corticosteroid. About 43% of the infants had one of the antenatal risk factors for early-onset sepsis. Overall survival was 72.7%. CPAP was used as the primary mode of respiratory support in 88% of cases and the incidence of CPAP failure within 7 days was 29.6%. Almost 56% of neonates required surfactant therapy. INSURE method was used for surfactant administration in 80% cases. The failure rate of the INSURE method of surfactant administration was 27.1% and 37.5% at 72 hours and 7 days of life respectively. Sepsis was the commonest complication and accounted for nearly two-thirds of the mortality. The most common morbidity was sepsis (64.6%) followed by hemodynamically significant patent Ductus Arteriosus (25.8%). The culture positivity rate was 9.6% and Klebsiella was the most common organism isolated (45%). Nearly 11.5% of all cases developed any grade of IVH and 5.7% cases had severe IVH (IVH grade ≥ 3). About 11.5% of the cases had NEC of any stage and nearly one-third of these cases had NEC stage ≥ 2. Retinopathy of prematurity was identified in 6.2% of all cases and nearly 47% of these infants required therapy. Only 7.2% of the cases required oxygen therapy beyond 36 weeks PMA.
Conclusion: Nasal continuous positive airway pressure is a safe and effective mode of respiratory support in preterm neonates with respiratory distress with a failure rate of around 30%. Nearly one-third of neonates who receive INSURE method of surfactant administration may subsequently require mechanical ventilation.

Keywords: Prematurity, respiratory distress, continuous positive airway pressure, surfactant

Introduction
Respiratory distress due to a variety of causes is a common cause of admission to the neonatal intensive care unit [1, 2]. With the improvement in neonatal care over the last decade, the survival of more premature neonates has increased significantly [3]. Among premature neonates, Hyaline membrane disease continues to be the predominant cause of respiratory distress and an important cause of mortality [2, 4]. The incidence of HMD is reported to be 6.8-14.1% of preterm live births in our country [5, 14]. The severity of respiratory distress is inversely related to gestational age [7]. The increasing usage of continuous positive airway pressure in spontaneously breathing neonate with respiratory distress and availability of natural or synthetic surfactants has improved survival and also reduced the incidence of chronic lung disease [4, 6]. The safety and efficacy of application of continuous positive airway pressure for respiratory distress are well established and it has been shown to reduce mortality, the requirement of mechanical ventilation, and the duration of hospital stay [8, 9, 10, 11]. Similarly, multiple high-quality evidence has proven the clinical utility of surfactant in the management of respiratory distress in preterm neonates. The use of surfactant has been shown to reduce neonatal mortality by up to up to 40% and pneumothorax by 30-65% [11].

The risk of adverse outcomes, including death or chronic lung disease remains high in premature neonates with respiratory distress, with nearly 40% developing death or BPD by 36 weeks of postmenstrual age [8, 13].
This study was conducted to describe the clinical profile, the efficacy of treatment modality and clinical outcome of a cohort of premature neonates with respiratory distress admitted to the neonatal intensive care unit at a tertiary care neonatal unit in Delhi.

Methods

This was a prospective observational study conducted at the neonatal care units of Lady Hardinge Medical College and associated hospitals in New Delhi from January 2015 to September 2016.

Population

Inborn preterm neonates between 26 completed weeks of gestation up to 34 weeks of gestation with a clinical diagnosis of Respiratory distress syndrome were included in the study. Respiratory distress was defined by the presence of at least two of the following criteria: respiratory rate > 60/minute**,** subcostal/intercostal recessions**,** expiratory grunt/groaning. Respiratory distress syndrome (RDS) was defined as the presence of RD in a preterm neonate with onset at birth or within six hours of life, and requiring oxygen or respiratory support at admission and/or suggestive skiagram of chest whenever available. Neonates with a major congenital malformation, antenatally diagnosed congenital heart disease, hydrops, pulmonary haemorrhage or shock before enrolment and multiple births were excluded from the study.

