

Effect of surfactant in respiratory distress syndrome as early rescue therapy verses delayed selective therapy in 28 to 32 weeks of gestation

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Abstract

Background: This prospective interventional study is designed to compare effect of giving surfactant in Respiratory Distress Syndrome (RDS), stabilized on CPAP, as Early Rescue Therapy verses Delayed Selective therapy in Early Preterms 28 to 32 weeks, using INSURE method. The main objectives if the studies are to study survival rate and mortality rate in the two groups and to compare the various complications of RDS and surfactant therapy in two groups. **Methods:** Cases were selected from the Preterm newborn, 28-30 weeks of gestation, confirmed cases of RDS on the basis of Chest X-ray findings and shake test, admitted. Total 96 cases were enrolled, out of which 51 randomly allotted to Early Rescue therapy and 45 to Delayed Selective treatment. Surfactants were administered using INSURE technique. Observations, clinical findings, course of treatment, vitals and outcomes were noted. Data was analyzed using appropriate statistical methods. Efforts were made to study maximum parameters to find out, which treatment strategy provides better outcomes and feasible in our settings. **Results:** In Early group more cases (68.6%) are discharged than in Delayed group (66.7%). Survival rate is more in Early group. In Early group less mortality is seen 16(31.4%), than in Delayed group 15(33.3%). Mean total duration of stay in NICU is decreased in Early group (7.08±6.209 days) as compared to Delayed group (8.896±793 days). **Conclusion:** Early Rescue Therapy increases the survival rate of preterm than the Delayed selective Treatment. Survival rate is increased when surfactant is administered earlier, less than two hours of life, during the course of RDS. Mortality is reduced in Early administration of surfactant but pulmonary causes of mortality is more in them as compared to Delayed administration, where pulmonary as well as non-pulmonary causes of death both affect the mortality.

Keywords: Surfactant, Respiratory Distress Syndrome (RDS) or Hyaline Membrane Disease (HMD)

Introduction

Respiratory Distress Syndrome (RDS) or Hyaline Membrane Disease (HMD) is a disease primarily of premature infants, accounting for most of mortality and morbidity, as well as its long term sequelae are responsible for most hospital visits. Its incidence is inversely related to gestational age and birthweight.

RDS has been recognized as the most common complication of prematurity, with more than half of those with birth weight of between 501 grams and 1500 grams, showing signs of RDS. Surfactant deficiency or decreased secretion is the main cause, and hence the

cornerstone of treatment of RDS. Clinical trials have confirmed that surfactant therapy is effective in improving the immediate need for respiratory distress syndrome. Since the discovery of surfactant, various synthetic and natural surfactants have been used to either prevent RDS as Prophylactic therapy or treat RDS as Early or Delayed selective treatment[1].

Prophylactic therapy is found to be superior over selective therapy. While Early administration of surfactant should be preferred in all settings, in settings where its use within the first two hours of life is not possible, use of surfactant in respiratory distress syndrome requiring mechanical ventilation should be encouraged irrespective of timing.

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In under-resourced settings, prophylactic use of surfactant is unaffordable owing to its high cost. Hence, it is important to know if the timing of surfactant administration as a Rescue therapy (i.e. its use only in infants with signs of respiratory distress) makes any difference in neonatal mortality and morbidity.

It is found that in preterm with RDS on nasal CPAP has benefit on Early Rescue therapy when compared to those with prophylactic surfactant treatment followed by mechanical ventilation[2].

With the increasing use of nasal CPAP, prophylactic surfactant therapy is now being obsolete. It has been found that in infants with RDS on nasal CPAP Early administration of surfactant results in better outcomes compared with Delayed administration of surfactant.

But in developing countries due to lack of skilled persons and inadequate referral services, it is not possible to give surfactant within 2 hours of life to all preterms with RDS.

Therefore it is important to know if there is poor outcome of giving surfactant as Delayed therapy to such patients. It is also important to determine if there is a time point beyond which administration of surfactant offers no benefit in the course of disease.

