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A Comparative Study of the Efficacy of Surfactant Administration through a Thin Intratracheal Catheter and its Administration via an Endotracheal Tube in Neonatal Respiratory Distress Syndrome

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ABSTRACT

Background: The cornerstone of the treatment of respiratory distress syndrome (RDS) is respiratory support and surfactant replacement therapy. The administration of surfactant through a thin intratracheal catheter is one of the methods used to reduce one of the standard technique complications of a surfactant injection (Intubation-Surfactant-Extubation method [INSURE]). The aim of this study was to compare the effectiveness of this method on the treatment of RDS in neonates with one of the INSURE technique.

Methods: In this double blind clinical trial, 104 neonates with RDS were randomly allocated to two groups, one group received surfactant via an endotracheal tube (INSURE) and the other received surfactant without intubation (SWI) via a thin intratracheal catheter. Subsequently the outcomes of the two groups were compared.

Results: The incidence of hypoxemia during surfactant administration was significantly lower in the SWI group (11.5%) than in the INSURE group (28.8% , P< 0.05). no significant difference was observed in the need for intubation and mechanical ventilation during the first 72 hours of life, the duration of mechanical ventilation, the need for nasal continuous positive airway pressure (NCPAP), the need for oxygen, the incidence of bronchopulmonary dysplasia, intraventricular hemorrhage, pulmonary hemorrhage ,and death in the two groups.

Conclusion: Administration of surfactant through a thin intratracheal catheter is a safe and easy technique. This method is as effective as the INSURE method in improving the outcomes of RDS treatment.

Keywords: Neonatal respiratory distress syndrome, Surfactant, Surfactant without intubation

Introduction

Neonatal respiratory distress syndrome (RDS) refers to the insufficiency of the lungs that leads to certain signs, such as tachypnea, cyanosis, retraction, and grunting at birth or shortly thereafter (1). RDS is the most important cause of morbidity and mortality in premature infants (2).

The basis of RDS treatment is respiratory support and surfactant replacement therapy. The early use of nasal continuous positive airway pressure (NCPAP) and administration of surfactant reduce the need for mechanical ventilation and

its complications (3). Surfactant reduces the incidence of pneumothorax, pulmonary interstitial emphysema, chronic pulmonary disease, and death in the first 28 days of life (4).

The usual method of injecting surfactant (Intubation–Surfactant–Extubation [INSURE]) requires endotracheal intubation and a short time of positive pressure airway ventilation following administration of surfactant into the trachea. It subsequently may lead to pulmonary damage and long-term sequelae, particularly chronic pulmonary

disease, in addition to the complications of intubation (5).

Therefore, researchers have been seeking out other methods for the administration of surfactant that will obviate the need for endotracheal intubation and the subsequent short-term mechanical ventilation.

One of these methods is the administration of surfactant without endotracheal intubation, namely, surfactant-without-intubation (SWI) via a thin intratracheal catheter. It seems that this method is safer due to the lack of the need for intubation and mechanical ventilation with positive pressure and the continuation of oxygenation during administration of surfactant. The aim of this study was to compare the effectiveness of this method and INSURE technique on the treatment of RDS in neonates.

Methods

This double blind clinical trial was performed in Hajar Hospital of Shahrekord in 2016-2017. The study population included newborns with RDS. The protocol of this study was approved by the Research and Technology Deputy of the University (approval code:IR.SKUMS.REC.1395.69).

The inclusion criteria were: 1) clinical signs of RDS at the first hour of life in the newborns, 2) absence of severe abnormalities in the neonates, 3) absence of chorioamnionitis in mothers, 4) lack of the need for intubation and mechanical ventilation at birth, and 5) consent for participation in the study from the guardian of the neonate.

Exclusion criteria included the diagnosis of any disease other than RDS, such as early-onset sepsis, heart disease or pneumonia; lack of the need for surfactant administration after treatment with the NCPAP; and the need for continuation of mechanical ventilation immediately after surfactant administration.