Intervention

All inborn premature infants with a clinical diagnosis of respiratory distress syndrome were assessed for eligibility. Gestational age was estimated from the last menstrual period, first-trimester ultrasonography, if history was reliable and appropriate documentation, was available. In other scenarios, the expanded new Ballard score was used to assess gestational age. Eligible neonates were enrolled after obtaining written consent from one of the parents.
Demographic and clinical data were documented using a predefined proforma. The severity of respiratory distress was assessed using the Silverman Anderson score. All premature neonates with a clinical diagnosis of RDS who were spontaneously breathing and had Silverman score > 2 at the time of admission to the unit were initiated on nasal CPAP. Both ventilator and bubble CPAP (Fisher and Paykel) was used to provide nasal CPAP during the study period. Infants with poor respiratory effort or who developed recurrent apnoeic episodes or had poor respiratory effort after birth was intubated and received mechanical ventilation as the primary mode of respiratory support. Infants who required intubation in the delivery room were reassessed at the time of admission to the unit and extubated to receive CPAP if they had a good respiratory effort. If respiratory effort was assessed to be ineffective, the patient was put on mechanical ventilation. Respiratory distress and other clinical data were recorded. The target saturation was 90%-94% with minimal or no respiratory distress. Chest X-ray was done whenever possible within the first two hours of life to confirm the clinical diagnosis.
Surfactant was administered to infants who required mechanical ventilation at the time of admission to the unit. In infants who were started with CPAP, the decision to administer surfactant was as follows. Infants with radiological features suggestive of HMD who continued to have significant respiratory distress or high oxygen requirement/ pressure (defined as the fractional inspired oxygen concentration (FiO2) > 30% or CPAP pressure ≥ 6 cm of water) were considered eligible for surfactant administration. Continued to have respiratory distress was defined by the persistence of Silverman score more than 2. In the absence of radiograph, only clinical parameters were considered for surfactant administration. CPAP failure was defined by the presence of the following features: occurrence of recurrent apnea, worsening respiratory distress, arterial pH < 7.25 with PCo2 > 60 mm Hg even with CPAP of 7 cm H2O and FiO2 > 0.70. Conventional mechanical ventilation, when used as a primary modality of support, was considered successful if the neonate could be extubated and maintained on any noninvasive mode of respiratory support for at least 72 hours post-extubation. Extubation failure was defined by requirement of reintubation within 72 hours of extubation. Reintubation was considered in case of recurrent apnea, failure to maintain adequate oxygenation with FiO2 > 0.6 or PCO2 > 60 mm Hg and pH < 7.25, excessive work of breathing with severe retraction. High frequency ventilation was considered in case of failure to maintain adequate gas exchange (PaO2 > 50 mm Hg or PCO2 > 60 mm Hg and pH < 7.25) with a MAP (Mean airway pressure) > 12 cm H2O and FiO2 > 0.70 on conventional ventilation. Failure of conventional mechanical ventilation was considered in case of requirement of HFO or extubation failure within 72 hours. Diagnosis of Necrotising enterocolitis was as per modified Bells criteria. Hemodynamically significant PDA was defined by the presence of a PDA with a predominant left to right shunt with a size of more than 1.5 mm with LA: Ao ratio of > 1.5 by echocardiography. Intraventricular hemorrhage was diagnosed by cranial ultrasonography. Bronchopulmonary dysplasia was defined by the 2005 NICHD criteria.

Statistical analysis

The data were collected using a pre-designed pretested proforma and thereafter checked manually for accuracy and completeness It was entered into an electronic database created in the Microsoft® office excel® 2007 (Microsoft, Redmond, CA, USA) with inbuilt range and logical checks. Mean and standard deviation was calculated for continuous data. Incidence of associated complications and outcomes were calculated as the proportion of all cases. To compare the difference in proportion of outcome, chi square test was used. A P value less than 0.05 was considered significant. All statistical analysis was performed using SPSS version 21.0.

Results

A total of 21,886 infants was delivered during the study period. Of these, 4139 (18.9%) infants were preterm (less than 34 weeks of gestation) and of these 990 neonates were admitted to the neonatal unit. A total of 339 infants developed respiratory distress (254 singletons and 85 multiple births). Of the 254 eligible singletons, 232 infants were assessed for eligibility. Finally, 209 preterm neonates

were enrolled in the study. All the 209 neonates were followed up till death or discharge, and the clinical course was monitored.

