www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2015;4(1):e040118
doi: 10.7363/040118
Received: 2015 Jan 31; revised: 2015 Mar 14; accepted: 2015 Mar 26; published online: 2015 Apr 09

Original article

A retrospective evaluation of term infants treated with surfactant therapy

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Abstract

Aim: To investigate the clinical and therapeutic characteristics and outcomes of term infants who received surfactant therapy (ST) for severe respiratory failure in our neonatal intensive care unit (NICU).

Methods: The medical records of term infants (gestational age ≥ $37^{0/7}$ weeks) who received ST between 2003-2012 in NICU of Hacettepe University Ihsan Dogramaci Children's Hospital were evaluated retrospectively.

Results: During ten years period, 32 term infants received ST; the mean gestational age was 38.1 ± 0.88 wk and the mean birth weight was 2,936 ± 665 g. The underlying lung diseases were severe congenital pneumonia (CP) in 13 (40.6%), acute respiratory distress syndrome (ARDS) in 5 (15.6%), meconium aspiration syndrome (MAS) in 5 (15.6%), congenital diaphragmatic hernia (CDH) in 4 (12.5%), respiratory distress syndrome in 3 (9.4%) and pulmonary hemorrhage in 2 (6.3%) infants. The median time of the first dose of ST was 7.75 (0.5-216) hours. Pulmonary hypertension accompanied the primary lung disease in 9 (28.1%) infants. Mortality rate was 25%.

Conclusion: In term infants, CP, ARDS and MAS were the main causes of respiratory failure requiring ST. However, further prospective studies are needed for defining optimal strategies of ST in term infants with respiratory failure.

Keywords

Newborn, respiratory failure, respiratory distress syndrome, surfactant therapy, term, lung.

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How to cite

Sürmeli-Onay O, Korkmaz A, Yiğit S, Yurdakök M. A retrospective evaluation of term infants treated with surfactant therapy. J Pediatr Neonat Individual Med. 2015;4(1):e040118. doi: 10.7363/040118.

Introduction

Surfactant therapy (ST) has been established as an effective and safe therapy for immaturity-related pulmonary surfactant deficiency and it reduces initial inspired oxygen and ventilation requirements as well as the incidence of respiratory distress syndrome (RDS) if given prophylactically, mortality and pulmonary air leaks. Apart from preterm infants, term newborn infants may also require ST for RDS which may develop due to other neonatal lung diseases. In term infants, other neonatal lung diseases characterized by inactivated or dysfunctional pulmonary surfactant or hereditary surfactant protein deficiencies can cause severe respiratory failure necessitating ST. These include meconium aspiration syndrome (MAS), pneumonia (congenital or postnatal), pulmonary hemorrhage, acute respiratory distress syndrome (ARDS), bronchopulmonary dysplasia (BPD) and congenital diaphragmatic hernia (CDH), persistent pulmonary hypertension of the newborn [1-3]. Persistent pulmonary hypertension of the newborn is mostly associated with neonatal lung diseases. Mortality of respiratory failure in term infants was reported to be as high as 35%. ST should be considered as an urgent and life saving therapy in these infants, however in the literature there isn't any standard approach and clinical guideline for ST in this population.

In this retrospective study, we aimed to identify the clinical and therapeutic characteristics and outcomes of term newborn infants who received ST for severe respiratory failure in a ten-year period in our neonatal intensive care unit (NICU).

Materials and methods

Study design

We conducted a retrospective study including full-term newborn infants whose gestational ages were ≥ $37^{0/7}$ weeks and who had severe respiratory failure due to various pulmonary diseases in our tertiary care level NICU of Hacettepe University Ihsan Dogramaci Children's Hospital, Ankara, Turkey, between January 1st 2003 and December 31st 2012. The hospital files and electronic medical records of the patients were evaluated. The study was approved by the Ethics Committee of the University.

Clinical data

Maternal data included major medical (chronic hypertension, diabetes mellitus) and obstetric (premature rupture of membranes, histologic and/or clinical chorioamnionitis, preeclampsia, gestational diabetes) diseases and prenatal steroid therapy.

