# Safety of Early Rescue Surfactant Replacement Therapy for Preterm Neonates with Respiratory Distress Syndrome at Neonatal Intensive Care Unit of a Tertiary Hospital

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**DOI:** 10.3126/jnps.v39i3.27321

**Submitted on:** 2020-01-19

**Accepted on:** 2020-04-22

**Acknowledgements:** I would like to thank all paediatric faculties and post graduate residents for their effort and contribution to make this successful.

**Funding:** Nil

**Conflict of Interest:** None declared

**Permission from IRB:** Yes

**To cite this article:** Yadav SK, Giri A. Safety of early rescue surfactant replacement therapy for preterm neonates with respiratory distress syndrome at neonatal intensive care unit of a tertiary hospital. J Nepal Paediatr Soc. 2019;39(3):162-7.

## ABSTRACT

**Introduction:** Respiratory distress syndrome (RDS) is an acute disease of preterm neonates and is caused by the deficiency of pulmonary surfactant. Surfactant deficiency can lead to alveolar collapse, atelectasis, impaired gas exchange, severe hypoxia and acidosis. Surfactant replacement therapy (SRT) is an integral part of management of preterm neonates with respiratory distress syndrome. The objective of the study was to evaluate the safety of early rescue surfactant replacement therapy in RDS.

**Methods:** This was a prospective observational study conducted in a 17 bedded teaching and referral NICU of Eastern Nepal over a period of seven months. All preterm neonates with clinical and radiological features of RDS were enrolled in the study. The safety of early rescue SRT was evaluated by measuring the outcomes: incidence of pulmonary haemorrhage, apnea, hypoxia and cardiac arrest. All data were entered into the worksheet of SPSS software version (19.0) and descriptive statistics including percentages and frequencies was analysed. The level of statistical significance adopted was p-value $< 0.05$.

**Results:** The survival rate of preterm babies with SRT was 64.7% (22 babies). The incidence / prevalence of pulmonary haemorrhage, apnea, hypoxia, and cardiac arrest during or immediately after SRT was 14.7%, 5.9%, 5.9% and 2.9% respectively.

**Conclusions:** This study suggests that SRT is an effective, safe and feasible intervention in level-3 neonatal units and has the potential to reduce neonatal mortality. The study also emphasises on the fact that SRT should be provided in settings where there is adequate manpower, professional skills and desired infrastructure to administer surfactant.

**Key words:** preterm neonates; respiratory distress syndrome; surfactant replacement therapy

## INTRODUCTION

Preterm birth complications are the most common cause of death in children aged five years or less. Out of the 6.3 million children who died before the age of five years in 2013, about one million (15.4%) died because of these conditions.[1] The major morbidities that result in deaths in preterm neonates include respiratory distress syndrome (RDS), intraventricular haemorrhage and necrotising enterocolitis. RDS is caused by the deficiency of pulmonary surfactant in preterm neonates. Its incidence increases with decreasing gestational age, the risk being 60% in less than 28 weeks and 30% between 28 and 34 weeks of gestation. If left untreated, it leads to high mortality; the reported case fatality is 57 to 89% in low- and middle-income countries (LMICs).[2]

Introduction of surfactant replacement therapy (SRT) in the 1990s marked the beginning of a new era in the management of prematurity-related surfactant deficiency and its clinical sequelae, respiratory distress syndrome (RDS).[3] In preterm babies with respiratory distress syndrome, exogenous surfactant helps to reduce pulmonary air leaks by 50% and neonatal mortality by 30%.[4] Administration of natural surfactant reduces acute respiratory disease, air leaks, bronchopulmonary dysplasia and mortality in preterm infants.[5]

Surfactant replacement therapy (SRT) is now accepted as the standard treatment protocol for preterm babies with respiratory distress syndrome.[6] SRT is not free from adverse effects. It can cause pulmonary haemorrhage, apnea, hypoxia and cardiac arrest. So, this study was carried out to evaluate the safety of SRT in preterm neonates with RDS.