The mean gestational age was 29 (2.3) weeks and birth weight was 1145 (363) g. Nearly three-fourth were delivered vaginally. Nearly sixty percent of the mothers of the enrolled subjects received complete antenatal steroids (Table 1). Thirty-six percentages of the pregnancies were booked at LHMC, the rest of the cases included unbooked pregnancies and referred cases. Sixty-one percent of the mothers received any doses (includes partially covered or fully covered) of antenatal corticosteroids and only 36.5% of pregnant mothers received a full course of corticosteroid. Dexamethasone is the corticosteroid used in our hospital. Forty-four percentages of the pregnant women had a history of leaking per vaginum for more than 24 hours, which is considered a significant risk factor for early-onset neonatal sepsis. Vaginal delivery constituted the predominant mode of delivery and caesarean section was done in 27% of cases. Significant birth asphyxia as defined by an APGAR score of ≤ 3 at 1 minute of life was present in 12.5% of cases (Table 1).

Table 1: Baseline demographic characteristics of included patients

Baseline Characteristics	N=209
Gestational age (Weeks) (Mean±SD)	29.17±2.23weeks (26.0-34.0)
Birth weight (Grams) (Mean±SD)	1135.62±350.5 gm (600-2256)
Male (%)	45.5%
Antenatal booked pregnancy (%)	36%
Antenatal steroid (%)	61%
Antenatal steroid (Last dose 24 hours prior to delivery) (%)	36.5%
Cesarean delivery (%)	26.7%
Severe birth asphyxia (1 minute APGAR ≤ 3) (%)	12.5%
Duration of rupture of membrane >24 h (%)	43.7%

Number are expressed mean ± Sd, N (%) wherever applicable

Continuous positive airway pressure (CPAP) was used as the primary mode of respiratory support in 88.9% of neonates. A slightly more than half (n=96) infants in this group required surfactant during the clinical course. INSURE method was used for surfactant administration in all of these infants. About 29.6% (n=55) of neonates who received CPAP as a primary mode required mechanical ventilation subsequently. Invasive ventilation was used as a primary mode of respiratory support in 11% (n=23) infants as all these neonates had a poor respiratory effort at the time of admission to the unit. Surfactant was administered to all these neonates and they were continued on mechanical ventilation after surfactant instillation. Out of them, 13 (56.5%) infants were extubated successfully to CPAP (Table 2). Out of remaining 10 infants, 6 infants required high frequency ventilation during the clinical course and 4 infants had extubation failure within 72 hours.

Table 2: Primary outcome

Outcome	CPAP (%)	Intubation (%)
Treatment failure	55/186 (29.6%)	10/23 (43.5%)
Surfactant Therapy	96/186 (51.6%)	21/23 (91.3%)

Table 3: Secondary outcome

Morbidity	Number	Percentage
Sepsis (including suspect, probable and definite)	135	64.6%
Sepsis (positive screen)	74	35.4%
Meningitis	11	5.3%
Air leak	4	1.9%
Hemodynamically significant Patent Ductus Arteriosus	54	25.8%
Treatment for HsPDA	42	20.1%
Intraventricular hemorrhage(any grade)	24	11.5%
IVH ≥ grade 3	12	5.7%
NEC (any stage)	24	11.5%
NEC stage ≥ 2	16	7.7%
Any BPD	15	7.2%
Severe BPD	1	0.5%
Retinopathy of prematurity	13	6.2%
ROP requiring treatment	6	2.9%

Sepsis was the commonest morbidity amongst the study subjects. One hundred thirty five infants had a diagnosis of sepsis, which included the suspected sepsis (clinical features suggestive of sepsis and/or presence of 2 or more maternal risk factor for early-onset sepsis with birth weight ≤ 1000 grams), probable sepsis (clinical features with positive sepsis work-up) and proven sepsis (Culture positive). Clinical sepsis was defined by the presence of clinical signs and symptoms compatible with a diagnosis of sepsis. Nearly 35.4% (n=74) infants had a positive sepsis work-up. Culture positivity was around 9.6 % amongst all cases. Only 5.3% (n=11) had meningitis. Patent ductus arteriosus was the second most common morbidity with 26% (n=54) of the infants been diagnosed to have a hemodynamically significant PDA (hsPDA) out of which 78% (n=42) received pharmacotherapy and the rest were managed conservatively. Intraventricular haemorrhage complicated the clinical course in 11.5% (n=24) neonates, with half of them had IVH > grade 2. Necrotising enterocolitis (NEC) was diagnosed in 11.5% (n=24) infants. Two third of all cases of NEC had a stage ≥ 2. NEC accounted for 19.2% (n=11) deaths. The incidence of retinopathy of prematurity was

around 6%. Six neonates had severe ROP (ROP stage ≥ 3) which required laser therapy. Intravitreal anti-VEGF (Bevacizumab) was used in 2 babies. The incidence of any air leak was only 2%, while chronic lung disease (CLD) defined by an oxygen requirement at 36 weeks of gestation occurred in 7% of total cases (Table 3).

