Acta Biomed 2020; Vol. 91, N. : e2020189 DOI: 10.23750/abm.v91i4.8845 © Mattioli 1885

Original article

The Comparison of LISA and INSURE techniques in term of neonatal morbidities and mortality among premature infants

Musa Silahli[1], Mehmet Tekin[2].

[1]Neonatal Intensive Care Unit, Baskent University Konya Training and Research Hospital, Konya, Turkey.
[2]Department of Pediatrics, Baskent University Konya Training and Research Hospital, Konya, Turkey.

Summary. *Background and aim of the work:* Respiratory distress syndrome (RDS) is the most common cause of respiratory failure among premature infants. The most important choice for the treatment of RDS is still exogenous surfactant replacement therapy and respiratory support. Today, there are some different surfactant applying techniques. In this study, we aimed to evaluate the effects of the surfactant administration techniques in premature infants less than 33 weeks of gestational age. *Methods:* The medical data were collected retrospectively from the medical records of Baskent University, Konya Training and Research Hospital between 2010 and 2016. The patient divided into two subgroups as Less Invasive Surfactant Administration (LISA) group (n: 35) and Intubation- Surfactant administration and rapid Extubation (INSURE) group (n: 30). Two surfactant administration techniques were evaluated on the neonatal morbidities and mortality among premature infants. *Results:* There were no significant differences in maternal and neonatal characteristics between the two groups. Duration on the nasal continues positive airway pressure (nCPAP) is significantly higher in the LISA group as compared with the INSURE group ($p<0.001$). And also between two groups, there were no significant differences in term of neonatal mortality and morbidities. *Conclusion:* The technique of the surfactant administration has no effect on the postnatal morbidities. LISA method is safe and effective as much as INSURE method, which is still a good alternative in centers with lack of experience about LISA. We need to perform studies that have larger sample size and prospective randomized controlled trials. (www.actabiomedica.it)

Keywords: Bronchopulmonary dysplasia, Mechanical ventilation, Preterm infant, Surfactant administration.

Introduction

Respiratory distress syndrome (RDS) is the most common cause of respiratory failure among premature infants, especially less than 34 weeks of gestational age infants (1). The main causes of RDS are lack of the endogenous surfactant and lung immaturity (2). The most important choice for the treatment of RDS is still exogenous surfactant replacement therapy and respiratory support. Japan scientist Fujiwara published the results of the administration of bovine surfactant in preterm infants in the Lancet (4). Formerly, it was only applied to intubated infants and was usually given via the endotracheal tube during mechanical ventilation (MV). With time, different forms of surfactant and different applying techniques were tried. Meta-analyses of randomized controlled trials (RCTs) have confirmed that the natural surfactant administration in preterm infants with RDS reduces mortality, decreases the incidence of pulmonary air leak and the risk of bronchopulmonary dysplasia (BPD) or death at 28 days of age (3).

Before nasal CPAP, INSURE technique; intubation surfactant instillation during brief MV and

extubation has been previously been used (5, 6). Intubation solely for surfactant administration is a common practice in many countries. Although treating RDS with the surfactant improves clinical outcomes, MV can cause lung injury in preterm infants with RDS and contribute to the development of chronic lung disease and BPD.

With the understanding that intubation or MV of premature infants has some harmful effects such as BPD or need more oxygen supplementation; some papers about application surfactant with a thin catheter among spontaneous breathing infants with RDS have been published (7, 8, 9). The first published randomized and controlled study about LISA is the avoidance of mechanical ventilation trial (9). In this study, the surfactant treated group with LISA technique had a lower rate of subsequent MV. After these investigations, the less invasive technique has been widely used in many countries.

In this retrospective study, we aim to evaluate the results of LISA and INSURE techniques in terms of pulmonary outcomes and the other secondary outcomes.

Materials and Methods

This study is a retrospective study that was extracted from the medical records of the Konya Training and Research Center of Baskent University between 2010 and 2016. The study involved 65 premature infants less than 33 weeks of gestational age with diagnosed RDS. Infants who have the major lethal malformation and who need tracheal intubation for delivery room stabilization or higher than 33 weeks of gestational age, were excluded. All of the patients were transferred to the neonatal intensive care unit (NICU) with T – Piece resuscitator (Neopuff Infant Resuscitator; Fisher and Paykel, Auckland, New Zealand). And, all of the patients have been monitored on nCPAP with 5-8 cm H_2O positive end-expiratory pressure (PEEP). The surfactant has been administrated the infants who need supplemental oxygen higher than 0.4 FiO_2 and who do not maintain a SpO_2 level above 85.