According to a previous study (6), the need for mechanical ventilation in the first 72 hours of life in group I and II was 53% and 29%, respectively. Accordingly, the confidence interval was selected 90% and 80% as the power of study. Moreover, the sample size for each group was determined as 52; therefore, a total of 104 newborns was enrolled in the study.

Convenience sampling method was used to select participants from the neonates diagnosed with RDS in the neonatal intensive care unit (NICU) of Hajar hospital in Shahrekord. Participants were then randomly allocated into two groups by random allocation software.

Parental consent was obtained before starting

treatment for the newborns. In the case of parents' unwillingness for their child participation in the study, the neonate was excluded from the study. Furthermore, a checklist was used to collect data.

Newborns with signs of RDS underwent treatment with NCPAP starting with Neo puff (Fisher and Paykel, 2013) and continued as the infant was transferred to the NICU with the NCPAP (Sindi, 2014). Nasal prong was used as a connector to conduct ventilation. Positive pressure was 6 cm of H2O. To prevent severe abdominal distension, an orogastric (OG) tube was inserted for all neonates. Cardio-pulmonary monitoring and continuous monitoring of oxygen saturation were also carried out.

Intravenous aminophylline was prescribed for neonates with birth weight to prevent apnea of prematurity≤1250 g (7). In case of a need for FiO2 greater than 40% or the presence of a moderate to severe respiratory distress, 200 mg/kg surfactant (Curosurf) was administered (8) 30 minutes after NCPAP to maintain SpO2 above 87%.

For the administration of surfactant in group I (INSURE), the NCPAP was separated from the neonates, and then the tracheal tube was inserted. After the administration of the drug into the tracheal tube, mechanical ventilation was performed using the Neo puff for at least 1 minute or more if O2 saturation was less than 86%. The tube was then removed and the NCPAP was set up for the newborn.

In group II, a 5-F vascular catheter was used for the administration of surfactant according to the Hobart method (9, 10).

For this purpose, a section of the catheter's end part that should be inserted into the trachea (1-2 cm distance to the end of the catheter) was marked.

The surfactant-filled catheter that had been attached to the surfactant-containing syringe passed through vocal cords under direct laryngoscopy, so that the mark on the catheter was placed adjacent to the edges of the vocal cords.

Then, as the NCPAP continued, surfactant (Curosurf) was injected into the trachea within 2-4 minutes. Then the catheter was removed and the OG tube was aspirated to ensure that accidental infusion of surfactant into the stomach did not occur, and the NCPAP continued.

In both groups, surfactant administration would be stopped if the heart rate was reduced to

less than 100 bpm or increased to over 190 bpm. In case of SpO2 decrease to less than 80% or occurrence of severe coughing or choking, the administration was also ceased.

After the stability of the neonate's condition, the injection of surfactant was resumed (8). Twelve hours after surfactant administration, if the FiO2 of 30% or more was needed to keep SpO2 above 86%, the second dose of the drug (with a dosage of half) was administered (4, 11).

In case of NCPAP failure (O2 saturation of less than 90% despite the FiO2 40-70% and the CPAP 5-10 cm H2O; pH less than 7.2; $P_aCO2 \geq 60$ mmHg; and the occurrence of persistent apnea), the neonate underwent mechanical ventilation after endotracheal intubation (12).

Mechanical ventilation was discontinued if the neonate had spontaneous respiration; the values of blood gases were favorable; the ventilator breath rate was about 15 times per minute; PIP was less than 15 cmH2O; and FiO2 was less than 40%.

The neonates were followed up until 36 weeks of gestational age or the 28th days after birth (any one later).

Brain ultrasonography was performed once in the first 3 days of life and then on days 7 and 14 to diagnose intraventricular hemorrhage.

The data recorded in the checklist included gender, gestational age, weight and height of the neonate at birth, severity of RDS, number of gestations, antenatal corticosteroid administration, premature rupture of membrane (PROM) more than 18 hours, complications during surfactant administration (HR>190/min, HR<100/min, SpO2< 80% , and cough), the frequency of attempts to successfully insert the tracheal tube or the catheter into the trachea, the frequency of the surfactant administration, duration of the need for oxygen, the need for mechanical ventilation in the first 72 hours, the duration of mechanical ventilation (if done), the duration of NCPAP,

the incidence of bronchopulmonary dysplasia, intraventricular hemorrhage and pulmonary hemorrhage, hospitalization period, and mortality.

