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Full Length Research Paper

Evaluation of risk factors for surfactant re-dosing in neonates with respiratory distress syndrome

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Respiratory distress syndrome (RDS) is a common cause of mortality and complications in the preterm neonates. Specific treatment of this disease is endotracheal surfactant administration. Some neonates need more than one dose of drug (re-dosing) so that in addition to the cost, avoidace of treatment complications and, if necessary, timely prescribtion are of high importance. In this study, the effects of the contributing factors, including prescription or non-prescription of corticosteroid to the mother, the gestational age, fetal gender, birth weight, the first and fifth minute APGAR score, respiratory distress score, time of first dose of surfactant administration, type of delivery, type of surfactant, in the case of re-dosing of surfactant in neonates with RDS, and in NICU of Motahari Maternity-Children Hospital, Urmia, Iran were compared and the positive and negative effects of each of the above-mentioned factors were examined. Few studies have been conducted on the effect of the administration of the second dose of surfactant and its subsequent doses compared with the used doses. All hospitalized neonates, who were diagnosed with RDS after birth during 2011 to 2013, were included in the study. Data was collected from a designed form and analyzed by SPSS version 22. They included 213 (60.9%) male and 137 (39.1%) females with a mean weight of 1782.03 ± 387.04 g. 66 males (31%) and 32 females (23.4%) received more than one dose of surfactant. 227 neonates (64.9%) were discharged with a recovery and 123 neonates (35.1%) died. Findings of our study showed that neonates with the low birth weight have received more than one dose of surfactant. Moreover, neonates born between 32 to 36 weeks of gestation needed re-dosing of more surfactant. Neonates with first dose of surfactant for 6 to 24 h after birth need significantly more re-dosing of surfactant. There was a significant difference between the re-dosing of surfactant and type of delivery. In addition, re-dosing of more surfactant was needed with the increasing numbers of neonate per delivery. In contrast; the need to re-dosing of surfactant in the neoantes whose mothers had received one dose of prenatal corticosteroid was greater than the neoantes whose mothers had received two doses of prenatal corticosteroid. Moreover, the type of the surfactant products (curosurf and Survanta) had no effect on the re-dosing of doses of surfactant in the studied infants. The percentage of the use of more than one dose of surfactant was higher in male neonates than the female ones. Inaddition, the first and fifth minute APGAR scores were significantly lower in re-dosing group. In this study, the need for re-dosing of surfactant was significantly greater in the neonates with the higher respiratory distress score (>8) than the neonates with the mild to moderate respiratory distress scores (≤8).

Key words: Respiratory distress syndrome, surfactant, re-dosing.

