



## Surfactant Utilization Evaluation in a Major Teaching Hospital in West of Iran: An Observational, Prospective Study

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### ABSTRACT

**Background:** The respiratory distress syndrome (RDS) is a common pulmonary disorder that usually occurs as a result of preterm labor and is associated with lack of surfactant. The aim of this study was to evaluate the pattern of surfactant prescription in Alzahra teaching hospital in Tabriz, Iran.

**Methods:** This drug use evaluation (DUE) study was conducted in the neonatal intensive care unit (NICU) of Al-Zahra Hospital, Tabriz, Iran. The demographic and clinical data collection was performed using clinical records of patients. The pattern of surfactant replacement therapy was evaluated and compared with the European Consensus Guideline on the management of respiratory distress syndrome in 2016.

**Results:** A total of 252 premature infants who received surfactant between August 2017 and March 2018 were included. 80.8% of neonates were born by cesarean section. The most used surfactant was Curosurf®, which was used in 82.1% of cases. Only 34.9% of the infants received within 8 hours of birth. Moreover, 79% of infants received the standard dose of surfactant, while 9.5 % and 11.5% were given high and low doses of surfactant, respectively.

**Conclusion:** : The pattern of surfactant replacement therapy was not completely according to the guidelines, particularly regarding the time of administration. Considering the importance of dose and timely administration of surfactant, providing strategies to decrease these errors are important.

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### Introduction

Respiratory distress syndrome (RDS), previously known as hyaline membrane, is the major cause of respiratory distress in preterm newborn infants, which is associated with a significant risk of mortality and morbidity worldwide. It has been shown that about 30% of all deaths of premature infants are due to RDS or its complications. The risk for the development of RDS increases with reducing gestational age. In this regard, the incidence of RDS is more than 90 % in infants with a gestational age of 28 weeks or less. The primary cause of RDS by deficiency of pulmonary surfactant, which could lead to alveolar collapse, low lung

volume and compliance, respiratory intrapulmonary and extrapulmonary right-to-left shift, ventilation, and perfusion mismatching, lung inflammation and edema, respiratory epithelial injury, and hypoxia (1-3).

A combination of general supportive care to all preterm infants and specific initial interventions to provide sufficient respiratory support and increase pulmonary surfactant according to the clinical situation of the infants and gestational age has been recommended to manage RDS. Among them, exogenous surfactant replacement therapy has attracted great interest. A mounting of evidence has revealed that surfactant administration could decrease

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incidence and severity of RDS, risk of pulmonary interstitial emphysema, bronchopulmonary dysplasia, and mortality (4, 5).

Complications of surfactant administration such as lung hemorrhage, hypoxia, bradycardia, increased carbon dioxide pressure, and transient reduction in brain activity should not be ignored. In order to minimize the possible complications of surfactant administration, principal therapeutic issues in the exogenous surfactant replacement therapy, including technical aspects of administration, the timing of administration, indication for surfactant therapy, and selection of surfactant preparation, should be considered (4, 5).

A number of commercially available surfactants with different sources and formulation have been used widely in clinical trials and therapeutic centers. It has been shown that the safety, efficacy, and cost of commercially available surfactants are variable (6, 7). Owing to the increasing number of premature infants, clinical importance of surfactant replacement therapy, and the reported efficacy and safety profiles of surfactant in the literature, we aimed to evaluate the pattern of surfactant replacement therapy and compare with the standard guidelines in Al-Zahra hospital, Tabriz, Iran (8, 9).

## Methods

The present observational prospective study was carried in Al-Zahra Hospital, which is one of the major teaching hospitals of Tabriz University of Medical Sciences. All premature infants with RDS admitted to the NICU of the Hospital and received surfactant replacement therapy between August 2017 and March 2018 were considered in our study. Neonates with other indications for surfactant replacement therapy such as pulmonary hemorrhage, congenital pneumonia, and meconium aspiration were not evaluated in the present study.

This study was approved by the Regional Ethics Committee of Tabriz University of Medical Sciences ID: IR.TBZMED.

**Table 1.** Demographic and clinical data of study population.

Demographic/clinical data	Number (%)
Sex, (female/male)	108(42.9%)/144(57.1%)
Birth weight; <1000 grams	58(23%)
Birth weight; 1000-1500 grams	70(27.8%)
Birth weight; 1500-2000 grams	60(23.8%)
Birth weight; 2000-2500 grams	88(34.9%)
Neonate age; 24-28 weeks	58(23%)
Neonate age; 29-32 weeks	102(40.5%)
Neonate age; 33-36 weeks	79(31.3%)
Neonate age; 36-37 weeks	13(5.2%)
CS/ NVD	203(80.6%)/49(19.4%)
Antenatal corticosteroid use	121(48%)

CS, cesarean section; NVD, normal vaginal delivery.