The subjects were divided into two groups: those who had been applied LISA (n: 35) and those who had been applied INSURE (n: 30). The patients in both groups were monitored on nasal CPAP initially. Infants who have clinical findings with RDS such as grunting, retractions, and tachypnea and who have acidosis need 0.3 - 0.4 more oxygen as an appropriate week with pH less than 7.2, were applied surfactant with LISA or INSURE techniques. Several techniques have been described for minimal invasive surfactant therapy, including nasopharyngeal instillation (10), laryngeal mask placement (11) and aerosolization (12). Another method of less invasive surfactant administration in which the trachea is catheterized with a feeding tube has been reported (13). The LISA technique involves the insertion of a 5 French gauge feeding tube into the trachea with Magill's forceps. Surfactant is then administered over 1 minute, and the catheter removed after that. Our surfactant administration technique had a little bit different. First, the patient was positioned as appropriate. The catheter length was not shortened. 5F or 6F catheter was advanced through the vocal cords under direct vision using a laryngoscope, without the need for Magill's forceps and any sedation. Then, the gentle pressure was applied to the trachea avoiding reflux of the surfactant after the catheter passed through the vocal cords for 1 cm. After the catheter placement, the laryngoscope was removed. At this position, the second member of the NICU was administered the surfactant within 30 seconds. Then the catheter was removed. All of the patients received poractant, Curosurf (Chiesi Farmaceutici, Parma, Italy) at a dose of 200mg/kg was drawn up in a 5-mL syringe, and an additional 1 mL of air was drawn up into the syringe taking account of the dead volume of the instillation catheter.

Patients who received surfactant via the INSURE technique were first orally intubated with a single lumen appropriate sized endotracheal tube, and poractant at a dose of 200 mg/kg was instilled to the trachea in 30 seconds. Manual lung inflation by a self-inflating balloon device with gentle pressure was performed during the surfactant instillation, and then the patient was rapidly extubated. After extubation, nCPAP support was maintained. No premedication, such as

sedation or atropine, was used during both procedures. As a routine procedure in our NICU; informed parental consent for all treatments and invasive procedures including tracheal intubation and insertion of the tracheal catheter was obtained on the admission of the NICU.

Maternal data, including age, diabetes mellitus, preeclampsia, and mode of delivery, were obtained from medical records. Infant data at birth, including gestational age, gender, weight, RDS, intraventricular hemorrhage (IVH), hemodynamic significant patent ductus arteriosis (hsPDA), the frequency of sepsis, the frequency of exitus, the time of hospital stay, the time on nCPAP, need for MV, the time of invasive MV, pneumothorax, BPD, the retinopathy of prematurity (ROP), need for supplemental oxygen, were also recorded.

Statistical analysis

On the basis of Kanmaz et al's study about the LISA and INSURE techniques, 50% of applied INSURE patients required intubation and MV in the first 72 hours of life (13). When we evaluated the first 10 patients, we found a 35% reduction in the need for intubation in the first 72 hours of life in the LISA group. The study was designed to test the hypothesis that LISA would reduce the need for MV compared with INSURE from 50% to 15%. A power calculation was performed, and a necessary sample size of 56 was determined (28/28) using α=0,05 and β=0,2. We included 65 cases in our study, predicting a 10% case data loss. Descriptive statistics of scale variables are to be defined as mean ± standard deviation or median (range) as appropriate. Demographic and clinical continuous variables were compared by using a 2-tailed Student's t-test for normally distributed values or Mann Whitney U test for non-normally distributed values. Z scores of skewness, kurtosis, and Shapiro Wilks statistics were used to understand whether the continuous variables are normally distributed. Some none normally distributed continuous variables were transformed to normally distributed data using the two-step approach as described by Gary Templeton (14). Categorical variables were compared by using X^2 or Fisher's exact test as appropriate. For all tests, the level of significance was set at 0.05. The analyses were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

A total of 65 infants who are under 33 weeks gestational age, were enrolled into the study. The groups consisted of 35 infants receiving LISA group and 30 infants receiving INSURE group. INSURE, which is a conventional method, was applied more frequently in the early stages of our study, but LISA became more preferred by us with the positive information about LISA increased. However, there was no demographic difference between the groups (Table 1, Figure 1). There

Table 1. Demographic characteristics

	LISA (N: 35)	**INSURE (N:30)**	**P-value**
Mother's age, mean ± SD	26.9 ± 4.5	27.9 ± 6.1	0.46
Transformed values of birth weight, mean ± SD	1163 ± 382	1200 ± 383	0.70
Gestational week, mean ± SD	28.2 ± 2.3	28.3 ± 1.9	0.84
Gender, male, N	18	16	0.87
Delivery mode, C/S, N	31	29	0.22