Neonatal data included gender, gestational age (according to the last menstrual period), birth weight, intrauterine growth (according to growth curve of Fenton et al. [4]), mode of delivery, 5th minute Apgar score, presence of aggressive resuscitation at birth (bag and mask positive pressure ventilation [PPV], PPV through an endotracheal tube, chest compression or drug administration), complete blood count and peripheral blood smear, blood and tracheal aspirate cultures, serum CRP and procalcitonin levels on the first day of life or on the day of ST, arterial blood gas analysis before ST, oxygenation index (OI = mean airway pressure [MAP] x fractional inspired oxygen concentration [FiO_2] / PaO_2) before ST, chest X-ray findings before ST, the type of neonatal lung disease, the type, timing, dosing, frequency of ST, OI after ST, complications, accompanying neonatal morbidities such as patent ductus arteriosus (PDA), pulmonary hypertension, neonatal sepsis (culture-proven), necrotizing enterocolitis, intraventricular hemorrhage, BPD, echocardiographic findings if available, durations of mechanical ventilation, supplemental oxygen, hospital stay, presence of antibiotic and inotropic therapies and rate of mortality.

The definition of severe respiratory failure and need for ST were the need for mechanical ventilation with a $FiO_2 > 0.5$, MAP ≥ 7 cm H_2O, OI ≥ 15 and/or abnormal arterial blood gas analysis showing hypoxia ($PaO_2 < 50$ mmHg), hypercapnia ($PaCO_2 > 50$ mmHg) or acidosis (pH < 7.2) combined with radiological evidence of pulmonary disease on the chest X-ray. Chest X-rays of the patients were obtained from hospital files or from the hospital electronic Picture Archiving and Communication System (PACS) if available and re-evaluated by a senior neonatologist for the confirmation of the diagnoses.

ST was defined as "early" if it was given in the first 2 hours of life and was defined as "late" if it was given after the second hour of life. If ST was given in the first 28 days of life it was termed as "neonatal ST" and if it was given after 28 days of life, it was named as "post-neonatal ST". In our NICU natural, animal derived surfactant preparations are used

and in term newborn infants beractant (Survanta®, Abbott Lab., USA) is used for ST. All infants received ST after endotracheal intubation and with bolus administration at a dose of 100 mg/kg (4 ml/kg) in one or two divided doses.

Diagnostic criteria for various neonatal lung diseases were as follows:

1. RDS: the presence of respiratory distress (grunting, tachypnea, retractions, cyanosis); supplemental oxygen and/or PPV requirement; typical chest X-ray findings with reticulogranular patterns, air bronchograms or ground glass appearance *in the absence of* all signs of suspected/proven infection (pneumonia) such as:
   a. history of maternal chorioamnionitis or maternal urinary tract infection,
   b. elevated or decreased leukocyte count (> 25,000/mm^3 or < 5,000/mm^3),
   c. elevated serum CRP (> 2 mg/dl) or procalcitonin level (> 2 mg/dl) and positive blood or tracheal aspirate culture which was obtained on the first day of life [5].
2. Congenital pneumonia (CP): the presence of respiratory distress, supplemental oxygen and/or PPV requirement, extra-pulmonary clinical signs of sepsis beginning from birth; typical chest X-ray findings *in the presence of* any suspected/proven infection such as determined above.
3. Transient tachypnea of the newborn (TTN): mild to moderate respiratory distress occuring usually after elective cesarean section (CS) without labor and mainly characterized by tachypnea and need for supplemental oxygen or at most positive airway pressure with nasal CPAP, mild to moderate cardiomegaly, perihilar streaking and fluid-filled interlobar fissures on the chest X-ray, which usually resolves in 48-72 hours.
4. MAS: respiratory distress in an infant born through meconium stained amniotic fluid whose respiratory and radiological signs can not be otherwise explained.
5. CDH: respiratory distress accompanied by the presence of typical chest X-ray and/or abdominal ultrasonography findings (thoracic location of gastric/intestinal loops and/or other abdominal organs such as liver, spleen).
6. Pulmonary edema: accumulation of fluid in pulmonary interstitial tissue and/or pleural effusion leading to respiratory distress and typical radiological findings with interlobar fissure fluid accumulation and opacification of lung parenchyma which usually develops due to hydrops fetalis or heart failure.
7. ARDS: acute inflammation of the lung parenchyma leading to impaired gas exchange and hypoxic respiratory failure which is caused by a catastrophic pulmonary or non-pulmonary event, such as asphyxia, shock, sepsis or disseminated intravascular coagulation.
8. Pulmonary hemorrhage: acute onset of severe endotracheal bleeding with respiratory deterioration, drop in hematocrit and development of multilobar infiltrates on chest X-ray [6].