INTRODUCTION

Respiratory distress syndrome (RDS), which formerly was known as Hyaline membrane disease (HMD), is a common cause of mortality and complications in preterm neonates. RDS is a defect in lung maturation that is usually seen in the preterm births and is caused due to surfactant deficiency. Preterm birth is defined as the birth before the end of week 37 from the first day of the last menstrual period, which occurred in 5 to 15% pregnancies (Asnafei et al., 2004; Mahoney and Jain, 2013; Colin et al., 2010; Gortner and Tutdibi, 2011). Percentage of preterm births in the United States has been reported to be 11% whereas it includes 5 to 7% in European countries (Robert, 2002). This rate was reported to be 28% in a study conducted in Iran (Moravedji et al., 2005). A major cause of premature neonate birth is the premature rupture of the membrane. Premature birth has increased in the past twenty years due to the increased special attention to the obstetrical care, the improved status of evaluation and research in preterm birth, the increasing use of ultrasound to estimate the gestational age and pregnancies resulting from the infertility treatment (Roberts and Dalzell, 2006). Premature birth causes a higher incidence of neonatal disease, of which HMD or RDS and intraventricular hemorrhages (IVH) are the most important ones (Committee on Obstetric Practice, 2002; Colin et al., 2010; Gortner and Tutdibi, 2011). Pulmonary surfactant deficiency leads to massive atelectasis, loss of pulmonary residual capacity, and collision of the ventilation to perfusion ratio (Jobe, 1993; Gortner and Tutdibi, 2011). Consequences of this condition are decrease in lung compliance, decreased oxygenation with cyanosis, respiratory and metabolic acidosis that results in severe hypoxemia with the increased pulmonary vascular resistance and right-to-left shunt through the ductus arteriosus (Rodriguez et al., 2006). Neonates who are born preterm suffer from RDS due to the lack of enough surfactant concentration in the alveoli. These neonates have lungs with low compliance that need to try and spend a lot of energy for their distension in every breath and their alveoli always tend to collapse. If treatment does not start immediately, about 50% of them die. RDS is a common and deadly disease, which is inversely related to the gestational age (Shahfarhat et al., 2006; Engle, 2008; Mahoney and Jain, 2013; Colin et al., 2010; Gortner and Tutdibi, 2011) so that it occurs in 60 to 80% of neonates less than 28 weeks, 15 to 30% of neonates of 32 to 36 weeks, and 5% of neonates of more than 37 weeks gestational ages (Halliday, 2005). The discovery of the key role of surfactant in the pathophysiology of RDS by the researchers in 1959 led them to think about the prescription of surfactant aerosol for premature neonates with RDS, theory that has been introduced again recently (Avery and Mead, 1959; Pohlmann et al., 2013). Surfactant decreases the surface tension of alveolar lining liquid layer in the lung and prevents the smaller alveolar collapses. Human surfactant is a mixture of lipoproteins, such as palmytioyl phosphatidyl choline. Surfactant is synthesized by alveolar type 2 cells and secreted into the alveoli (Schurch et al., 1992). Normally, surfactant synthesis begins around week 25 of the gestation under the influence of several hormones. Surfactant production usually reaches a sufficient level about 32 to 34 weeks of pregnancy (Roberts and Dalzell, 2006; Colin et al., 2010). With the introduction of exogenous surfactant in recent decades for the treatment of RDS in patients under artificial ventilation, an obvious improvement in the mortality and air leak syndrome was observed due to the decreased need to oxygen therapy and ventilator pressures (Fanaroff and Martin, 2006; Ramanathan, 2008; Polglase et al., 2009; Fujiwara and Maeta, 1980; Robertson and Halliday, 2009). In general, surfactant reduces mortality due to the RDS if, particularly, it is accompanied by the administration of corticosteroids to the mother before birth (Behrman, 2004; Eriksson et al., 2012). The most important role of surfactant in the prevention and treatment of RDS is to reduce the surface tension in the alveoli (Dolfin et al., 1994; Iarukuva et al., 1999). The use of surfactants is increasing in other respiratory disorders, such as meconium aspiration syndrome (Fanaroff, 2001). There are two types of surfactants to treat; exogenous surfactant derived from animal resources or natural surfactant and synthetic surfactants. Natural surfactant contains palmytioylphosphatidyl choline with surfactant protein-B, sp-C, and without sp-A, sp-D. Synthetic surfactant is a mixture of surface active phospholipids and the releasing agents (Goldsmith, 2003; Verhagen et al., 2001; Rangasamy, 2009). In the early 80s, Fujiwara and Maeta. prescribed a mixture of natural and synthetic surfactant for the preterm neonates with RDS. They found a high decrease in oxygen consumption and the ventilator pressure (Stevens et al., 2007). At present, surfactant is given to the preterm neonates with a dose of 100 or 200 mg per kg of body weight and may need to prescribe other doses. Response to surfactant therapy depends on several factors, including quality of the produced surfactants (Liechty et al., 1991), the time and manner of administration (Dijk et al., 2012), the recommended dose (Cogo et al., 2009), and finally the condition of the resuscitation of neonate in the delivery room (Bjorklund et al., 1997; Chong-Woo and Won-Ho, 2009; Colin et al., 2010). Results of the conducted clinical trials in this area

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Table 1. APGAR scoring for the neonates at birth.

Sign	0	1	2
Heart rate	No	Less than 100	More than 100
Respiratory effort	No	Slow and irregular	Good-crying
Muscular tone	flappy	Brief flexion of limps	Active movement
Response to the stimulations	No	Face grimase	Coughing or sneezing
The color of the neonate's body	Blue-pale	Pink body- blue face	Completely pink

Table 2. Downes scoring system.