Materials and Methods

The present study was conducted in Department of Paediatrics, Gandhi Memorial Hospital, Shyam Shah Medical College, Rewa, Madhya Pradesh, for a period of 12 month from November 2014 to November 2015. It includes data of 96 preterm neonates (both inborn and out born) admitted in intensive care unit with RDS.

Study design: This is a prospective interventional randomized cohort study done in newborn intensive care unit in tertiary care hospital, Rewa after obtaining approval from institutional ethical clearance committee.

Inclusion Criteria

1. Early preterms 28 to 32 completed weeks of gestation
2. Preterms admitted in hospital within 2 hours of life
3. Preterms who have signs of respiratory distress

Exclusion Criteria

1. Preterms having birth weight < 1kg
2. Preterms having congenital heart diseases
3. Preterms having meconium aspiration syndrome
4. Preterms having congenital pneumonia or signs of Early onset Sepsis
5. Preterms having polycythemia

Methodology: Preterm Newborns of 28 to 32 completed weeks of gestation admitted in the intensive care unit with complain of respiratory distress fulfilling the inclusion criteria were included in the study while those fulfilling exclusion criteria at any point of study were excluded.

Respiratory distress syndrome was diagnosed based on following criteria:

1. Respiratory rate > 60/min
2. Silvermann Anderson Scoring: score greater than 3
3. Negative Shake test
4. Ski gram of chest showing poor expansion with air bronchograms or reticular pattern or ground glass opacity.

Bed-side Chest X-ray was done to confirm the diagnosis of RDS as well as to rule out congenital malformations or congenital pneumonia.

In both groups, cases were put on bubble nasal CPAP since admission. Confirmed and symptomatic cases of RDS were randomly divided onto two groups, Early Rescue group and Delayed selective treatment group. Cases were stabilized using appropriate measure as per protocols.

In Early Rescue group patient was put on nasal bubble CPAP starting at 5 cm of water and 40% FiO₂ and given surfactant soon after diagnosis was confirmed using bed side chest X- ray, but within two hours of birth using INSURE technique and again put on nasal bubble CPAP. Delayed therapy group was initially put on bubble nasal CPAP starting at 5 cm of water and 40% FiO₂, confirmed using bed side chest X- ray, and given surfactant after CPAP failure by INSURE method, after 2 hours of life, and again put on bubble nasal CPAP.

In both groups INSURE (Intubation Surfactant Extubation) technique is used to give surfactant. And after extubation patient again put on bubble nasal CPAP.

Results

The present study had been carried out in the Department of Pediatrics, Shyam Shah Medical College and Gandhi Memorial Hospital, Rewa, M.P. from November 2014 to November 2015.

Cases were selected from newborn patients admitted to Neonatal intensive Care unit after informed consent from attendants.

All the neonates were randomly divided into the two groups, Early and Delayed group.

Table-1: Distribution based on gestational age

Gestational Age(In Completed Weeks)	Early Rescue group		Delayed therapy group		Total	
	Number	(%)	Number	(%)	Number	(%)
28	9	17.6	6	13.3	15	15.6
29	2	3.9	1	2.2	3	3.1
30	11	21.6	10	22.2	21	21.9
31	0	0	3	6.7	3	3.1
32	29	56.9	25	55.6	54	56.3
Total	51		45		96	

Majority of cases (56.3%) belong to 32 completed weeks of gestation. 56.9% in early group versus 55.6% in Delayed group.

Table-2: Distribution of neonates as AGA/SGA.

	Early Rescue group, N (%)	Delayed therapy group, N (%)	Total N (%)
AGA	50(98.1)	39(86.6)	89(92.70)
SGA	1(1.9)	6(13.4)	7(7.30)
Total	51(53.1)	45(46.9)	96(100)

Majority of cases are appropriate for gestational age (92.7%) as compared to small for gestational age (7.3%).

Table-3: Weight-wise distribution of neonates in the two groups.