## METHODS

This was a prospective observational study conducted in a 17- bedded Neonatal Intensive Care Unit in a tertiary care teaching institute located in Eastern Nepal. Perinatal Mortality Rate (PMR) of our institute is 9/1000 live births and Neonatal Mortality Rate (NMR) is 5/1000 live births. Total delivery at this hospital is around 11000 per year and preterm births are 11%. The study was conducted over a period of seven months from 2019 May to 2019 November. Preterm babies with gestational age ranging from 26 weeks to 35 weeks and birth weight from fewer than 1000 gm to 2100 gm with respiratory distress syndrome were included in this study whereas preterm babies with lethal congenital anomalies (e.g. Anencephaly, myelomeningocele, gastroschisis, diaphragmatic hernia) were excluded. All preterm babies who had clinical and radiological features of RDS were considered for early SRT. Silverman score was used for assessment of severity of respiratory distress in preterm babies, which was done at 30 min to one hour of life in all babies.[7] Under all aseptic precautions, the surfactant (Survanta; Abbott Laboratories, USA; Dose: 4 ml/kg) was administered intratracheally in preterm babies with features of RDS within two hours according to standard procedures in four divided aliquot applying INSURE approach {intubation, surfactant administration and extubation to Bubble Continuous Positive Airway Pressure (bCPAP)}.[8] After introduction of surfactant, intermittent inflation breath was given via Self Inflating Ambu Bag. Heart rate, $SPO_2$ and ECG monitoring was done throughout the procedure. Intra tracheal surfactant was given as an early rescue therapy within two hours of RDS. Repeat dose of surfactant therapy was considered in babies who still needed Bubble CPAP or if they required $FiO_2 \geq 0.35$ and mean airway pressure (MAP) > 7 cm $H_2O$ to maintain a $PaO_2$ 50 - 70 mm Hg and $PaCO_2 < 50$ mm Hg.[9] For the diagnosis of RDS in preterm babies following criteria were used: (i) Clinical features of respiratory distress which is defined as presence of any two of the following features[10]: (a) respiratory rate > 60/min (b) Subcostal / intercostal recessions (c) Expiratory grunt / groaning. In addition, presence of nasal flaring, suprasternal retractions, decreased air entry on auscultation of the chest wall also indicate the presence of respiratory distress. An infant who has an advanced degree of respiratory distress may exhibit additional signs, such as cyanosis, gasping, choking, apnea and stridor.[11] (ii) Radiological features of RDS which are under-aerated lungs, reticulo-granularity, air bronchograms, diffuse granularity, and white-out lungs in severe cases. The severity of RDS was classified on the basis of radiological features as follows: Mild: normal / decreased aeration and reticulo-granularity, Moderate: decreased aeration, air bronchograms and indistinct diaphragm and heart borders, Severe:

confluent opacification of lungs with loss of mediastinal and diaphragmatic borders.

The safety of early SRT in RDS was evaluated by measuring the outcomes: (i) Incidence / prevalence of pulmonary haemorrhage which is defined as proportion of neonates developing pulmonary haemorrhage (blood from the endotracheal tube associated with increase in ventilatory support, oxygen requirement or blood product replacement) during or immediately after SRT. (ii) Incidence/ prevalence of complications such as apnea, hypoxia/arrest during or immediately after SRT which is defined as proportion of neonates with apnea (cessation of breathing for > 20 seconds or for lesser duration but accompanied by bradycardia or cyanosis), hypoxia ($SpO_2$ < 85%) or arrest requiring cardiopulmonary resuscitation.

Ethical clearance was received from Institutional Review Committee (IRC) of our institute and written/verbal informed consent was taken from parents after explaining the benefits and possible complications of SRT. All the data were entered into the worksheet of SPSS software version (19.0) and descriptive statistics including percentages and frequencies were analysed. The level of statistical significance adopted was p-value < 0.05.

## RESULTS

There were 480 neonates who were admitted to neonatal intensive care unit (NICU) for various indications during the study period. The most common indications for NICU admissions were birth asphyxia, meconium aspiration syndrome, neonatal sepsis and respiratory distress syndrome (RDS). Out of 480 neonates admitted in NICU, 39 were preterm. Thirty four preterm babies satisfied the inclusion criteria and enrolled in the study (five excluded: four were out born and one neonate had myelomeningocele).