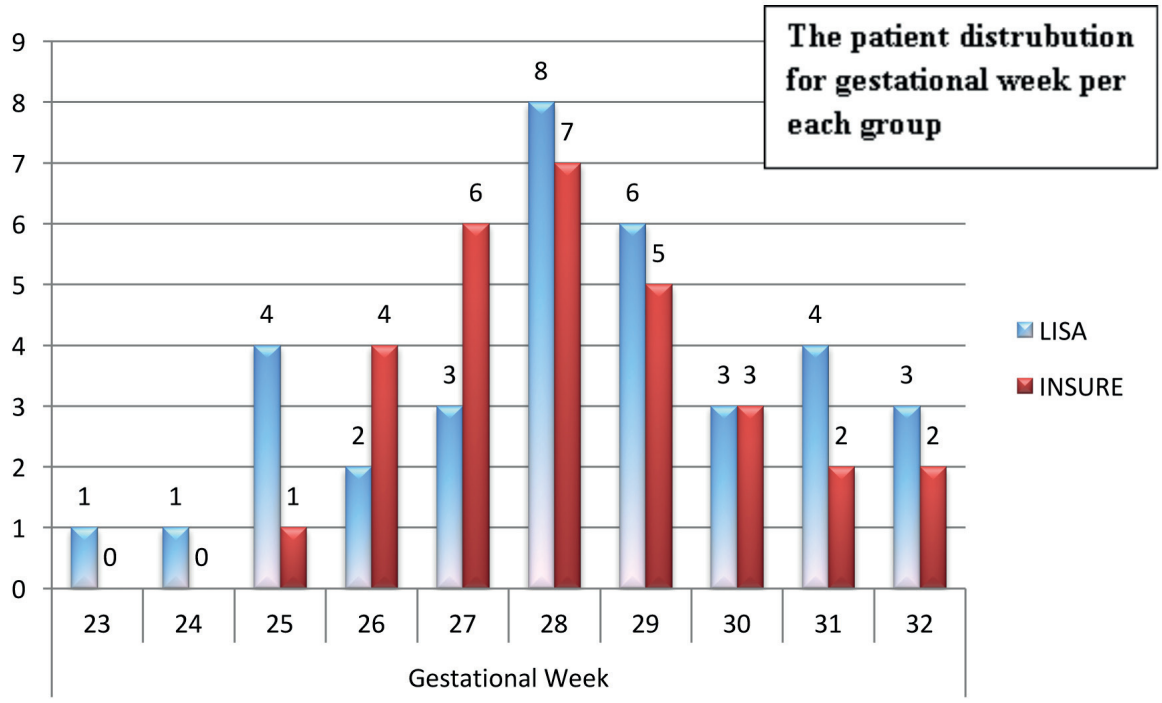

Figure 1. This figure shows that the patient distribution of the groups in term of gestational week was similar.

Table 2. Pulmonary Outcomes

	LISA (N: 35)	**INSURE (N:30)**	**P-value**
Days on nCPAP, median (min-max)	7 (3-43)	3(1-21)	**<0.001**
Transformed values of days on nCPAP, mean ± SD	12.2 ±5.9	4.4±7.7	**<0.001**
Need for MV, N (%)	9 (26)	12 (40)	0.22
Days of O2 supplementation, median (min-max)	19(6-84)	24 (3-114)	0.47
Days on the MV, median (min-max)	0 (0-10)	0(0-48)	0.29
BPD, n (%)	17 (49)	13 (43)	0.70
Need for MV first 72 hours, n (%)	3 (8,6)	7 (23,3)	0,167
Two or more dose surfactant, n (%)	9 (25,7)	11 (36,7)	0,422

Abbreviations:
nCPAP: nasal Continuous Positive Airway Pressure
MV: Mechanical Ventilation
BPD: Bronchopulmonary Dysplasia

were no statistically significant differences in days of supplemental oxygen, days on MV, need for MV, need for MV during the first 72 hours of life, the requirement of more than one dose of surfactant, and BPD between two groups (Table 2). Days on the nCPAP are significantly higher in the LISA group than the INSURE group (p <0.001). Secondary outcomes, including exitus, hospital stay duration, and existing of pneumothorax, IVH, ROP, and sepsis, were evaluated. There were no statistically significant differences between