Score	0	1	2
Percentage of inspiratory oxygen (FiO_2) required to maintain PO_2>50 mm/Hg	Room air (21%)	< 40%	> 40%
Intercostal retraction	No	Mild to moderate	Severe
Expiratory sighs (Grunting)	No	Is heard with stethoscope	Is heard without stethoscope
Auscultation of lung sounds	Heard well	Decreased	Hardly heard
Number of breath per minute	< 60	60-80	> 80

indicated that the use of different doses of surfactant significantly decreased the rate of mortality compared with single dose or placebo (Hoekstra et al., 1991; Corbet et al., 1995; Kotecha and Kotecha, 2012). Most studies conducted in this area investigated and compared the effect of synthetic and animal surfactants based on the recommended doses in the related protocols (Rangasamy et al., 2009). Few studies have been done on the effect of the administration of the second dose of surfactant and the subsequent doses compared to the used doses (Chong-Woo and Won-Ho, 2009; Dunn et al., 2008; Speer et al., 1992; Soll and Ozak, 2009). Some meta-analysis studies have been performed on the relationship between two surfactants. The results showed that the greater improvement in the oxygenation status, the need for ventilators, the reduced risk of pneumothorax, and higher survival rate existed in the neonates with the respiratory distress group without pneumonia who received some more doses of surfactant than the group with a single dose of surfactant (Chong-Woo and Won-Ho, 2009; Soll and Ozak, 2009; Kattwinkel et al., 2008). According the great costs of re-dosing of surfactant, its possible complications, the complications of delayed surfactant therapy, and a lack of studies conducted on the risk factors for re-dosing of surfactant doses, this study was conducted to examine the risk factors in order to gain a timely recognition of risk factors, prevention and early intervention so that the the complications of delayed treatment could be prevented. This may have a significant effect in the duration of the neonate's hospitalization, decrease in the costs and the complications that result from hospitalization, decrease in complications of late prescription of surfactant doses and decrease in use of more aggressive methods. Knowledge of these risk factors could be a clinical guide to be used in NICU.

MATERIALS AND METHODS

In this applied-analytic study, which was approved by the research committee of the University, all hospitalized neonates diagnosed with RDS after birth in NICU of Motahari maternity-children Hospital, Urmia, Iran during 2011 to 2013 were included in the study. Time of injection of the first dose, re-dosing, the number and frequency of prescription, the type of surfactant received for each child, birth weight, mode of delivery (normal vaginal delivery or cesarean), age of pregnancy, gender, prescription of the pre-natal steroid to mothers (two intramuscular doses of 12 mg, betamethasone with an 24 h interval), the score of RDS (based on the number of breath per minute – the intensity of intercostal retraction - quality of breath sounds on auscultation – expiratory sighs or grunting - the percentage of the required oxygen), the first and fifth minute APGAR scores (based on the heart rate - respiratory condition – muscular tone - response to stimulation – the color of body) were recorded for each neonate (Table 1). Two types of surfactant (Curosurf- with a pocrine origion that was made by Chiesi Fctory in Italia and survanta- with a bovine origin that was by Abbot Factory in America) were used by endotracheal administration (100 mg/kg dose). Some patients needed to prescribe the second and third dose in 6 to 12 h after the first dose. Breathing of patients after surfactant administration was conducted by mechanical ventilation or Nasal-CPAP. The results of the treatment were recorded as recovery, death, or complications in neonates. Finally, the impact of the intended risk factors on re-dosing of surfactant dose was measured. The following criteria were used to diagnose RDS: tachypnea (respiratory rate above 60/min), expiratory grunting and intercostal retraction, cyanosis in room air, a view of reticulonodular and bronchogram in Chest X-Ray, hypoxia and hypercapnia in ABG. All patients were examined in terms of sepsis and monitored continuously including; cardio-respiratory, body temperature, arterial oxygen saturation and therapeutic efforts were conducted for hypoxia, acidosis, and hypothermia. Indications for the intubation and mechanical ventilation included persistent apnea, arterial pH less than 7.20, arterial Pco_2 greater than 60 mm Hg, arterial PO_2 less than 50 mm Hg in 70 to 100% inspirated oxygen concentration (Table 2).