Table 4: Overall Survival according to gestation

Gestational age (weeks)	Number (%)	Survival (%)
< 28	57(27.3)	29(50.8%)
28-29$^{6/7}$	66(31.7%)	47(71.2%)
30-31$^{6/7}$	51(24.4%)	45(88.2%)
32-34$^{6/7}$	35(16.8)	31(88.6%)
Total*	209(100%)	152(72.7%)

Overall survival among the cohort was 72.7%. The incidence of mortality was higher at lower gestational age. About 51% of infants born below 28 weeks of gestation survived as compared to nearly 90% survival among neonates borne beyond 32 completed weeks (Table 4). Similarly, survival was about 56% of infants with birth weight less than 1000 grams and 92% of infants with birth weight more than 1500 grams. Sepsis was the commonest cause of death, contributing to two-thirds of all mortality (Table 5).

Table 5: Overall Survival according to birth weight

Birth weight (grams)	Number (%)	Survival (%)
≤ 1000	98(46.9%)	55(56.1%)
1001-1499	72(34.4%)	61(84.7%)
≥ 1500	39(18.6%)	36(92.3%)
Total*	209(100%)	152(72.7%)

Overall survival among the cohort was 72.7%. The incidence of mortality was higher at lower gestational age. About 51% of infants born below 28 weeks of gestation survived as compared to nearly 90% survival among neonates borne beyond 32 completed weeks. Similarly, survival was about 56% of infants with birth weight less than 1000 grams and 92% of infants with birth weight more than 1500 grams. Sepsis was the commonest cause of death, contributing to two-thirds of all mortality.

Discussion

Respiratory distress syndrome is the most common cause of respiratory failure in preterm neonates [2, 6]. In the current study, the incidence of RDS was around 21% in preterm infants below 35weeks of gestation. The incidence of RDS has been reported to be 6%-14.2% among preterm neonates in India [5, 14]. Mean gestational age and birth weight in the study are 29 weeks and 1130 grams respectively. Nearly 60% of the enrolled subjects were below 30 weeks of gestation and about 28% of subjects were extremely premature (< 28 weeks).

Continuous positive airway pressure was the preferred modality of respiratory support used in the study. As a primary modality, invasive ventilation was used in only 11% of preterm neonates with respiratory distress. Ninety-six (51.6%) infants initially stabilized on CPAP required surfactant administration based on the unit protocol. In all of them INSURE method was used for the administration of surfactant. These infants were intubated briefly for surfactant administration. Bovine surfactant (Survanta) was used at a dose of 100 mg/kg and instilled through the endotracheal tube in four aliquots. About 29.5% of neonates with CPAP as the primary mode of respiratory support required intubation and mechanical ventilation. Out of 96 neonates who received InSuRe, 26 neonates (27.1%) required intubation within 72 hours and 36 neonates (37.5%) required intubation within the first 7 days. Intubation was considered in the case of recurrent apnea (more than 2 episodes per hour for more than 4 hours or requiring more than one bag and mask ventilation) presence of hemodynamic instability and inability to maintain target saturation with a CPAP pressure of 7 cm and FiO2 of more than 0.70. Data from various observational studies and RCTs suggest that the rate of CPAP failure to be higher in smaller babies. In many of these larger RCTs, the rate of CPAP failure has been documented to be 30% to 55%, approaching almost 60% in neonates borne below 26 weeks of gestation [8, 15, 16]. Studies from low and middle-income countries have reported the failure of INURE method to vary from 32% to 45% [17, 18, 19, 20, 21]. Antenatal corticosteroids are considered as one of the important antenatal strategies to improve neonatal outcomes. The usage of antenatal steroids in these surfactant trials was more than 90% [8, 15, 16] as compared to 61% in the present study. The definition of CPAP failure was more liberal when compared with the high-quality surfactant trials done in developed countries. A more liberal definition of CPAP failure may be of value in increasing CPAP success, particularly in low resource settings.