	Early Rescue group, N (%)	Delayed therapy group, N (%)	Total N (%)
VLBW	29(56.9)	23(51.1)	52(54.16)
LBW	22(43.1)	22(48.9)	44(45.84)
Total	51(53.1)	45(46.9)	96(100)

VLBW neonates are more in both groups. Overall 54.16% VLBW and 45.84% LBW neonates are enrolled in the study. Mean age of giving surfactant in early group is 56.67 minutes versus 977.36 minutes in Delayed group.

Table-4: Age of Giving Surfactant in Two Groups.

Age of surfactant (minutes)	Died		Survived		Total
	N	%	n	%	
< 2 hr	16	31.4	35	68.6	51
2--6 hr	7	15.6	11	24.4	18
6--12 hrs	4	8.9	6	13.3	10
12-24 hrs	3	6.7	5	11.1	8
>24 hr	1	2.2	8	17.8	9

In Delayed group majority of cases are given surfactant at 2-6 hours of age with mortality of 15.6%.

Table-5: Basic Characteristics of the Two Cohorts.

Basic characters	Early group(n=51)	Delayed group(n=45)	p-value
Mean gestational age (mean±SD)	30.75±1.59	30.89±1.45	0.65
Mean birth weight	1.43±0.50	1.49±0.51	0.57
Male (%)	30(58.6)	29(64.4)	
Female (%)	21(41.2)	16(35.6)	
AGA (%)	50(98)	39(86.7)	
SGA (%)	1(2)	6(13.3)	
LSCS (%)	14(27.5)	6(13.3)	
NVD (%)	37(72.5)	39(86.7)	
VLBW (%)	29(56.8)	23(51.1)	
LBW (%)	22(43.2)	22(48.9)	
Mean duration of hospital stay	7.08±6.209	8.89±6.793	0.176
Mean number of times of giving surfactants	1.24±0.47	1.18±0.39	0.52

Table-6: Pulmonary complications in the two groups.

Pulmonary complications	Early Rescue group		Delayed therapy group		Total	
	Number	%	number	%	number	%
No complication	31	60.8	29	64.4	60	62.5
Pulmonary haemorrhage	15	29.4	9	20	24	25
Pneumothorax	3	5.9	3	6.7	6	6.3
Collapse	5	9.8	7	15.6	12	12.5
Emphysema	0		1	2.2	1	1.0
BPD	0		1	2.2	1	1.0

Overall 62.5% of cases do not develop any pulmonary complications. Pulmonary haemorrhage is the most common complication 25% followed by collapse in 12.5% and pneumothorax in 6.3%.

Table-7: Comparison of primary outcomes in two groups based on birth weight.

Surfactant Therapy	Birth Weight	Survived	Death	Total	P- Value
Early [N=51]	VLBW	16	13	29	0.017
	(<1.5 Kg)	31.4%	25.5%		
	LBW	19	3	22	
	(>1.5 Kg)	37.2%	5.9%		
Delayed [N=45]	VLBW	12	11	23	0.035
	(<1.5 Kg)	26.7%	24.4%		
	LBW	18	4	22	
	(>1.5 Kg)	40.0%	8.9%		

Discharge rate is more in Early group 68.6% and mortality is more in Delayed group 66.7%.

Significantly more deaths in birth weight <1.5 kg. Mortality Is More InVLBW Infants In Both Early and Delayed group.

- In Early group more cases (68.6%) are discharged than in Delayed group (66.7%). Survival rate is more in Early group. In Early group less mortality is seen 16(31.4%), than in Delayed group 15(33.3%). Mortality rate is less in early group.
- Mean total duration of stay in NICU is decreased in Early group (7.08±6.209 days) as compared to Delayed group (8.896.±793 days).
- Among the discharged patients mean duration of stay is decreases in Early group (8.51±6.84 days) than in Delayed group (11.00±7.25 days). Hence cases in early group discharged earlier.
- Mean number of times of giving surfactant in early group(1.24±0.47) is more than in Delayed group (1.18±0.39).
- 62.5% of all cases who received surfactant, do not develop any respiratory complications or air leak syndromes.
- Among all patients pulmonary haemorrhage is the most common complication (25%) followed by collapse (12.5%) and pneumo-thorax (6.3%). Emphysema and BPD is developed only in 1% patient each.