Neonates with fatal congenital anomalies, congenital heart defects, those patients, in whom the tracheal intubation was not possible for reasons such as abnormalities of the airways and

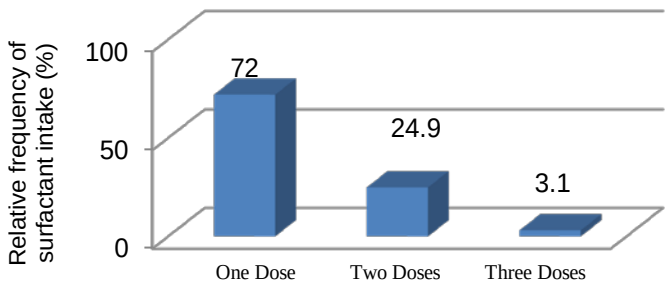

Figure 1. Distribution of relative frequency of surfactant intake in hospitalized neonates with RDS.

Table 3. Distribution of absolute and relative frequency of complications after treatment.

Type of complication	Percentage	Cases (n)
Pneumothorax	26	33
IVH	23.6	30
Co-multiple complications	17.3	22
DIC	12.6	16
Pulmonary hemorrhage	10.2	13
Sepsis	8.7	11
Pneumonia	1.6	2
Total	100	127

patients with the lung diseases other than RDS, were excluded from the study. According to the preliminary studies (pilot study), it was found that approximately P=0.36% (referral rates) had re-dosing surfactants, at 95% level of confidence and error d= 0.05. 350 patients, who had received at least one dose of surfactant, were studied. Non-probability sampling was used. Therefore, all neonates with RDS admitted to our hospital were selected for the purposes of the study according the inclusion and exclusion criteria from the beginning of the study. SPSS v 21 was employed to analyze and process the data obtained from the patients through statistical indices of descriptive analysis and chi-square test. The P-value less than 0.05 were statistically considered significant. Neonates with indication of surfactant therapy were not excluded from the study. Thus, there is no control group in this study. All information of the patients would be confidential with the researcher and the researcher would be faithful to the Helsinki Convention.

RESULTS

In this study, 350 neonates with the diagnosed RDS were hospitalized and treated by surfactant. Of them, 213 neonates were male (60.9%) and 137 were female (39.1%). The average weight of the neonates was 1782.03 ± 783.04 gr (the minimum weight was 500 gr and the maximum weight was 4250 gr). Of 350 neonates hospitalized, 239 (68.3%) were singletone, 79 (22.6%) twin, 24 (6.9%) triplet, and 8 (2.3%) quadruplet. The average gestational age of neonates with the RDS was 31.44 ± 3.74 weeks (the minimum 22 weeks and the maximum 40 weeks). Of 350 studied neonates, 241 cases (68.9%) were cesarean section (C/S) and 109 cases (31.1%) were normal vaginal delivery (NVD). 203 mothers (58%) received prenatal corticosteroids and 147 mothers (42%) did not receive corticosteroids. The number of mothers receiving one dose of corticosteroids before delivery was 144 cases (70.9%) and 59 mothers (29.1%) of them received two doses. Of 350 neonates hospitalized, the reported RDS Score was mild (<5) in one case (0.3%), moderate (5 to 8) in 228 cases (65.13%), and severe (>8) in 121 cases (34.57%). The degree of the first minute APGAR was high (7 to 10) in 133 neonates (38%), moderate (4 to 6) in 174 neonates (49.7%), and low (0 to 3) in 43 neonates (12.3%). The degree of the fifth minute APGAR was high in 238 neonates (68%), moderate in 94 neonates (26.9%), and low in 18 neonates (5.1%). Time of receiving the first dose of surfactant was less than 2 h after birth in 97 cases (27.7%) less than, 2 to 6 h after birth in 149 neonates (42.6%), 6 to 24 h after birth in 76 cases (21.7%), and more than 24 h after birth in 28 cases (8%). Of 350 studied neonates, 252 cases (72%) received one dose of surfactant and 98 cases (28%) received more than one dose of surfactant. Of 98 neonates that received more than one dose, 87 neonates (24.9%) received two doses, and 11 neonates (3.1%) received three doses (Figure 1).

Assisted ventilation after receiving surfactant was Oxy-Hood in 3 (0.3%) of 35 neonates, N-CPAP in 249 neonates (71.1%), and different types of ventilation with endotracheal intubation in 98 neonates (28%). Side effects of surfactant was observed in 127 (36.3%) of 350 hospitalized neonates with RDS. There was no complication of surfactant in 223 neoantes (63.7%). Of 127 neonates that suffered from the side effects of surfactant, pneumothorax was reported in 33 cases (26%), IVH in 30 cases (23.6%), more than one complication in 22 cases (17.3%), DIC in 16 cases (12.6%), pulmonary hemorrhage in 13 cases (10.2%), sepsis in 11 cases (8.7%), and pneumonia in 2 cases (1.6%) (Table 3).