Perinatal asphyxia/hypoxia was defined as an arterial cord blood pH < 7.0 and a 5th minute Apgar score < 5 with clinical and neurological signs of hypoxic organ failure. Echocardiography is a routine procedure in our NICU for the patients suffering from respiratory failure. In all infants echocardiography were performed before ST. Pulmonary hypertension was defined as elevated right ventricular and pulmonary artery pressure leading to right-to-left ductal or foramen ovale shunt detected by echocardiography.

The other variables were the duration of mechanical ventilation, the duration of oxygen support, the duration of hospitalization, the rate of BPD and mortality.

Statistical analysis

Statistical data were analyzed by using SPSS 16.0 software on a personal computer. Continuous variables were compared by using two-tailed *t* test for parametrically distrubuted data or Mann-Whitney for non-parametrically distributed data. Categorical variables were analyzed by χ^2 test or Fisher's exact test. A p value < 0.05 was accepted as statistically significant.

Results

Among 14,786 inborn term newborn infants, 32 (0.2%) have been found to receive ST for severe respiratory failure in the NICU of Hacettepe University Ihsan Dogramaci Children's Hospital, Ankara, Turkey during a ten-year period. Most of the infants (20, 62.5%) were male and nearly all of them (29, 90.6%) had been delivered by CS. Ten (31.3%) infants had maternal histological or clinical chorioamnionitis. Sixteen (51.6%) infants received aggressive resuscitation at birth. The leading causes of severe respiratory failure were CP (13, 40.6%) followed by ARDS (5, 15.6%), MAS (5, 15.6%), CDH (4, 12.5%), RDS (3, 9.4%) and pulmonary hemorrhage (2, 6.3%). ARDS developed due to severe sepsis and multiorgan failure in 3 (15.5%), severe hypoxia developed due to formula aspiration in 2 (6.3%)

infants. Pulmonary air leak syndrome (pulmonary interstitial emphysema and/or pneumothorax) occured in 6 (18.8%) infants after ST. Secondary pulmonary hypertension accompanied the primary lung diseases in 9 (28.1%) infants. Intravenous iloprost (PGI_2), oral sildenafil citrate, intravenous magnesium sulphate and inhaled nitric oxide were administered alone or in combination therapy for pulmonary hypertension in these infants. All infants received antibiotic therapy and 19 (59.3%) received inotropic therapy with dopamine or dobutamine. The demographic and clinical characteristics of the infants are summarized in **Tab. 1**.

Respiratory characteristics of the infants are given in **Tab. 2**. Twenty-eight (87.7%) infants were hypoxic before ST. Most of the infants (28, 87.5%) received ST in the neonatal period while 4 (12.5%) received ST in the post-neonatal period. All of the infants requiring ST in the post-neonatal period were ARDS. Great majority (25, 78.1%) of the infants received ST after the second hour of life with multiple doses (27, 84.4%). Radiological improvement was achieved after the last dose of ST in 26 (81.3%) infants while no change was detected in 6 (18.7%) infants. Mortality rate in our study group was 25.0% (n = 8). Mortality rates were 75.0% (3/4) in CDH, 50% (1/2) in pulmonary hemorrhage, 40% (2/5) in MAS, 15.3% (2/13) in CP.

Table 1. Demographic and clinical characteristics of all term infants who received ST (n = 32).

Gestational age (wk), mean ± SD (range)	38.1 ± 0.8 (37-40.5)
Birth weight (g), mean ± SD (range)	2,936 ± 665 (1,090-3,900)
Gender (M/F), n (%)	20 (62.5)/12 (37.5)
Intrauterine growth restriction, n (%)	5 (15.6)
CS, n (%)	29 (90.6)
Maternal diabetes, n (%)	1 (3.2)
Preeclampsia, n (%)	4 (12.5)
Chorioamnionitis, n (%)	10 (31.3)
Apgar score (5th minute), mean ± SD (range)	7.6 ± 1.6 (3-10)
Agressive resuscitation at birth, n (%)	16 (51.6)
Perinatal asphyxia, n (%)	10 (31.3)
Lung diseases, n (%)	
RDS	3 (9.4)
Non-RDS	29 (90.6)
Congenital pneumonia	13 (40.6)
ARDS	5 (15.6)
MAS	5 (15.6)
CDH	4 (12.5)
Pulmonary hemorrhage	2 (6.3)
Accompanying diseases or complications, n (%)	
PDA	23 (71.9)
Pulmonary air leak syndrome	6 (18.8)
Secondary pulmonary hypertension	9 (28.1)
Sepsis	4 (15.4)
BPD	2 (6.3)