Statistical Analysis- Statistical analysis was done using computer software (SPSS version 20). The qualitative data were expressed in proportion and percentages and the quantitative data expressed as mean and standard deviations. The difference in proportion was analysed by using chi square test and the difference in means were analysed by using student T Test [unpaired] and one way ANOVA.

Significance level for tests was determined as 95%, p value is significant if P< 0.05). The critical values for the significance of the results were considered at 0.05 levels.

Discussion

Clinical trials have confirmed that surfactant therapy is effective in improving the immediate need for respiratory support and clinical outcome of premature newborn when compared with placebo (European Exosurf study, 1992[4]) or when compared with controls in which surfactant administration was not possible due to financial constraints. *Femitha et al* [5] in their study to audit outcome of surfactant therapy found survival of 71.3% in preterms given surfactant, and also found that survival increased with gestational maturity and birth weight.

Trials have studied a wide variety of surfactant preparations, natural as well as synthetic [6]; used either prophylactically or in the treatment of established RDS.

Using either strategy, surfactant significantly reduces incidence of air leak syndrome, broncho-pulmonary dysplasia, and results in significant improvement in survival of preterm.

This study is designed to compare effect of giving surfactant in Respiratory Distress Syndrome (RDS) as Early Rescue Therapy verses Delayed Selective therapy in spontaneously breathing Early Preterm Neonates 28 to 32 completed weeks of gestation.

Sandri F, Plavka R, Ancora G et al made a systemic review on 6 randomized and quasi-randomized controlled clinical trials, comparing Early selective surfactant administration (within the first 2 hours of life) verses Delayed selective surfactant administration to infants with established RDS.

In these studies surfactant is administered in infants intubated for respiratory distress, not specifically for surfactant dosage. The meta-analyses demonstrate significant reductions in the risk of neonatal mortality, chronic lung disease and chronic lung disease of death at 36 weeks associated with Early treatment of intubated infants with RDS.

Intubated infants randomized to Early selective surfactant administration also demonstrated a decreased risk of acute lung injury including a decreased risk of pneumothorax, pulmonary interstitial emphysema, and overall air leak syndromes.

A trend toward risk reduction for bronchopulmonary dysplasia (BPD) or death at 28 days was also evident. No differences in other complications of RDS or prematurity were noted [7]. Similarly, study population

in the studies referred to, include <30 weeks of gestation. All studies evaluated a population at high risk for RDS, but differed slightly in their inclusion criteria.

Konishi included babies of 500 g to 1500 g, AGA babies. The European Exosurf Trial (European Study 1992) included infants between 26 and 29 weeks' gestational age. *Gortner et al* included neonates between 27 and 32 weeks' gestational age.

The OSIRIS trial (OSIRIS 1992) did not specify specific inclusion criteria for gestational age or weight. *Plavka* included newborns with a gestational age of less than 30 weeks. *Lefort et al* studied infants less than 34 weeks' gestational age.

In present study we have taken Early preterm infants 28-32 completed weeks of gestation, both AGA and SGA babies, excluding ELBW infants. Total 96 cases are enrolled with 51(53.1%) in Early group and 45(46.9%) in Delayed group, with Mean gestational age of 30.75±1.59 weeks in Early group and 30.89±1.45 weeks in Delayed group (p=0.65).

Majority of cases belongs to 32 completed weeks of gestation 56.9% (n=29) in Early group and 55.6% (n=25) in Delayed group [4,7,8,9,10].

Most of these clinical trials are done in preterm babies who were intubated for respiratory distress, not specifically for surfactant dosage, and surfactant administration is done within first 2/3 hours of life.

In the present study, we have taken diagnosed cases of RDS who are spontaneously breathing, stabilized on nasal bubble CPAP since admission.

As due to lack of technical staff and equipment it is not possible to intubate and provide mechanical ventilation to all preterm with RDS.

Studies have shown nasal CPAP application and Early selective surfactant treatment is better than prophylactic therapy and early intubation in spontaneously breathing neonates [7].