Of 22 neonates who suffered from co-multiple complications after treatment, IVH+ DIC was reported in 10 neonates (45.47%), pulmonary hemorrhage + IVH in 5 cases (22.74%), pneumothorax + IVH in 1 case (4.54%), IVH + DIC + pulmonary hemorrhage in 1 case (4.54%), pneumothorax + sepsis in 1 case (4.54%), pneumothorax + pulmonary hemorrhage in 1 case (4.54%), and pulmonary hemorrhage + DIC in 1 case (4.54%) (Table 4).

Of 350 neonates with RDS who were hospitalized, 227 (64.9%) were discharged in a recovery status and 123 cases (35.1%) died. Of 213 male neonates, 138 cases (64.8%) were discharged with the recovery status and 75 cases (35.2%) died. Of 137 female neonates, 89 cases (65%) were discharged in a recovery status and 48 cases

Table 4. Distribution of absolute and relative frequency of co-multiple complications after treatment.

Co-multiple complications	Percentage	Cases (n)
IVH and DIC	45.47	10
Pulmonary hemorrhage + IVH	22.74	5
Pneumothorax+ DIC	4.54	1
Pneumothorax+ IVH	4.54	1
IVH+ DIC + pulmonary hemorrhage	4.54	1
Pneumothorax+ IVH + Pneumonia	4.54	1
Pneumothorax+sepsis	4.54	1
Pneumothorax+ Pulmonary hemorrhage	4.54	1
Pulmonary hemorrhage+ DIC	4.54	1
Total	100	22

Table 5. Effect of the birth weight on the re-dosing of surfactant in the neonates with RDS.

Weight of neonate (gr)	Dose of surfactant		Total (%)
	One dose {No. (%)}	Multiple dose {No. (%)}	
Less than 1700	129 (68.62)	59 (31.38)	188 (100)
1700-2500	80 (74.1)	28 (25.9)	108 (100)
More than 2500	43 (79.63)	11 (20.37)	54 (100)
Total	252 (72)	98 (28)	350 (100)

p value = 0.4.

(35%) died. Considering the complications after receipt of surfactant, it was found that 127 cases had complications, of which 27 (21.3%) were discharged in a recovery status and 100 cases (78.7%) died. Of 188 neonates weighing less than 1,700 g, 129 cases (68.62%) received one dose of surfactant and 59 cases (31.38%) received more than one dose of surfactant. Of 108 neonates weighing 1700 to 2500 g, 80 cases (74.1%) had received one dose of surfactant and 28 cases (25.9%) had received more than one dose of surfactant. Of 54 neonates weighing more than 2500 g, 43 cases (79.63%) had received one dose of surfactant and 11 cases (20.37%) had received more than one dose of surfactant. According to Chi-Square test, there was no significant difference between the weight of neonates and re-dosing of more doses of surfactant (p value=0.4) (Table 5).

71 of 97 neonates whose first dose of surfactant was less than 2 h after birth, received one dose of surfactant and 26 cases (26.8%) received more than one dose in 2 to 6 h after birth. In 149 neonates, whose first dose of surfactant was in 2 to 6 h after birth, 108 cases (72.5%) received one dose of surfactant and 41 cases (27.5%) received more than one dose. Of 76 neonates whose first dose of surfactant was administered in 6 to 24 h after birth, 47 cases (61.8%) received one dose of surfactant and 29 cases (38.2%) received more than one dose of surfactant. Of 28 neonates whose first dose of surfactant administered in more than 24 h after birth, 26 cases (92.9%) received one dose of surfactant and 2 cases (7.1%) received more than one dose. Of 350 studied neonates, 252 cases (72%) received one dose of surfactant and 98 cases (28%) received more than one dose of surfactant. According to Chi-Square test, time of the first dose of surfactant at a range less than 24 h had a direct effect on the re-dosing of surfactant (p value=0.01) (Figure 2).