Table 3. Secondary Outcomes

	LISA (N: 35)	**INSURE (N:30)**	**P-value**
Hospital stay, mean ± SD	46.2 ± 24	44.9 ± 28	0.84
Existing of pneumothorax, n (%)	1 (3)	1 (3)	0.71
Existing of IVH, n (%)	5 (14)	3 (10)	0.60
Existing proven sepsis, n (%)	13 (37)	11 (37)	0.99
Exitus, n (%)	4 (11)	5 (17)	0.52
ROP, n (%)	5 (14)	4 (13)	0.99

Abbreviations:
IVH: Intraventricular hemorrhage
ROP: Retinopathy of Prematurity

the two groups (Table 3). The need for MV was significantly higher in BPD existing group (P= 0.04). The need for MV was seen as a risk factor of BPD. And also the need for MV was seen significantly higher in the exitus group as expected. It was detected significant differences for sepsis and BPD as days on nCPAP. The days on nCPAP were significantly higher in BPD existing group (p<0.01) and the proven sepsis group (P= 0.022). When birth weight was evaluated, it was significantly lower in the group of need for MV (P=0.01), IVH existing group (P=0.02), suspected sepsis group (P=0.03), proven sepsis group (P=0.02), BPD existing group (P <0.01), exitus observed group (P=0.02) and ROP group (P=0.036) as expected. Birth weight (853 ± 242 VS 1233 ± 395, P= 0.007) and gestational week (26.4 ± 2.1 VS 28.5 ± 1.9, P= 0.05) were significantly lower in the group that was observed more exitus. For gestational age, similar findings were also observed. BPD was the most important predictor for the duration of hospital stay (P<0.001). The other factors associated with hospital stay duration included sepsis and ROP. The duration of hospital stay was significantly higher in the proven sepsis (P=0.007) and suspected sepsis (P=0.032) groups. Furthermore, ROP observed group had more hospital stay days (P=0.018). The need for supplemental oxygen was significantly associated with proven sepsis. The proven sepsis group had more days for supplemental oxygen (P<0.001). Infants, who were born from preeclamptic mother, had more days on MV even if statistics are not significant (P= 0.051). The other parameter with statistically significant about days of MV is BPD. Days on MV were higher statistically significant in BPD cases (P < 0.001). The factors associated with BPD were birth weight, gestational week, any MV, duration of MV, and days on nCPAP in our study. The birth weight and gestational week were significantly lower in BPD group 959 ± 204 gram VS 1474 ± 385 grams (P< 0.001) and 27.1 ± 1.3 VS 29.6 ± 1.9 (P<0.001), respectively.

Discussion

Preterm infants require invasive or non-invasive respiratory support, especially in the early few days of life. Neonatologists tend to prefer non-invasive treatment modalities for respiratory distress management with the improvement of technology in the NICU over time. Although the LISA technique is a more gentle and popular method, it brings important concerns such as apnea, bradycardia, desaturation, and hypotension. Additionally, spontaneous breathing is essential to effectively maintain the neonate on CPAP and also to move the surfactant from the trachea toward the lower airways (15). Although we have encountered similar short-term problems during LISA application in our study, we did not have any data about them.

In this retrospective study, contrary to our expectation, we did not find any difference in the need for any MV, the need for MV during the first 72 hours

of life, the requirement of more than one dose of surfactant, the duration of supplemental oxygen, and the duration of MV between these two surfactant administration techniques. Kanmaz et al. found that the need for MV during the first 72 hours of life is significantly lower in the LISA group than in the INSURE group (13). This reason was not fully understood. Because pulmonary outcomes in the early period of life including pneumothorax, pulmonary interstitial emphysema, atelectasis, and pulmonary hemorrhage were not found significant differences between the groups in Kanmaz's study. Although there were no differences between acute pulmonary complications, we could not understand the need for early intubation was higher in INSURE group. This result may be related to differences in clinician's ventilation modalities. Contrary to Kanmaz et al's study we found that LISA group had higher nasal CPAP duration. This may be related to the use of different nasal prongs in our study. Used nasal prongs in INSURE group, which the majority of them were applied in the older period, had a more harmful effect on the nasal septum. So the clinician may have acted quickly to wean off the nasal CPAP.

Contrary to Kanmaz et al.'s results, we did not find any difference in terms of the MV duration and the MV requirement in the first three days of life between the two groups. But similar to us, they found that supplemental oxygen days and any MV requirement were no significant differences between the groups.

It is also known that intubation and inappropriate mean airway pressure or barotrauma is linked to BPD. In our study, we did not see any statistically significant differences for BPD between LISA and INSURE groups contrary to the study of Kanmaz and colleagues. It may be related to more understandable effects on the immature lung traumas such as barotrauma, endotrauma, and atelectotrauma. Gentle ventilation techniques and advanced intensive care equipment may be associated with this result. For BPD, the most important risk factors were found as the need for MV, duration of MV, gestational week, and birth weight. Similar to Gopel's study(9), we did not find any differences regarding the surfactant administration technique.