The data were summarized for each group using frequency and percentage for qualitative, mean with standard deviation for quantitative and normally distributed, medians with interquartile range (IQR) for quantitative and non-normally distributed variables.

Normality distribution was assessed with the Kolmogorov test. Differences between variables in the intervention and control groups were analyzed using the independent t-test for normally and Mann-Whitney U test for non-normally distributed variables. Qualitative variables were compared using Fisher's exact or Chi-square test. Statistical significance was defined as P<0.05 in all tests and analysis was performed by SPSS version 23.

Results

In this study, 104 neonates born in Hajar Hospital of Shahrekord admitted due to RDS were enrolled and allocated to two groups of 52 each, namely INSURE and SWI. Of the total newborns, 44 (42.3%) were girls. The qualitative and quantitative characteristics of the studied neonates in the two groups are summarized in Tables 1 and 2.

According to the significance values, the two groups were similar in terms of gender, gestational age, weight, and height at birth, RDS severity, antenatal corticosteroid administration, and hospital stay duration.

However, there was a significant difference in terms of the number of gestations within the two groups in that the frequency of twins was significantly higher in the INSURE than in the SWI group.

In Table 3, the frequency distributions of treatment outcomes in the two groups are shown. A significant difference was observed in

Table 1. Qualitative characteristics of neonates in the two groups

Variable		Group				P value
		INSURE		SWI		
		Frequency	Percent	Frequency	Percent	
Gender	Male	31	59.6	29	55.8	0.691
	Female	21	40.4	23	44.2	
Antenatal corticosteroid administration	Yes	15	28.8	15	28.8	1
	No	37	71.2	37	71.2	
RDS severity	Moderate	21	40.4	25	48.1	0.43
	Severe	31	59.6	27	51.9	
Number of gestation	1	32	61.5	42	80.8	0.044
	2	17	32.7	7	13.5	
	3	3	5.8	3	5.8	

Table 2. Quantitative characteristics of neonates in the two groups

Variable	Group		P value
	INSURE	SWI	
	Mean±Standard deviation	Mean±Standard deviation	
Gestational age (week)	33.06±2.3	32.9± 2.6	0.756
Birth body weight (gr)	2067.1±572.5	1937.6±554.7	0.244
Birth body height (cm)	43.9± 4.5	42.4±4.3	0.081
Duration of hospital stay (day)	12.7±7.7	12.3±8.4	0.799

Table 3. Frequency distributions of treatment outcomes in the groups

Variable		Group				P value
		INSURE		SWI		
		Frequency	percent	Frequency	percent	
Need to Mechanical ventilation at first 72h	No	39	75	44	84.6	0.222
	Yes	13	25	8	15.4	
Number of attempt for successful intubation or catheter insertion	1	47	90.4	50	96.2	0.437
	2	5	9.6	2	3.8	
Number of surfactant administration	1	43	82.7	42	80.8	0.80
	2	9	17.3	10	19.2	
Intraventricular hemorrhage	No	48	92.3	51	98.1	0.363
	Yes	4	7.7	1	1.9	
Pulmonary hemorrhage	No	47	90.4	49	94.2	0.715
	Yes	5	9.6	3	5.8	
Bronchopulmonary dysplasia	No	43	82.7	47	90.4	0.25
	Yes	9	17.3	5	9.6	
Death	No	47	90.4	49	94.2	0.715
	Yes	5	9.6	3	5.8	
Tachycardia during the procedure	No	44	84.6	49	94.2	0.111
	Yes	8	15.4	3	5.8	
Bradycardia during the procedure	Yes	0	0	0	0	1
	No	52	100	52	100	
Hypoxemia during the procedure	No	37	71.2	46	88.5	0.028
	Yes	15	28.8	6	11.5	
Cough during the procedure	No	52	100	50	96.2	0.495
	Yes	0	0	2	3.8	