Of 162 neonates who received Curosurf, 114 cases (70.4%) had received one dose and 48 cases (29.6%) had received more than one dose curosurf. Of 188 neonates who received Survanta, 138 cases (73.4%) had received one dose and 50 cases (26.6%) had received more than one dose of Survanta. According to the Chi-Square test, there was no significant difference between types of consumed products and redosing of surfactant (P=0.52). Of 213 male neonates, 147 (69%) had received one dose of surfactant and 66 cases (31%) had received more than one dose of surfactant. Of 137 female neonates, 105 cases (76.6%) had received one dose of surfactant and 32 cases (23.4%) had received more than one dose of surfactant. According to the Chi-square test, there was no significant difference between redosing surfactant and the gender of the neonate (p value =0.12). Of 176 neonates with the gestational age less than 32

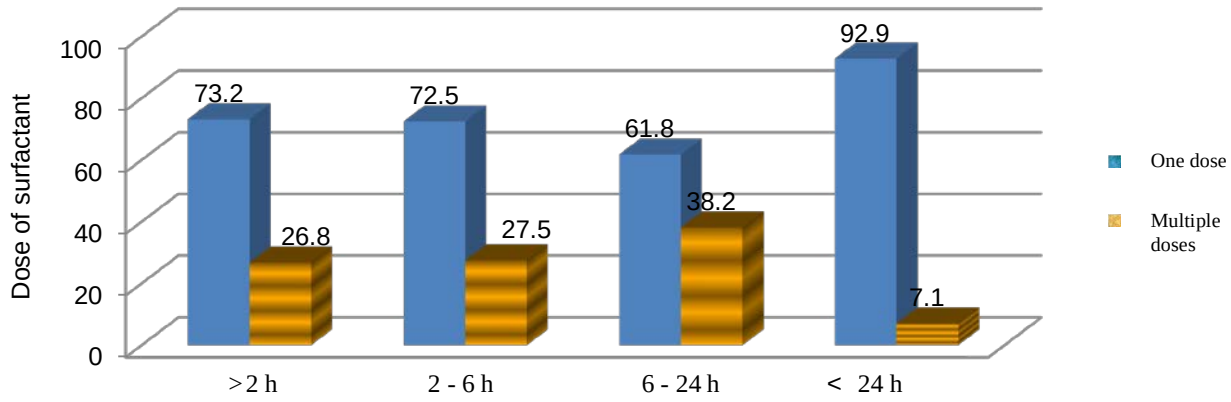

Figure 2. Effect of the time of reception of the first dose of surfactant on re-dosing.