Risk factors of BPD in our patients, we found that lower gestational age, lower gestational weight, any need for MV, duration of MV and, proven sepsis. Also, days on nasal CPAP are significantly higher in the BPD observed group. This situation may be explained that we prefer non-invasive ventilation approaches and rapid extubation as soon as possible. Another reason for this, less traumatic nasal prongs and nasal masks may encourage us to more non-invasive ventilation than expected. Another risk factor of BPD was proven sepsis. Positive blood culture with clinical sepsis findings may be starting the inflammatory processing in the lungs.

The main limitation of our study is a retrospective methodology. In addition, our study has covered for a long period of time and, there have been many improvements including devices and more gentle ventilation strategies. Therefore, they may have an influence on our results. Lastly, we did not have the opportunity to analyze other surfactant types because we preferred poractant in our practice for the volume advantage.

As a result, we found that the LISA method is safe and effective as much as the INSURE method, which is still a good alternative in centers with a lack of experience about LISA. Further progressive randomized controlled trials are needed to investigate the effect of these two methods on morbidities, particularly BPD.

Conflict of Interest

The authors have declared that no competing interests exist.

Statement of Ethics

Ethics committee approval was not obtained due to retrospective methodology. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

References

1. Horbar JD, Badger GJ, Carpenter JH, et al. Members of the Vermont Oxford Network. Trends in mortality and morbidity for very low birth weight infants, 1991-1999. **Pediatrics 2002**;110:143-51.
2. Avery ME, Mead J. Surface properties in relation to atelectasis and hyalinemembrane disease. **AMA J Dis Child 1959**;97:517-23.
3. Seger N, Soll R. Animal derived surfactant extract for treatment of respiratory distress syndrome. **Cochrane Database Syst Rev. 2009**;2: CD007836.
4. Fujiwara T, Chida S, Watabe YJ, Maeta H, Morita T, Abe T. Artificial surfactant therapy in hyaline membrane disease. **Lancet 1980**; i: 55–59.
5. Dani C, Bertini G, Pezzati M, Cecchi A, Caviglioli C, Rubaltelli FF. Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks' gestation. ***Pediatrics*** **2004**; 113: e560–63.
6. Reininger A, Khalak R, Kendig JW, et al. Surfactant administration by transient intubation in infants 29 to 35 weeks' gestation with respiratory distress syndrome decreases the likelihood of later mechanical ventilation: a randomized controlled trial. ***J Perinatol*** **2005**; 25: 703–08.
7. 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 (postmenstrual age </=27 weeks). **Paediatr Anaesth 2007**, 17:364–369.
8. Kribs A: Early administration of surfactant in spontaneous breathing with nCPAP through a thin endotracheal catheter–an option in the treatment of RDS in ELBW infants? **J Perinatol 2009**, 29:256.
9. Göpel W, Kribs A, Ziegler A, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. **Lancet 2011**, 378:1627–1634.
10. Kattwinkel J, Robinson M, Bloom BT, Delmore P, Ferguson JE: Technique for intrapartum administration of surfactant without requirement for an endotracheal tube. **J Perinatol 2004**, 24:360–365.
11. Trevisanuto D, Grazzina N, Ferrarese P, Micaglio M, Verghese C, Zanardo V: Laryngeal mask airway used as a delivery conduit for the administration of surfactant to preterm infants with respiratory distress syndrome. **Biol Neonate 2005**, 87:217–220.
12. Finer NN, Merritt TA, Bernstein G, Job L, Mazela J, Segal R: An open label, pilot study of Aerosurf(R) combined with nCPAP to prevent RDS in preterm neonates. **J Aerosol Med Pulm Drug Deliv 2010**, 23:303–309.
13. Kanmaz HG, Erdeve O, Canpolat FE, Mutlu B, Dilmen U: Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. **Pediatrics 2013**, 131:e502–e509.
14. Templeton, Gary F. "A Two-Step Approach for Transforming Continuous Variables to Normal: Implications and Recommendations for IS Research," **Communications of the Association for Information Systems**: 2011, 28; 4.

Received: 10 September 2019
Accepted: 24 November 2019
Correspondence:
Mehmet Tekin
Department of Pediatrics, Baskent University Konya Training and Research Hospital
Saray street, 42080 Selcuklu, Konya, Turkey.
Telephone: +90332-257-0606
Fax: +90332-257-0637
E-mail: dr.mehmettekin@gmail.com