More than 50% of preterm neonates with respiratory distress syndrome required surfactant administration. The study was conducted at one of the largest neonatal units under the government sector, which acts as a referral centre for high-risk deliveries, particularly premature deliveries. Many such high-risk mothers belonged to lower socioeconomic groups and did not have an adequate antenatal check-up. Only 61% of these high-risk mothers received antenatal steroids and 47% had leaking per vaginum for more than 24 hours before delivery. About 12.5% of these neonates required positive pressure ventilation in the labour room. Delivery room CPAP was also not used as a part of routine for initial stabilization during the study period. The combination of all these factors might have contributed to the increased severity of respiratory distress in the current study population. Incidence of failure of primary modality of support might be higher in babies who received mechanical ventilation as primary mode of respiratory support, but the number of patients who received conventional ventilation as the primary modality of support was less.

Sepsis was the commonest morbidity in the study cohort. Many investigators have reported a high Incidence of sepsis in such vulnerable populations. The incidence of sepsis was found to be around 42% in a recent randomized controlled trial comparing prophylactic versus early surfactant therapy in spontaneously breathing preterm neonates below 30 weeks of gestation receiving CPAP [22]. A similar incidence of sepsis has also been reported from a few other studies from India [23, 24]. Kandraju *et al*. have reported the incidence of culture-positive sepsis to be around 21% in their study [25]. The incidence of culture-positive sepsis was 9.6% in the present study. Klebsiella was the commonest organism isolated in the present study followed by staphylococcus. In a recent multicentric trial from India, Klebsiella spp, *Escherichia coli, and* Acinetobacter spp. Emerged as the most common gram-negative isolates whereas coagulase-

negative Staphylococcus, *Staphylococcus aureus*, and Enterococcus spp were the most common gram-positive isolates. Although Acinetobacter spp emerged as the most common isolated organism in the entire study cohort, Klebsiella spp was the predominant isolate in one of the centres enrolled in the study [28]. Another study from the same centre also has documented a predominance of Klebsiella and staphylococcus as the predominant organisms isolated in neonatal sepsis [29]. The incidence of patent ductus arteriosus in premature neonates has been reported to vary from 21% to 53% from various studies from LMICs [23, 26, 27]. The incidence of bronchopulmonary dysplasia remains quite high in extremely premature infants, with a reported incidence from 30%-45% [30, 31]. Studies from LMICs have reported an incidence of BPD to vary from 4% to 23% in preterm neonates born below 34 weeks of gestation [23, 25, 26, 27]. The incidences of other complications were comparable with the reported incidences from various other studies from India.

Overall survival of the study cohort was 72.7%, with survival improving significantly in neonates borne beyond 30 weeks of gestation. Nearly 90% of neonates borne beyond 30 weeks of gestation survived. About 27% of neonates were extremely preterm with a survival rate of 50.8%. Kirsten *et al*. have reported a mortality rate of up to 37% in preterm infants with respiratory distress [18]. Kandraju *et al*. have enrolled 153 preterm neonates borne after 28 completed weeks of gestation with respiratory distress to compare early routine versus late selective surfactant therapy in neonates receiving CPAP and have reported a mortality rate of around 13% [25]. Few other studies from India also have reported a higher mortality rate in these vulnerable populations [23, 24].

Conclusion

Nasal continuous positive airway pressure is a safe and effective mode of respiratory support in preterm neonates with respiratory distress with a failure rate of around 30%. Nearly one-third of preterm neonates who receive INSURE method of surfactant administration may subsequently require mechanical ventilation.