CURPAP trial concluded that prophylactic surfactant therapy was not superior to nCPAP and Early selective surfactant in decreasing the need for mechanical ventilation and other morbidities of prematurity in spontaneously breathing very preterm infants on nCPAP. Of 208 inborn infants, 25 to 28 weeks of

gestational age, who were not intubated at birth, 105 were randomly assigned to prophylactic surfactant or nCPAP within 30 minutes of birth. 33 (31.4%) infants in the prophylactic surfactant group (n=103), needed mechanical ventilation in the first 5 days of life compared with 34 (33.0%) in the nCPAP group (RR 0.95, 95%P=0.80).

Death and type of survival at 28 days of life and at corrected 36 weeks of gestational age, and incidence of main morbidities of prematurity (secondary outcomes) were similar between groups.

A total of 78.1% of infants in the prophylactic surfactant group and 78.6% in the nCPAP group survived in room air at corrected 36 weeks of gestational age [7].

The Surfactant Positive Pressure and Pulse Oximetry Randomized Trial (SUPPORT) by the NICHD Neonatal Research Network, infants between 24 and 27 week of gestational age were assigned to intubation and surfactant treatment within 1 hour after birth or to CPAP treatment, including the possibility of surfactant administration if intubation criteria were met, demonstrated that CPAP with subsequent surfactant therapy (if needed) is an equivalent alternative to intubation and primary surfactant treatment.

Overall, death or BPD was not significantly different between the study groups.

A significantly lower mortality rate was found in infants who were born between 24 and 25 weeks and treated with CPAP compared to the same age group treated with intubation and surfactant therapy (death during hospitalization: 23.9% vs. 32.1%, P=0.03; death at 36 weeks: 20.0% vs. 29.3%, P=.01) [11].

Surfactant administration policy used in our study is Early surfactant administration in confirmed cases of RDS within 2 hours of life, with mean age of 56.67±50.50 minutes, and Delayed administration in cases who full-fill criteria of CPAP failure with mean time of 977.36±1105.80 minutes (p<0.001).

Konishi et al administered the Early dose of surfactant within the first 30 minutes of life with a mean time of 18 minutes to surfactant administration in the Early group [8]. The European Exosurf Trial (European Study) and the OSIRIS Trial (OSIRIS 1992) both defined early treatment as prior to two hours of life. The median time to surfactant administration in the early group in the OSIRIS trial (OSIRIS 1992) was 118

minutes in the early group. *Gortner et al* and *Lefort et al* used one hour of life as the cut-off for early treatment.

The average time to surfactant administration in the early group in the study by *Gortner et al* was 31 minutes. The study by *Plavka et al* considered Early treatment as surfactant administration given immediately after intubation, with an eligibility criteria for the study as intubation and assisted ventilation needed within 3 hours after delivery for significant RDS with a mean time of 5 minutes to surfactant administration in the Early group [4,7,9,10].

Majority of cases (N=18) in Delayed group received surfactant within 2-6hour, among them 11 (61.1%) cases survived and 7 (38.9%) cases died. 10 cases received 6-12 hours among which 6 (60%) cases survived and 4 (40%) cases died. 8 cases who received surfactant in 12-24 hours of age 5 (62.5%) cases survived and 3 (37.5%) cases died. 9 cases received surfactant >24 hours, among them 88.9% (n=8) cases survived and 11.1% (n=1) case died.

Overall maximum mortality is seen among cases where surfactant is given at 2-6 hours of age. Probable reason being majority of the cases in Delayed group given surfactant during this period.

Total duration of stay in NICU in Early group 7.08±6.209 days is significantly less than Delayed group 8.89±6.793 days (p- 0.176). Similarly among the discharged patients mean duration of stay was less in early group (8.51± 6.84 days) than delayed group (11.00 ±7.25).

Therefore cases in early group discharged earlier. In the study 60.8% (n=31) cases in Early group and 64.4% (n=29) cases in Delayed group do not develop any pulmonary complications.