weeks, 127 cases (72.2%) received one dose and 49 cases (27.8%) received more than one dose of surfactant. Of 122 neonates with the gestational age 32 to 36 weeks, 86 cases (70.5%) received one dose of surfactant and 36 cases (29.5%) received more than one dose of surfactant. Of 52 neonates with the gestational age of 36 weeks, 39 cases (75%) received one dose of surfactant and 13 cases (25%) received more than one dose of surfactant. According to the chi-square test, the gestational age at birth had no effect on re-dosing surfactant (p value=0.83). Of 241 neonates of the cesarean delivery, 165 cases (68.5%) received one dose of surfactant and 76 cases (31.5%) received more than one dose of surfactant. Of 109 neonates of normal vaginal delivery, 87 cases (79.8%) received one dose of surfactant and 22 cases (20.2%) received more than one dose of surfactant. According to Chi-square test, there was a significant difference between type of delivery and re-dosing surfactant obtained (p value=0.02). Of 239 singletone neonates, 168 cases (70.3%) received one dose of surfactant and 71 cases (29.7%) received more than one dose of surfactant. Of 79 twin neonates, 64 cases (81%) received one dose and 15 cases (19%) received more than one dose of surfactant. Of 24 triplet neonates, 15 cases (62.5%) received one dose of surfactant and 9 cases (37.5%) received more than one dose of surfactant. Of 8 quad neonates, 5 cases (62.5%) received one dose of surfactant and 3 cases (37.5%) received more than one dose of surfactant. According to Chi-square test, there was no significant difference between the number of neonates in a delivery and re-dosing surfactant (p value=0.17). Of 203 mothers who received corticosteroids, 141 neonates (69.5%) had received one dose of surfactant and 62 cases (30.5%) received more than one dose of surfactant. Of 147 mothers who did not receive corticosteroids, 111 cases (75.5%) had received one dose of surfactant and 36 cases (24.5%) had received more than one dose of surfactant. According to the Chi-Square test, there was no significant difference between corticosteroids used by mothers and the need for re-dosing surfactant to the hospitalized neonates with RDS (p value=0.21). Based on the degree of the received corticosteroids in mothers (one dose vs two doses), the results indicated that of 144 mothers who had received one dose of corticosteroids before delivery, 97 neonates (67.4%) had received one dose of surfactant and 47 cases (32.6%) had received more than one dose of surfactant. Of 59 mothers who had received two doses of prenatal corticosteroids, 44 neonates (64.6%) had received one dose of surfactant and 15 cases (25.4%) had received more than one dose of surfactant. According to Chi-square test, there was no relationship between receiving corticosteroids and re-dosing of surfactant doses (p value=0.31). Of 133 neoantes with high first minute APGAR score (7 to 10), 108 cases (81.2%) had received one dose of surfactant and 25 cases (18.8%) had received more than one re-dosing. Of 174 neonates with an average APGAR score (4 to 6), 111 cases (63.8%) had received one dose of surfactant and 63 cases (36.2%) had received more than one re-dosing of doses. Of 43 neonates with low APGAR scores (0 to 3) in the first minute, 33 cases (76.7%) had received one dose of surfactant and 10 cases (23.3%) had received more than one dose of surfactant. According to the Chi-square test, the first minute APGAR score had no effect on re-dosing of surfactant (p value=0.003). Of 238 neonates with the high fifth minute APGAR score (7 to 10), 177 cases (74.4%) had received one dose of surfactant and 61 cases (25.6%) had received more than one re-prescription. Of 94 neonates with the average APGAR scores (4 to 6), 60 cases (63.8%) had received one dose of surfactant and 34 cases (36.2%) had received more than one re-dosing. Of 18 neonates with the low fifth minute APGAR score (0 to 3), 15 cases (83.3%) had received one dose of surfactant and 3 cases (16.7%) had received more than one dose of surfactant. According to the Chi-square test, the fifth minute APGAR had no effect on re-dosing of surfactant (p value=0.002). There was one neonate with mild respiratory distress that had received only one dose of

Table 6. Effect of respiratory distress on the prescription of surfactant in neonates with the RDS.

Respiratory distress	Prescription of surfactant		Total (%)
	One dose {No. (%)}	More than one dose {No. (%)}	
Mild(<5)	1 (100)	0 (0)	1 (100)
Moderate(5-8)	174 (76.3)	54 (23.7)	228 (100)
Severe(>8)	77 (63.6)	44 (36.4)	121 (100)
Total	252 (72)	98 (28)	350 (100)

p value=0.03.

surfactant. Of 228 neonates with moderate respiratory distress (5 to 8), 174 cases (76.3%) received one dose of surfactant and 54 cases (23.7%) received more than one dose of surfactant. 121 neonates with severe respiratory distress (>8) were reported. 77 cases (63.6%) had received one dose of surfactant and 44 cases (36.4%) had received more than one dose of surfactant. According to the Fisher Exact test, respiratory distress had positive effect on the redosing of surfactant (p value=0.03) (Table 6).