References

1. Singh M, Deorari K, Aggarwal R, Paul VK. Assisted ventilation for hyaline membrane disease. Indian Pediatr. 1995; 32:1267-1274.
2. Gnanaratnem J, Finer NN. Neonatal acute respiratory failure. Curr Opin Pediatr. 2000; 12(3):227-232.
3. Zeitlin J, Mortensen L, Cuttini M *et al*. Euro-Peristat Scientific Committee. Declines in stillbirth and neonatal mortality rates in Europe between 2004 and 2010: results from the Euro-Peristat project. J Epidemiol Community Health. 2016; 70(6):609-615.
4. Thukral A, Sankar M, Chandrasekaran A, Agarwal R, Paul V. Efficacy and safety of CPAP in low- and middle-income countries. Journal of Perinatology. 2016; 36:21-28.
5. Paul VK. Neonatal morbidity and mortality: report of the national neonatal and perinatal database. Indian pediatrics. 1999; 36(2):167.
6. Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database Syst Rev. 2007; (4):CD003063.
7. St Clair C, Norwitz ER, Woensdregt K, Cackovic M, Shaw JA, Malkus H *et al*. The probability of neonatal respiratory distress syndrome as a function of gestational age and lecithin/sphingomyelin ratio. Am J Perinatol. 2008; 25(8):473-480.
8. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB *et al*. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008; 358(7):700-708.
9. Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG. Continuous distending pressure for respiratory distress syndrome in preterm infants. Cochrane Database Syst Rev. 2002; (2):CD002271
10. Diblasi RM. Nasal continuous positive airway pressure (CPAP) for the respiratory care of the newborn infant. Respir Care. 2009; 54(9):1209-1235.
11. Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. N Engl J Med. 1971; 284(24):1333-1340.
12. Seger N, Soll R. Animal derived surfactant extract for treatment of respiratory distress syndrome. Cochrane Database Syst Rev. 2009; CD007836.
13. Kirpalani H, Millar D, Lemyre B, Yoder BA, Chiu A, Roberts RS *et al*. A trial comparing noninvasive ventilation strategies in preterm infants. N Engl J Med. 2013; 369(7):611-620.
14. Report of National Neonatal perinatal Database (NNPD), 2002-2003. Available from http://www.newbornwhocc.org/nnpo_html
15. Dunn MS, Kaempf J, de Klerk A *et al*. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics. 2011; 128(5):e1069-76.
16. Finer NN, Carlo WA, Walsh MC *et al*. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010; 362(21):1970-9.
17. Kanmaz HG, Erdeve O, Canpolat FE, Mutlu B, Dilmen U. Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. Pediatrics. 2013; 131(2):502-509.
18. Kirsten GF, Kirsten CL, Henning PA, Smith J, Holgate SL, Bekker A *et al*. The outcome of ELBW infants treated with NCPAP and InSurE in a resource-limited institution. Pediatrics. 2012; 129(4):952-959.
19. Afjeh SA, Sabzehei MK. The INSURE method in VLBW preterm infant with RDS. Pajoohandeh J. 2010; 15(5):199-203.
20. Tagare A, Kadam S, Vaidya U, Pandit A. Outcome of intubate surfactant rapidly extubate (InSuRE): an Indian experience. Indian J Pediatr. 2014; 81(1):20-23.
21. Sankar MJ, Gupta N, Jain K, Agarwal R, Paul VK. Efficacy and safety of surfactant replacement therapy for preterm neonates with respiratory distress syndrome in low- and middle-income countries: a systematic review. J Perinatol. 2016; 36(Suppl)1:36-48
22. Sandri F, Plavka R, Ancora G, Simeoni U, Stranak Z, Martinelli S *et al*. CURPAP Study Group. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics. 2010; 125(6):1402-9.
23. Narang A, Kumar P, Dutta S, Kumar R. Surfactant therapy for hyaline membrane disease: The Chandigarh

experience. Indian Pediatr. 2001; 38:640-646.
24. Femitha P, Rojo Joy, Adhisivam B, Prasad K, Bahubali D Gane, Vishnu Bhat B. Surfactant Replacement Therapy (SRT) in Respiratory distress syndrome (RDS). Curr Pediatr Res. 2012; 16(2):134-136.
25. 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.
26. Sanghvi KP, Merchant RH. Single dose surfactant rescue therapy in neonatal respiratory distress syndrome. Indian Pediatr. 1998; 35(6):533-6.
27. Gortner L, Wauer RR, Hammer H, Stock GJ, Heitmann F, Reiter HL *et al*. Early versus late surfactant treatment in preterm infants of 27 to 32 weeks' gestational age: a multicenter controlled clinical trial. Pediatrics. 1998; 102(5):1153-60.
28. Investigators of the Delhi Neonatal Infection Study (DeNIS) collaboration. Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: A cohort study. Lancet Glob Health. 2016; 4:752-60.
29. Bandyopadhyay T, Kumar A, Saili A, Randhawa VS. Distribution, antimicrobial resistance and predictors of mortality in neonatal sepsis. J Neonatal Perinatal Med. 2018; 11(2):145-153.
30. Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR *et al*. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network., Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010; 362(21):1970-9.
31. Stenson BJ, Tarnow-Mordi WO, Darlow BA, Simes J, Juszczak E, Askie L *et al*. BOOST II United Kingdom Collaborative Group; BOOST II Australia Collaborative Group; BOOST II New Zealand Collaborative Group, Oxygen saturation and outcomes in preterm infants. N Engl J Med. 2013; 368(22):2094-104.