Pulmonary haemorrhage is the most common complication in both groups, 29.4% (n=15) in Early group versus 20% (n=9) in Delayed group, but more in Early group. Surfactant used in the study is Neosurf, extract of natural bovine surfactant, studies have proved benefit of natural surfactant over synthetic [6], we are using this preparation, as it is under government supply in our settings.

Primary outcomes of this study are discharge or death. 68.6% (n=35) cases in Early group are successfully discharged as compared to 66.7% (n=30) in Delayed group. In European Exosurf Study out of 212 babies randomized to Early group 105 babies and out of 208 to

selective surfactant 142 babies developed RDS requiring surfactant (50% versus 68%; 95% CI of difference, 9% to 27%). At age 28 days, 175 Early and 163 selective babies survived (83% versus 78%, 95% CI, -3% to 12%)[4].

Mortality is 31.4% (n=16) in Early group versus 33.3% (n=15) in Delayed group p-value 0.83. Though mortality is less in Early group but the difference is not statistically different. Similar results are found in other studies also.

Gortner in his trial had 154 randomized to Early surfactant treatment, 163 to late surfactant found mortality 3.2% versus 1.8%; death or bronchopulmonary dysplasia (day 28) 25.9% versus 23.9%.

In ORISIS study early administration or Delayed selective administration; 96% versus 73% received surfactant, at median ages of 118 and 182 min. The risk of death or dependence on extra oxygen at the expected date of delivery was 16% (95% CI 25% to 7%) lower among infants allocated Early administration [9,10].

In both the groups it is found that survival rate of AGA babies (Early group 66.7%; Delayed group 60%) are more as compared to SGA babies. (Early group 1.9%; Delayed group 6.6%); more survival rate in Early group as compared to Delayed group but the difference is not significant p value- 0.91.

when compared in Early group survival rate in AGA cases (66.7%) is more than SGA cases (1.9%) (p-0.49) but difference is not significant.

And in Delayed group also survival rate in AGA babies (60%) is significantly more than SGA babies (6.6%), with p-value 0.35.

Konishi M1, Fujiwara T et al in their study found that the rate of intubation, severity of RDS, rate of surfactant administration, pulmonary air leaks, and days on the ventilator did not differ between AGA and SGA babies.

However, the requirement for prolonged nasal continuous positive airway pressure ($p < 0.001$), supplemental oxygen therapy ($p < 0.01$), and the incidence of bronchopulmonary dysplasia at 28 days and 36 weeks (both $p < 0.01$) was greater in SGA-infants[8]. In this study overall significantly more survival is seen ($p < 0.002$) LBW babies when compared with VLBW babies. 84.1% LBW patients survived compared to 53.8% VLBW patients.

Conclusion

- Early Rescue Therapy increases the survival rate of preterm than the Delayed selective Treatment.
- For spontaneously breathing preterm neonates, having RDS, but not intubated during first 2 hours of life for RDS, and stabilized on bubble nasal CPAP, Early surfactant administration does not provide significant benefit in reducing mortality over Delayed therapy.
- Survival rate is increased when surfactant is administered earlier, less than two hours of life, during the course of RDS.
- Preventive measure for associated co-morbidities and their Early diagnosis and prompt treatment should be done as, they are significantly related to mortality and seen more patients having Delayed administration of surfactant.
- VLBW and Gestation age < 30 weeks are significant independent risk factors for mortality.
- Pulmonary haemorrhage and pneumothorax have significant relation with poor outcome, therefore must be prevented, timely diagnosed and promptly treated.

What this study adds to existing knowledge?

For spontaneously breathing preterm neonates, having RDS, but not intubated during first 2 hours of life for RDS, and stabilized on bubble nasal CPAP, Early Rescue Therapy increases the survival rate than the Delayed selective Treatment.

Contribution by authors: PB: design of the study, data acquisition, data analysis, writing of manuscript; VT: contributed to the design and planning of the study, intellectual contribution; JS: contributed to study design, revision of the manuscript for important intellectual content.

All authors approved the final manuscript.

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