Table 4. Duration of NCPAP, mechanical ventilation and oxygen therapy in the two groups

Variable	Group				P value
	INSURE		SWI		
	Median	Interquartile range	Median	Interquartile range	
NCPAP duration(h)	37.5	(25.5 – 53.75)	40.5	(28 – 56.75)	0.571
MV duration(h)	30	(5 – 86.5)	10	(6.25 – 22.25)	0.268
Oxygen therapy duration(h)	144	(73.5 – 268.5)	96	(75.25 – 154.25)	0.12

the incidence of hypoxemia during surfactant administration within the two groups (P<0.05) in that the incidence of hypoxemia during surfactant administration was significantly lower in SWI (11.5%) than in the INSURE group (28.8%).

The number of attempts to successfully enter the tracheal tube or catheter into the trachea, the frequency of surfactant administration, and incidence of tachycardia, bradycardia or cough during surfactant administration, the need for mechanical ventilation in the first 72 hours of life, the incidence of bronchopulmonary dysplasia, intraventricular hemorrhage, pulmonary hemor-rhage, and death were not significantly different within the two groups.

None of the neonates had bradycardia during surfactant administration.

According to Table 4, duration of NCPAP,

mechanical ventilation, and the need for oxygen in the two groups were not significantly different.

Discussion

RDS is one of the common diseases of premature neonates. The aims of treatments for neonatal RDS include preventing mechanical ventilation and reducing its duration as much as possible.

Preterm neonates are very vulnerable and even a short period of mechanical ventilation may have a damaging effect on the growth and function of their lungs. Mechanical ventilation may also cause systemic inflammatory response (13).

It is therefore useful for lungs and other organs, such as brain, which may be affected by systemic inflammation, to reduce the use of mechanical ventilation (14).

On the other hand, fluctuations in oxygen saturation in the infant is associated with certain diseases such as bronchopulmonary dysplasia, intraventricular hemorrhage and retinopathy of prematurity. These fluctuations are common in surfactant administration by the INSURE (9).

SWI is one of the methods that has been designed to reduce the need for mechanical ventilation and the complications due to RDS. The most commonly investigated technique in the previous numerous studies is the administration of surfactant into the trachea by using a thin catheter.

In this study, the effects of surfactant administration through vascular catheter into the lung of neonates with RDS were investigated to compare with the outcomes of administration of surfactant by the INSURE method.

The gestational age of the neonates in this study was 28-37 weeks with the mean age of 32.9±2.6 and 33.63±3.2 in SWI and INSURE groups, respectively. In other studies, the mean gestational age of infants was less than 32 weeks.

In this study, the groups were matched by gestational age, gender, weight, and height of birth. Only 28.8% of the neonates in the present study had a history of antenatal corticosteroid intake, which is found lower in other studies (15, 16).

Of the 104 studied neonates, 60 (57.7%) newborns were boys. Regarding the severity of RDS in the current study, 55.8% of cases had severe RDS while the rest had moderate RDS.

There was no significant difference in the severity of RDS within the two groups. In previous studies, RDS severity was not investigated.

In this study, a vascular catheter was used in order to administer surfactant in the SWI group. It was unlike the usual catheter insertion in the study conducted by Dargaville et al. (16) in that they used forceps under direct laryngoscopy. Vascular catheter insertion, however, was comparatively firmer in the current study and required no use of forceps in the trachea.

The complications of surfactant administration through the vascular catheter were very low in the present study which was consistent with the study conducted by Kanmaz et al. (17) in that they indicated the simplicity and security of the SWI.

There was no significant difference in the incidence of cough during surfactant administration within the groups (3.8% and 0% in SWI and INSURE groups, respectively). Whereas in the studies performed by Mirnia et al. and Heydarzadeh et al., coughing was reported to be higher in the thin endotracheal catheter group (TEC) (18, 19).

In the current study, there was a significant difference in the incidence of hypoxemia during surfactant administration (11.5% and 28.8% in SWI and INSURE groups, respectively), which was consistent with the results of a study conducted by Heydarzadeh et al. (19).