REC.1396.631. The study was conducted according to the declaration of Helsinki on ethical principles for medical research, including human subjects. The patients' information kept being confidential to the researchers.

During the study period, an attending clinical pharmacist reviewed the medical records of the premature infants for demographic and clinical data, including, sex, age, and birth weight of neonates, mode of delivery, antenatal corticosteroid use, neonatal resuscitation method, level of mechanical support, type of surfactant preparation, the timing of administration, and dose of surfactant.

The primary outcome of the study included comparison the pattern of surfactant replacement therapy in premature infants with RDS with the European Consensus Guidelines on the Management of Respiratory Distress Syndrome (10). Our secondary outcome was evaluation the type of surfactants among these premature infants in our center.

Data analysis was performed in IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA). Chi-square and/or Fisher's exact tests were used for the analysis of the categorical data. Moreover, the Mann-Whitney U test was used for non-normal distributed variables. The continuous data were presented as mean  $\pm$  SD (standard deviation). The p-values less than 0.05 were assumed as statistically significant.

## Results

At the end of the study, a total of 252 premature infants with RDS who received surfactant replacement therapy were analyzed. The majority of infants were male (57.1%). The highest and lowest birth weights were 550 and 2269 grams, respectively. Cesarean section was the common mode of delivery (80.6%). Demographic and clinical characteristics of the infants have been summarized in Table 1. Totally, resuscitation was provided for 65.5 % of the premature infants. In 98% of the premature infants, non-invasive methods were used. The combination of Nasal CPAP with Humidified High-Flow Nasal Cannula (HHFNC) was the most commonly used resuscitation method (Table 2).

**Table 2.** Methods of resuscitation in study population.

Resuscitation method	Number (%)
CPAP	36(14.3%)
PPV (tracheal tube)	35(13.8%)
PPV(bag/mask)	25 (9.9%)
First steps of resuscitation	18(7.1%)
First steps of resuscitation + CPAP	17 (6.7%)
Routine care	15 (5.9%)
First steps of resuscitation + Routine care	8(3.2%)
PPV(tracheal tube) + CPAP	5 (2%)
PPV(bag/mask) + PPV(tracheal tube)	2 (0.8%)

CPAP, continuous positive airway pressure therapy; PPV, positive pressure ventilation.

Totally 121 mothers received antenatal corticosteroid therapy. Notably, 88 newborn infants whose mothers received antenatal corticosteroid therapy have birth weights less than 2000 g and 53 infants were born with gestational age less than 30 weeks, respectively. Among maternal risk factors, more than 50% are related to maternal hypertension. Notably, there was a statistically significant positive correlation between antenatal corticosteroid use and neonatal birth age ( $P=0.05$ ). Moreover, the correlation between Antenatal corticosteroid and the birth weight of newborns is positive ( $P=0.01$ ).

The type of surfactant preparation and timing of

administration have been summarized in Table 3. The most commonly used commercially available surfactant was Curosurf® (86.1%), followed by Survanta® (12.7%) and Bles® (1.2%). Considering the time of administration, only 34.9% of the infants received surfactant replacement therapy according to the European Consensus Guidelines on the Management of Respiratory Distress Syndrome within 8 hours of birth. Moreover, regarding the dose of surfactant in the guideline, 79% of infants ( $n=199$ ) received the standard dose of surfactant, while 9.5 % ( $n=24$ ) and 11.5% ( $n=29$ ) were given high and low doses of surfactant, respectively (Table 3).

**Table 3.** Type, administration time, dose, and cost of surfactant in study population.

Type, administration time, dose, and cost	Number (%)
Type, CUROSURF® (poractant alfa)	217(86.1%)
Type, SURVANTA® (beractant)	217(86.1%)
Type, BLES® (bovine lipid extract surfactant)	3(1.2%)
Time of administration after birth, <2 hours	88(34.9%)
Time of administration after birth, 2-8 hours	122(48.8%)
Time of administration after birth, 8-24 hours	33(13%)
Time of administration after birth, >24 hours	8(3.3%)
Dose( correct dose/high dose/low dose)	199(79%)/ 24 (9.5%)/ 29(11.5%)
Total cost, CUROSURF® (poractant alfa), Rials	4267169746
Total cost, SURVANTA® (beractant), Rials	419519943
Total cost, SURVANTA® (beractant), Rials	60214598

## Discussion

The present study showed that time and dose of surfactant replacement therapy in premature infants with RDS was not completely according to the guidelines in our center. Previously, some studies have conducted to evaluate the pattern of surfactant in infants. In Challis et al., population-based cohort study in Sweden, evaluation of 7980 surfactant administrations in 5209 infants showed that 38.9% infants with 22 to 31 weeks did not receive timely surfactant administration and led to higher odds of intraventricular hemorrhage (adjusted OR [aOR], 1.71; 95% CI, 1.23-2.39), pneumothorax (aOR, 2.59; 95%