DISCUSSION

Respiratory distress syndrome is a type of defect in the lung development, which is often seen with preterm labor and is caused by the lack of surfactant (Asnafei et al., 2004; Mahoney and Jain, 2013). Pulmonary surfactant deficiency leads to extensive atelectasis, loss of residual pulmonary capacity and collision of the ventilation to perfusion ratio (Jobe, 1993). Preterm neonates may suffer from respiratory distress syndrome due to low concentration of surfactant in the alveoli. The discovery of the key role of surfactant in the pathophysiology of RDS by the researchers in 1959 led them to think about the prescription of surfactant aerosol for premature neonates with RDS (Avery and Mead, 1959). In our study, the average weight of the premature neonates was 1782.03 ± 783.04 g and the average gestational age of newborns with the respiratory distress admitted in the hospital was 31.44 ± 3.74 weeks. The findings of the study indicated that 64.9% were discharged with the recovery condition and the percentage of death in neonates under treatment was 35.1%. Therefore, it could be concluded that surfactant therapy in the children with RDS could reduce mortality (Soll and Ozak, 2009; Ma and Ma, 2012). Although, our study did not aim to investigate the outcome of the neonates under treatment with re-dosing surfactant, our results are compatible with Dunn et al.'s (2008), Roger Soll et al.'s (2009) and Chong-Woo and Won-Ho, (2009) study. They had shown that certain recovery was observed in the degree of oxygenation of a group of neonates who received greater surfactant doses than the control group (Dani et al., 2010; Paola et al., 2011). Our findings indicated that neonates weighting less than 1700 g (31.38%) have reveived more than one dose of surfactant that is compatible with Dani et al. (2010) and Paola et al. (2011). Although, there was no significant difference between the greater weights of neonates in the study, the diagram and table of the neonates' weight showed percent of receiving surfactant has been increased with decrease in the neonates' weight. This finding is compatible with the results reported by Cogo (2009), Katz and Klein (2006), Dani (2010) and Paola (2011). Results of the neonates' gestational age indicated that those neonates born between 32 to 36 weeks needed for re-dosing greater surfactant, which is compatible with Katz and Klein (2006) study. The reason for the lower re-dosing of surfactant in neonates with the gestational age less than 32 weeks than neonates with the gestational age of 32 to 36 weeks may be due to the effect of other variables, such as birth weight, mothers receiving corticosteroids, the first and fifth minute APGAR score. Therefore, it is recommended that future researchers examine it. The neonates with the first dose of surfactant at 6 to 24 h after birth needed to significantly prescribe surfactant for other time. However, the first dose of surfactant in the range of less than 24 h had a direct effect on re-dosing surfactant. This finding is different from the results of Katz and Klein (2006). This difference could be caused by the effects of other variables. Our results indicated that there was a significant difference between the re-dosing surfactant and the type of delivery so that the neonates born by the caesarean section (31.5%) needed for re-dosing of surfactant compared to the neonates born by NVD (20.2%) as demonstrated by Kornacka and Kufel (2011). Although, there was not a significant difference between the number of twins and re-dosing of surfactant, the results did show (according to the related table and diagrams), redosing of surfactant needed to be more with the increased number of fetus in each pregnancy. The numbers of neonates with respiratory distress, admitted in Motahari Hospital of mothers who received prenatal corticosteroid dose and needed for re-dosing of surfactant were greater than the mothers who did not receive corticosteroids although not significantly and in contrast to Crowther et al. (2011). It may be influenced by other factors, including birth weight, gestational age, and so forth (Eriksson et al., 2012). In the case of using one

and two doses of by their mothers, neonates needed re-dosing surfactant whose mothers had received a prenatal corticosteroid dose compared with mothers who had received two doses of corticosteroid more. The need for re-dosing surfactant for neonates whose mothers had recieved one dose of corticosteroid was greater than the neonates whose mothers had recieved two doses of corticosteroid. This finding is compatible with the findings of Katz and Klein (2006). They reported that re-dosing of surfactant in the neonates, whose mothers receive a little corticosteroid, were greater. Our study showed that the type of surfactant products (Survanta vs Curosurf) did not have effect on the re-dosing of surfactant in the neonates. This result is different from the findings of Singh et al. (2011) but same as Rangasamy (2009, 2007) and Fakoor and Dinparast, (2009) study. Singh et al. (2011) demonstrated that the need for re-dosing the porcin surfactant in the preterm neonates was greater than to the bovine surfactant. Our findings indicated that compared to the female neonates, the male neonates received more than one dose of surfactant. Moreover, there was a significant difference between the first minute APGAR (mean APGAR score 4 to 6). In addition, vsuch difference was found between the fifth minute APGAR (mean APGAR score 4 to 6). The reason for the need for re-dosing more surfactant in the upper mean first and fifth minute APGARs than the lower first and fifth minute APGAR may be the greater mortality of the neonates in this APGAR and the effect of other above-mentioned variables. The neonates with the higher score of respiratory distress (8< - severe) significantly needed re-dosing with a dose of surfactant more than the neonates with the mild to moderate score of respiratory distress as demonstrated by Paola (2011).

Conclusion

The results of the study proved that the need for re-dosing surfactant was significantly high at the time of the prescription of the first dose of surfactant 6 to 24 h, in the C/S delivery, in the medium first and fifth minute APGAR score (4 to 6) and respiratory distress score greater than 8.

Conflict of interests

The authors have not declared any conflict of interests.

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