There was no significant difference in the need for the second dose of surfactant in the groups (19.2% and 17.3% in SWI and INSURE groups, respectively). In this regard, the results of the present study were consistent with previous studies (17, 18, 19, 20). However, they were not in line with the findings of a study conducted by Aguar et al. in that a second dose of surfactant was needed in the non-intubation group (35.6% vs. 5.6%) (15).

There was no significant difference in the number of attempts to perform successful intubation or insertion of intratracheal catheter within the groups. The need for two attempts in SWI and INSURE groups were 3.8% and 9.6%, respectively, which indicates that the insertion of the catheter into the trachea can be done easily.

In this study the need for mechanical ventilation in 72 hours after the birth was not significantly different within the two groups, although it was lower in SWI (15.4%) than in INSURE group (25%). The obtained result was inconsistent with the results of several previous studies (9, 11, 15).

However, in some other studies, the need for mechanical ventilation in the first 72 hours after birth was observed to be significantly lower in SWI than in the INSURE group (6, 8, 16, 17, 18, 19, 21, 22, 23, 24).

It has been reported in one study that the need for mechanical ventilation in the first 72 hours of life was lower in the control than that of SWI group (4).

In the present study, the mechanical ventilation duration in the two groups was not significantly different, which is consistent with the results of several study findings (11, 15, 16, 18, 19, 22). However it is not in line with the studies that reported the higher duration of mechanical ventilation in SWI group (6, 9, 14, 17, 21, 23, 24).

With regard to the current study results , the need for mechanical ventilation in the first 72 hours after birth and its duration were lower in the SWI group than in the INSURE group. However, this difference was not statistically significant, which may be due to the low number of cases needing mechanical ventilation in each group.

The overall frequency of mechanical ventilation in neonates in both groups was lower in this study than in previous studies (6, 8, 16, 17, 18, 21, 22, 23, 24). This may be due to the higher gestational age of the infants in this study because the severity of RDS is associated with gestational age.

Although the median duration of the need for oxygen in our study was 96 and 144 hours in SWI and INSURE groups, respectively, the duration of the need for oxygen was not significantly different within the two groups. The obtained results were consistent with several study findings (9, 15, 18, 19, 22), however, there were some inconsistencies with the studies reported the lower duration of the need for oxygen in SWI group (4, 11, 16, 17, 21, 23, 24).

NCPAP duration was the same in the two groups of the present study, which is inconsistent with the results of previous studies, in which the duration of the NCPAP was longer in the INSURE group (9, 17, 18, 19, 21), however, it was consistent with the findings of other studies (11, 15, 22).

Although intraventricular hemorrhage was 1.9% in the SWI group and less than that in the INSURE group (7.7%), there was no statistically significant difference in its incidence within the groups. The obtained results were consistent with several studies (9, 11, 15, 18, 19), however, it was not consistent with the results of other studies in which the incidence of intraventricular hemorrhage was higher in the INSURE group (16, 20, 25).

This finding was also inconsistent with the study conducted by Krajewski et al., in which intraventricular hemorrhage was higher in SWI group (22).

The incidence of pulmonary hemorrhage in the two groups was approximately similar in the current study (5.8% and 9.6% in SWI and INSURE groups, respectively). A similar result was also reported by Kanmaz et al. (17).

In this study, the incidence of broncho-pulmonary dysplasia in SWI and INSURE groups was 9.6% and 17.3%, respectively. Moreover, there was no statistically significant difference within the groups, which was consistent with the result of previous studies (9, 11, 15, 18, 19). However, it was inconsistent with the findings of studies in which the incidence of BPD was lower in the SWI group (4, 14, 17, 21, 25).

Furthermore, there were no significant differences in the incidence of neonatal death within the two groups, which was consistent with some previous study findings (9, 11, 16, 21, 24), however, it was inconsistent with other studies, in which the deaths in the SWI group were lower (4, 6, 8, 14, 18, 19, 20, 25).