CI, 1.76-3.83), longer duration of assisted ventilation (aOR, 1.34; 95% CI, 1.04-1.72), and receipt of postnatal corticosteroids (adjusted OR [aOR], 1.57; 95% CI, 1.22-2.03) compared with those received surfactant according to the international guidelines. Whereas, in our study, approximately 35% of the infants received surfactant replacement therapy according to the European Consensus Guidelines on the Management of Respiratory Distress Syndrome. It showed adherence to international guidelines were even lower in our study compared with Challis et al., study in Sweden (11, 12). Moreover, in Challis et al., study, omission of surfactant treatment took place in 5.7%

of infants were receiving mechanical ventilation and led to lower survival rate (aOR, 0.49; 95% CI, 0.30-0.82).

RDS is one of the most important side effects of cesarean delivery without the onset of labor pain. The risk of RDS decreases with the onset of labor pain before cesarean delivery and can be prevented by delaying elective cesarean section by up to 38 weeks of gestation. It has been shown the rate of occurrence of RDS is higher with cesarean delivery. In this regard, cesarean section was the common mode of delivery in our study (80.6%) (13).

According to the European Consensus Guidelines for the management of respiratory distress syndrome 2016, the use of prophylactic CPAP is considerably effective in preventing and treating RDS. Moreover, it could reduce the risk of bronchopulmonary dysplasia and the use of exogenous surfactants. Notably, the use of prophylactic CPAP was the most method in our study (14). Dani et al., in a prospective randomized study, showed that the use of Nasal CPAP could significantly improve the duration of oxygen therapy ( $P = 0.025$ ), mechanical ventilation ( $P = 0.031$ ), and the need for the administration of second dose of surfactant ( $P = 0.006$ ) (15).

Several studies have been conducted to compare safety and efficacy of commercially available surfactants. In our study, Curosurf® was the most used surfactant. In a pilot study, it has been demonstrated that the use of Curosurf® is associated with a greater improvement in blood gases during the first 24 hours after administration compared with Beractant® (16). Furthermore, in the Proquitté et al. study at the Neonatal Clinic of the University of Berlin, 82 neonates received Alveofact® and 105 neonates received Curosurf®. Data analysis showed that there are no statistically significant differences regarding mean gestational age (28.4 vs. 28.4 weeks), birth weight (1210 vs. 1258 g) and time of first surfactant application (60 vs. 90 min postnatal) between those received Alveofact® and Curosurf®. Besides, no significant differences were observed in need for Fio<sub>2</sub>, blood gases, bronchopulmonary dysplasia (BPD) incidence on day 28 (41.7% vs. 42.8%), intraventricular hemorrhage (18.3% vs. 14.3%), pneumothorax (9.8% vs. 4.8%), and mortality (17% vs. 17.1%) between the study groups (17).

It is important to mention that Bles® was used in 1.2% of the infants. In two published studies comparing Bles® with Survanta® and Curosurf®, Lam et al., compared the clinical response using oxygenation indices in premature infants who were randomly assigned to Bles® or Survanta®. Neonates in the Bles® group showed a faster onset of action and less oxygenation within 8 hours of the first dose, and less mechanical ventilation (18). In another study, Lemyre et al., compared the efficacy and safety of Bles® and Curosurf® in newborns under 32

weeks of gestation. Data analysis indicated no significant difference in the rate of live birth, BPD, mortality, and complications. However, the duration of oxygen therapy in infants who received Curosurf® significantly decreased (19). Furthermore, evaluation the records of 5169 neonates showed that there were no statistically significant differences regarding the rate of mortality (8.3% vs 8.5%) among those received Infasurf® and Survanta® (20).

Owning the fact that the efficacy and safety profiles of available surfactants are partially similar in most of the published studies, considering other factors such as cost and availability of surfactant seems to be essential. In addition, considering the dose and time of administration of surfactant, the pattern of surfactant use in our study was not completely consisted with the international guidelines (10). Considering the importance of dose and timely administration of surfactant, providing strategies to decrease these errors is of greatest importance. Consequently, developing strategies to increase the compliance surfactant replacement therapy with guideline may be key. Previously, it has been shown that clinical pharmacists play an important role in optimizing pharmaceutical care and their active presence in medical rounds could help physicians in optimizing pharmacotherapy of patients (21-23). Considering the potential role of the clinical pharmacists on improvement of educational programs of health care providers and implementation of treatment strategies according to the standard guidelines and availability of medicines, conducting more studies with adequate sample size is recommended to evaluate the potential role clinical pharmacists on the pattern of surfactant replacement therapy and quality of treatment in the setting of NICU.

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