In total, 34 preterm babies with RDS who received SRT were included in this study. Among them, 53% were males and 47% were females. Among 34 babies, 76.5% were spontaneous vaginal deliveries. Among the neonates enrolled in the study, mean gestational age was 30.70 ± 2.05 weeks and mean birth weight was 1666.17 ± 407.63 gm as shown in Table 1. Similarly, 76% of babies developed respiratory distress within one hour of birth and

**Table 1.** Demographics and clinical parameters of preterm babies (n = 34)

| Variables | Mean ± Std Deviation | Range |
|---|---|---|
| Gestational age (weeks) | 30.70 ± 2.05 | (26 - 35) weeks |
| Birth weight (gm) | 1666.17 ± 407.63 | (850 - 2100) gm |
| Silverman score | 6.73 ± 1.28 | (5 - 10) |
| Respiratory distress after birth (min) | 72.05 ± 49.28 | (30 - 190) min |
| Apgar at 1 min | 6.61 ± 1.59 | (3 - 9) |
| Apgar at 5 min | 9.20 ± 0.88 | (6 - 10) |
| Duration of bCPAP (hr) | 67.64 ± 20.78 | (18 - 100) hrs |
| Duration of mechanical ventilation (hr) | 25.58 ± 30.43 | (0 - 72) hrs |
| Duration of radiological lung expansion (hr) | 75.61 ± 21.67 | (20 - 96) hrs |
| Ist dose of surfactant administration (min) | 97.94 ± 30.80 | (60 - 180) min |
| 2nd dose of surfactant administration in 6 babies (hr) | 19.33 ± 4.13 | (12 - 24) hrs |
| Length of hospitalization (days) | 12.5 ± 5.11 | (5 - 21) days |

mean Silverman score was 6.73 ± 1.28 and the mean onset of respiratory distress was 72.05 ± 49.28 minutes after birth. Thirty two babies received surfactant within one hour of respiratory distress and mean time of instillation of 1st dose of surfactant was 97.94 ± 30.80 minutes after birth. Only six babies required second dose of surfactant and mean time was 19.33 ± 4.13 hrs as shown in Table 1. The mean duration of hospital stay was 12.5 ± 5.11 days which is depicted in Table 1.

Among the mothers of preterm babies, 38.3% received complete antenatal steroid and 53% received incomplete steroid (two doses of Dexamethasone). Fifty nine percent of the babies did not require any form of resuscitation whereas

**Table 2.** Antenatal steroid and neonatal parameters

| Variables | Number (%) |
|---|---|
| **Antenatal steroid** | |
| No | 3 (8.8) |
| Incomplete | 18 (52.9) |
| Complete | 13 (38.3) |
| **Resuscitation at birth** | |
| Not required | 20 (58.8) |
| Initial steps | 12 (35.3) |
| Bag and mask | 2 (5.9) |
| **Cause of death** | |
| No mortality | 28 (82.3) |
| Sepsis | 2 (5.9) |
| Sepsis with DIC | 4 (11.8) |
| **Outcome of babies** | |
| Discharged | 22 (64.8) |
| Mortality | 6 (17.6) |
| Left against medical advice (LAMA) | 6 (17.6) |

35% of babies required initial steps of resuscitation. Similarly, sixty four percent of the babies were discharged and 18% of babies died of sepsis with / without disseminated intravascular coagulation (DIC) as shown in Table 2.

Table 3 depicts that the preterm neonates who had received SRT and died of sepsis with / without DIC were ≤ 1000 gm of birth weight and 26-28 weeks of gestation. Out of 22 babies who survived, most of them had birth weight in between 1001-2000 gm and 29-32 weeks of gestation as shown in Table 3. The babies who had received SRT, five (14.7%) had pulmonary haemorrhage, two (5.8%) had apnea, two (5.8%) developed hypoxia and one had cardiac arrest requiring CPR as depicted in Table 4.

## DISCUSSION

RDS also known as hyaline membrane disease (HMD) is seen almost exclusively in preterm infants. The risk of RDS decreases with increasing gestational age: 60% of babies born at fewer than 28 weeks' gestation, 30% of babies born between 28 and 34 weeks' gestation, and fewer than 5% of babies born after 34 weeks' of gestation develop RDS.[12]

**Table 3.** Outcome of babies with respect to birth weight and gestational age

| Variables | Outcome of babies (n=34) | | | | P-value |
|---|---|---|---|---|---|
| | Dis-charged | Mortality | LAMA | Total | |
| **Birth weight (gm)** | | | | | |
| ≤ 1000 | 0 | 4 | 1 | 5 | < 0.001 |
| 1001-2000 | 17 | 2 | 3 | 22 | |
| 2001-2100 | 5 | 0 | 2 | 7 | |
| **Gestational age (weeks)** | | | | | |
| 26-28 | 0 | 5 | 1 | 6 | |
| 29-32 | 19 | 1 | 3 | 23 | < 0.001 |
| 33-35 | 3 | 0 | 2 | 5 | |

SRT is an integral part of management of preterm neonates with RDS. SRT has been a major stepping stone in the history of neonatology that has saved innumerable lives all over the world.