ST: surfactant therapy; CS: cesarean section; RDS: respiratory distress syndrome; ARDS: acute respiratory distress syndrome; MAS: meconium aspiration syndrome; CDH: congenital diaphragmatic hernia; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia.

Table 2. Respiratory characteristics of all term infants who received ST (n = 32).

Arterial blood gas analysis before ST, n (%)	
Acidosis (pH < 7.2)	19 (59.4)
Hypoxia (PaO_2 < 50 mmHg)	28 (87.5)
Hypercapnia ($PaCO_2$ > 50 mmHg)	11 (34.4)
OI, mean ± SD (range)	
Before ST	19.9 ± 3.2 (15-26)
After ST	13.4 ± 3.8 (8-22)
Type of ST, n (%)	
Neonatal (0-28 days)	28 (87.5)
Post-neonatal (> 28 days)	4 (12.5)
The timing of ST, n (%)	
Early (≤ 2 hr)	7 (21.9)
Late (> 2 hr)	25 (78.1)
Surfactant dose, mean ± SD (range)	1.72 ± 0.99 (1-5)
≥ 2 doses of ST, n (%)	27 (84.4)
Radiological improvement after ST, n (%)	26 (81.3)
Duration of mechanical ventilation (day), median (range)	4.5 (0.02-25)
Duration of oxygen support (day), median (range)	7 (0.02-69)
Duration of hospitalization (day), median (range)	11 (0.02-79)
Mortality, n (%)	8 (25.0)

ST: surfactant therapy; OI: oxygenation index.

Discussion

Although ST is one of the most important and life-saving therapies in neonatal respiratory failure, the clinical and therapeutic characteristics of term newborn infants who received ST have not been investigated in detail up today. Therefore, unlike preterm infants with RDS, clinical guidelines of ST in term infants with respiratory failure have not been developed yet [7-9]. For that reason, we tried

to identify the clinical characteristics of term infants who needed ST for respiratory failure and analyze the therapeutic results.

Like in preterm infants, the incidence of respiratory morbidities are related with gestational age in term infants. The risk decreases with advancing gestational age and infants born at 37^{0-6} weeks are at 1.7 times more risk for respiratory complications than those born at 38^{0-6} weeks, which in turn are at 2.4 times more risk than the infants born at 39^{0-6} weeks [10]. This downtrend was demonstrative especially for RDS, in which the risk decreases from about 39/1,000 for 37^{0-6} gestational weeks to about 8/1,000 for 39^{0-6} gestational weeks [11]. In a review including 5-year retrospective data of term infants requiring respiratory support, the incidence of respiratory morbidity following CS without labor was 7.4-11.4% at 37^{0-6} weeks of gestation, 4.2-8.4% at 38^{0-6} weeks of gestation and 0.8-1.8% after $39^{0/7}$ weeks of gestation [12]. Among our study group, the incidence of term infants who required ST for respiratory failure was 0.2% and the mean gestational age was 38.1 ± 0.8 (37-40.5).

Another impressive point of our study was that nearly all term infants (90.6%) had been delivered by CS, which is a significant risk factor for early neonatal respiratory morbidities both in preterm and term infants. Labor tends to protect against RDS and TTN as it decreases lung liquid secretion and increases surfactant [14]. Absence of labor is associated with an increased risk for respiratory problems leading to "iatrogenic" RDS in term or near-term babies [14-16]. In our study, only 3 (9.4%) infants could be delivered vaginally after the onset of the labor. The rest of the infants (29, 90.6%) were delivered by urgent or elective CS which was related with the high incidence of high-risk pregnancies in our hospital. In our study, this high rate of CS without labor should have contributed to the severity of neonatal lung diseases.

The gender difference has been reported in neonatal respiratory failure and male infants have been found to be more susceptible to respiratory failure than female infants [13]. Similarly, male predominance was noteworthy in our study.