In the present study, the duration of hospital stay in the two groups was the same, which was consistent with the results of previous studies (15, 18, 19). In contrast, in the study conducted by Gopel et al., the duration of hospital stay was significantly lower in SWI group than in INSURE group (24).

According to the results of this study, the outcomes of surfactant treatment within the two groups were not significantly different, which could be due to the equivalence of mechanical ventilation frequency and its duration in the two groups.

Mechanical ventilation is a major cause of lung injury, bronchopulmonary dysplasia, and intraventricular hemorrhage, therefore, the reduction in its use can be beneficial for lungs and other vulnerable organs, such as brain (5, 9, 14).

The required volume of Curosurf surfactant applied in this study is lower than other types, such as Survanta and Bles. The use of other types of surfactants by this method was not investigated in the current study.

The amount of surfactant administered via a thin catheter that reaches the lungs is unknown.In a study conducted by Niemarkt et al., the effects of surfactant administration through intratracheal catheter was compared with intubation in lambs. It was found that surfactant sedimentation in the lungs was lower in the catheter group than in the intubation group. However, the improvement rates of oxygenation and PaO2 were the same (26).

In this study, there was no significant difference in the incidence of complications (except for hypoxemia) during surfactant administration and the consequences of treatment. The inconsistency in the results of the present study and other previous studies can be attributed to the difference in the gestational age and severity of RDS among the study populations.

Overall, it can be argued that the use of a thin catheter to administer surfactant into the trachea is simple and helpful. Its better or at least similar effects compared to those of the INSURE reduce the complications of RDS and improve the overall outcome in newborns with RDS.

Conclusion

Taken altogether, it can be concluded that the administration of surfactant using a catheter into the trachea is safer than the INSURE. Moreover, it is at least as effective as the INSURE method in

reducing the duration and the need for mechanical ventilation, duration of the oxygen therapy and the NCPAP, and the incidence of bronchopulmonary dysplasia, intraventricular hemorrhage, pulmonary hemorrhage, and neonatal death due to RDS.

Acknowledgments

Conflicts of interests

The authors declare that there is no conflict of interest.