Surfactant is necessary for inflation of lung alveoli by reducing its surface tension. Clinical trials have confirmed that SRT is effective in improving the immediate need for respiratory support and the clinical outcome of premature newborns. In this study, 34 preterm infants fulfilled inclusion criteria and enrolled in study. All babies received early rescue SRT. The survival rate of preterm babies with SRT was 64.7% (22 babies) and 17.8% of babies died of sepsis with / without DIC. Among the enrolled babies, 14.7% had pulmonary haemorrhage, 5.9% had apnea, 5.9% had hypoxia, and one neonate developed cardiac arrest that required CPR. Five case-series from Brazil, India, South Africa and Turkey reported the proportion of neonates developing pulmonary haemorrhage during/after SRT varied from 5 to 12%. All of them were conducted in level-3 NICUs.[13,14] None of the included studies reported the incidence of apnea or cardiac arrest during or immediately after SRT. So, the results of these studies are more or less similar to ours. A similar study conducted by Femitha P et al. in Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Pondicherry, India found sepsis (43.5%), apnea (4.9%) and pulmonary haemorrhage (3.9%) as a co-morbid condition.[15] In another study conducted at Kathmandu Medical College Teaching Hospital

**Table 4.** Safety profile of Surfactant (n=34)

| Variables | Pulmonary hemorrhage | | p-value | Apnea | | p-value | Hypoxia | | p-value | Cardiac arrest | | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Birth Wt (gm)** | **Yes** | **No** | < 0.001 | **Yes** | **No** | 0.315 | **Yes** | **No** | 0.315 | **Yes** | **No** | 0.05 |
| ≤ 1000 | 4 | 1 | | 1 | 4 | | 1 | 4 | | 1 | 4 | |
| 1001 - 2000 | 1 | 21 | | 1 | 21 | | 1 | 21 | | 0 | 22 | |
| 2001 - 2100 | 0 | 7 | | 0 | 7 | | 0 | 7 | | 0 | 7 | |
| **Gestational age (weeks)** | **Yes** | **No** | < 0.001 | **Yes** | **No** | 0.007 | **Yes** | **No** | 0.007 | **Yes** | **No** | 0.09 |
| 26 - 28 | 4 | 2 | | 2 | 4 | | 2 | 4 | | 1 | 5 | |
| 29 - 32 | 1 | 22 | | 0 | 23 | | 0 | 23 | | 0 | 23 | |
| 33 - 35 | 0 | 5 | | 0 | 5 | | 0 | 5 | | 0 | 5 | |

reported pulmonary haemorrhage in 62.5% of babies as co-morbid condition.[16] One RCT by Flores-Nava G et al. reported the incidence of pulmonary haemorrhage and found no difference between SRT and control groups.[17] One observational study from Uruguay that compared the outcomes of neonates who received SRT with those of historical controls in 19 NICUs across five Latin American countries and found the proportion of neonates with pulmonary haemorrhage (and patent ductus arteriosus) was significantly higher in neonates who received surfactant.[18] The result of this study does not favour our findings. In contrast, another study from Chile that reported data from the network of NICUs participating in the national program on surfactant use found no difference in the proportion of neonates developing pulmonary haemorrhage before and after introduction of SRT. However, the proportion with pulmonary haemorrhage was very high about 30% in both groups.[19]

Ours is a single centric study from one part of the country. The findings may not be applicable all over the country. This is a cross-sectional study conducted over a period of seven months. This study has not followed the preterm babies for the development of long-term sequelae like retinopathy of prematurity, bronchopulmonary dysplasia and neurological development.

## CONCLUSIONS

SRT is an effective, safe and feasible intervention in level-3 neonatal units and has the potential to reduce neonatal mortality. The study also emphasises on the fact that SRT should be provided in settings where there is adequate manpower, professional skills and desired infrastructure to administer surfactant.

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