As a common pathophysiologic pathway for CP, ARDS, MAS and pulmonary hemorrhage, alveolar inflammation results in disturbed vascular permeability with leakage of proteins and inflammatory agents into the alveoli and these proteins disturb surface tension-lowering properties of surfactant. ST has been used in these neonatal pulmonary morbidities in order to overcome this surfactant inactivation and secondary dysfunction [9, 10, 12]. Although there is no randomized controlled trial, ST that counterbalances surfactant inactivation seems to improve oxygenation and lung function in many newborn infants with pneumonia and ARDS [1, 17-20]. Similarly, low lamellar body count and low microbubble count in TTN have given an impression that TTN may also be related with surfactant dysfunction [21]. According to a prospective survey, ST was given in 33.9% of infants with RDS, 7.0% with pulmonary infection, 1.0% with MAS, 2.9% with amniotic fluid aspiration, 4.2% with TTN and 5.6% of infants with other pulmonary disorders [22]. The majority of our patients (40.6%) had severe CP who required invasive mechanical ventilation and medical therapy from the first hours of life. In accordance with this, the frequency of infants with maternal chorioamnionitis was high (31.3%). Following CP, MAS and ARDS were the most important causes of severe respiratory failure in our study group. In addition, accompanying morbidities such as pulmonary air leak syndromes and secondary pulmonary hypertension should have contributed to the severity of respiratory failure. In a recent study, slow improvement of oxygenation after ST and mechanical ventilation and a high rate of pneumothorax complication were reported in term infants with RDS [23]. However, in our study, pulmonary hypertension was accompanying 28% of the infants with severe pulmonary morbidities, therefore early echocardiographic investigation and appropriate medical therapy are important in decreasing the risk of mortality.

In our study, despite aggressive mechanical ventilation with high mean OI, 59.4% of the infants were acidotic, 87.5% were hypoxic and 34.4% were hypercapnic before ST. These results show the severity of lung diseases in our study group. Moreover, 84.4% of the infants needed multiple doses of ST.

Our previous study on late preterm infants who received ST showed that 62.7% of the late preterm infants with RDS received ST after the first 2 hours of life [24]. Full-term infants have more physical respiratory capacity and greater lung surfactant pool size when compared with late preterm infants and they are expected to show a better respiratory performance and stability in the early hours of life when compared with late preterm infants. However, in our study significant ratio of full-term

infants had respiratory deterioration evidenced by impaired arterial blood gas analysis before ST despite aggressive mechanical ventilation in the first hours of life. Therefore it is important not to delay ST and to administer it in the early hours of life before severe pulmonary damage occurs in term infants with severe respiratory failure. The limitations of our study were the absence of control group and the difficulty to show the efficacy of ST on each disease because of the small number of subjects. According to our results, mean OI before ST decreased significantly and radiological improvement was achieved in 81.3% of the infants after the last dose of ST. So from that point of view, although surfactant replacement is an evidenced based therapy in the management of RDS in preterm or late preterm infants and decreases the risk of mortality and air leak syndromes, it should also be considered as an urgent and life-saving therapy in the management of severe neonatal pulmonary parenchymal lung diseases in term infants.

Polin et al. [3] reviewed the literature and concluded that ST improves oxygenation and reduces the need for ECMO without an increase in morbidity in neonates with MAS, ST of infants with CDH does not improve clinical outcomes. In accordance with the literature, ST did not lead to clinical or radiological improvement in infants with CDH [25]. However, it was noteworthy that none of the term infants with RDS or ARDS died after ST. This result supports the success of ST when used at the right time and place.

ST is effective both in RDS and non-RDS lung diseases except CDH in term newborn infants and should be administered as soon as possible when secondary surfactant deficiency is suspected without waiting for improvement only by mechanical ventilation and supportive medical therapy. The most dramatic response to ST was revealed from the infants with RDS and ARDS. The inresponsive lung disease to ST was CDH. In future, maybe we will be administering surfactant more than today by improving minimally-invasive and aerosolized surfactant administration techniques [2, 26]. However, prospective, randomized-controlled studies and careful re-evaluation of retrospective studies should be organized for the development of clinical guidelines of ST in term newborn infants.

Declaration of interest

The Authors declare that there is no conflict of interest.

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