References

1. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants-- 2013 update. Neonatology. 2013; 103(4):353-68.
2. Ceylan A, Gezer S, Demir N, Tuncor O, Peker E, Kirimi E. The importance of administration of early surfactant and nasal continuous positive airway pressure in newborns with respiratory distress syndrome. Turk Pediatr Ars. 2014; 49(3):192-7.
3. Lista G, Castoldi F. Surfactant administration in spontaneous breathing with N-CPAP for RDS. Acta Biomed. 2014; 85(1):35-8.
4. Kribs A, Hartel C, Kattner E, Vochem M, Kuster H, Moller J, et al. Surfactant without intubation in preterm infants with respiratory distress: First multi-center data. Klin Padiatr. 2010; 222(1):13-7.
5. Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med. 2007; 357(19): 1946-55.
6. Kribs A, Roll C, Gopel W, Wieg C, Groneck P, Laux R, et al. Nonintubated surfactant application vs conventional therapy in extremely preterm infants: a randomized clinical trial. JAMA Pediatr. 2015; 169(8):723-30.
7. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants, 2010 update. Neonatology. 2010; 97(4):402-17.
8. Kribs A, Pillekamp F, Hunseler C, Vierzig A, Roth B. Early administration of surfactant in spontaneous breathing with nCPAP: feasibility and outcome in extremely premature infants (post menstrual age≤27 weeks). Pediatr Anesth. 2007; 17(4):364-9.
9. Bao Y, Zhang G, Wu M, Ma L, Zhu J. A pilot study of less invasive surfactant administration in very preterm infants in a Chinese tertiary center. BMC Pediatr. 2015; 15:21.
10. Dargaville PA, Aiyappan A, Cornelius A, Williams C, De Paoli AG. Preliminay evaluation of a new technique of minimally invasive surfactant therapy. Arch Dis Child Fetal Neonatal Neonatal Ed. 2011; 96(4):F243-8.
11. Mohammadizadeh M, Ardestani AG, Sadeghnia AR. Early administration of surfactant via a thin intratracheal catheter in preterm infants with respiratory distress syndrome: Feasibility and outcome. J Res Pharm Pract. 2015; 4(1):31-6.
12. Carlo WA, Ambalavanan N. Respiratory tract disorders. In: Kliegman RM, Stanton BF, Geme ST, Schor NF, editors. Nelson textbook of pediatrics. 20th ed. Philadelphia: Elsevier; 2016. P. 848-67.
13. Kuipers MT, VanderPoll T, Schultz MJ, Wieland CW. Bench-to-bedside review: Damage associated molecular patterns in the onset of ventilator-induced lung injury. Crit Care. 2011; 15(6):235.
14. Gopel W, Kribs A, Hartel C, Avenarius S, Teig N, Groneck P, et al. Less invasive surfactant administration is associated with improved pulmonary outcomes in spontaneously breathing preterm infants. Acta Paediatr. 2015; 104(3):241-6.
15. Aguar M, Cernada M, Brugada M, Gimeno A, Gutierrez A, Vento M. Minimally invasive surfactant therapy with a gastric tube is as effective as the intubation, surfactant, and extubation technique in preterm babies. Acta Paediatr. 2014; 103(6): e229-33.
16. Dargaville PA, Aiyappan A, De Paoli AG, Kuschel CA, Kamlin CO, Carlin JB, et al. Minimally-invasive surfactant therapy in preterm infants on continuous positive airway pressure. Arch Dis Child Fetal Neonatal Ed. 2013; 98(2):F122-6.
17. Kanmaz HG, Erdeve O, Canpolat FE, Mutlu B, Dilmen U. Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. Pediatrics. 2013; 131(2):502-9.
18. Mirnia K, Heidarzadeh M, Hosseini MB, Sadeghnia A, Balila M, Ghogazadeh M. Comparison outcome of surfactant administration via tracheal catheterization during spontaneous breathing with InSurE. Med J Islamic World Acad Sci. 2013; 109(1007):1-6.
19. Heidarzadeh M, Mirnia K, Hoseini MB, Sadeghnia A, Akrami F, Balila M, et al. Surfactant administration via thin catheter during spontaneous breathing: randomised controlled trial in Alzahra hospital. Iran J Neonatol. 2013; 4(2):5-9.
20. Klebermass-Schrehof K, Wald M, Schwindt J, Grill A, Prusa AR, Haiden N, et al. Less invasive surfactant administration in extremely preterm infants: impact on mortality and morbidity. Neonatology. 2013; 103(4):252-8.
21. Lau CS, Chamberlain RS, Sun S. Less invasive surfactant administration reduces the need for mechanical ventilation in preterm infants: a meta-analysis. Glob Pediatr Health. 2017; 4:1-9.
22. Krajewski P, Chudzik A, Strzałko-Głoskowska B, Gorska M, Kmiecik M, Wieckowska K, et al. Surfactant administration without intubation in preterm infants with respiratory distress syndrome-our experiences. J Matern Fetal Neonatal Med. 2015; 28(10):1161-4.

23. Dargaville PA. Innovation in surfactant therapy I: surfactant lavage and surfactant administration by fluid bolus using minimally invasive techniques. Neonatology. 2012; 101(4):326-36.
24. Gopel W, Kribs A, Ziegler A, Laux R, Hoehn T, Wieg C, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open- label, randomized, controlled trial. Lancet. 2011; 378(9803):1627-34.
25. Mehler K, Grimme J, Abele J, Huenseler C, Roth B, Kribs

A. Outcome of extremely low gestational age newborns after introduction of a revised protocol to assist preterm infants in their transition to extrauterine life. Acta Paediatr. 2012; 101(12):1232-9.
26. Niemarrkt HJ, Kuypers E, Jellema R, Ophelders D, Hutten M, Nikiforou M, et al. Effects of less-invasive surfactant administration on oxygenation, pulmonary surfactant distribution and lung compliance in spontaneously breathing preterm lambs. Pediatr Res. 2014; 76(2):166-70.