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An Evaluation of Two Different Surfactant Application Methods in Preterm Infants

Prematüre Bebeklerde İki Farklı Sürfaktan Uygulama Yönteminin Değerlendirilmesi

*Ragıp Afşin Alay (0000-0002-0376-4765), **Mustafa Kara (0000-0001-6568-1538), *Turgay Aras (0009-0001-8500-9199), **Kadir Şerafettin Tekgündüz (0000-0001-6375-5644)

*Atatürk University Faculty of Medicine, Department of Child Health and Diseases, Erzurum, Türkiye

**Atatürk University Faculty of Medicine, Department of Neonatology, Ataturk University, Erzurum, Türkiye

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Abstract

Introduction: Less invasive surfactant application (LISA) techniques are being investigated in order to reduce alveolar damage during exogenous surfactant application. This study analyses the therapeutic outcomes of the LISA and INSURE (INtubation SURfactant and Extubation) exogenous surfactant application techniques in premature babies.

Materials and Methods: Ninety-three premature babies born at the 36th week of pregnancy or earlier in the neonatal intensive care unit and administered surfactant using the INSURE (n=44) and LISA (n=49) methods were included in this prospective study. The two groups were evaluated in terms of treatment outcomes and the presence of complications of prematurity.

Results: The study population consisted of 37 (39.8%) girls and 56 (60.2%) boys. Twelve (27.3%) of the babies in Group 1 (the INSURE group) received Poractant, 24 (54.5%) Beractant, and eight (18.2%) Calfactant surfactant preparation. Poractant surfactant preparation was administered to all the babies in Group II (the LISA group). No significant differences were detected when the patients in groups I and II were compared in terms of repeat surfactant requirements, Clinical Risk of Babies (CRIB) scores, PaCO2, body temperature, days of mechanical ventilation, days of nasal continuous positive airway pressure, duration of use of oxygen hoods, and length of stay (p>0.05). No significant differences were also observed between the two groups in terms of complications developing during follow-up (pneumothorax, pulmonary hemorrhage, bronchopulmonary dysplasia [BDP], intraventricular bleeding, and retinopathy of prematurity [ROP]) (p>0.05). However, the risk of BPD and ROP development was significantly greater in babies with high CRIB scores p=0,0003 and p=0,03).

Conclusion: Our comparison of the less invasive LISA and INSURE methods revealed no statistically significant difference in terms of treatment outcomes or complications. Further prospective studies involving new approaches and forms of treatment, their applicability, and larger numbers of cases are now needed.

Öz

Giriş: Ekzojen sürfaktan uygulaması sırasında alveolar hasarı azaltmak için daha az invaziv sürfaktan uygulama (LISA) teknikleri araştırılmaktadır. Bu çalışma, prematüre bebeklerde LISA ve INSURE (Entübasyon Sürfaktanı verilmesi Ekstübasyon) ekzojen sürfaktan uygulama tekniklerinin terapötik sonuçlarını analiz etmektedir.

Keywords
Respiratory distress syndrome, prematurity, surfactant, LISA, INSURE

Anahtar kelimeler
Solunum sıkıntısı sendromu, prematürelik, sürfaktan, LISA, INSURE

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Address for Correspondence/Yazışma Adresi: Ragıp Afşin Alay, Atatürk University Faculty of Medicine, Department of Child Health and Diseases, Erzurum, Türkiye
E-mail: drraalay@gmail.com

Yöntem ve Gereçler: Bu prospektif çalışmaya, 36. gebelik haftasında veya daha erken bir zamanda yenidoğan yoğun bakım ünitesinde doğan ve INSURE (n=44) ve LISA (n=49) yöntemleri kullanılarak sürfaktan uygulanan doksan üç prematüre bebek dahil edildi. Daha sonra iki grup tedavi sonuçları ve prematüre komplikasyonlarının varlığı açısından değerlendirildi.

Bulgular: Çalışma popülasyonu 37 (%39,8) kız ve 56 (%60,2) erkek bebekten oluşuyordu. Grup 1'deki (INSURE grubu) bebeklerin 12'sine (%27,3) Poractant, 24'üne (%54,5) Beractant ve sekizine (%18,2) Calfactant sürfaktan preparatı uygulandı. Grup II'deki (LISA grubu) tüm bebeklere Poractant sürfaktan preparatı uygulandı. Grup I ve II'deki hastalar tekrarlayan sürfaktan gereksinimleri, Bebeklerde Klinik Risk (CRIB) skorları, PaCO2, vücut sıcaklığı, mekanik ventilasyon günü, nazal sürekli pozitif hava yolu basıncı günü, oksijen başlığı kullanım süresi ve hastanede kalış süresi açısından karşılaştırıldığında anlamlı bir fark saptanmadı (p>0,05). Takip sırasında gelişen komplikasyonlar (pnömotoraks, pulmoner hemoraji, bronkopulmoner displazi [BDP], intraventriküler kanama ve prematüre retinopatisi [ROP]) açısından da iki grup arasında anlamlı bir fark gözlenmedi (p>0,05). Ancak yüksek CRIB skorlu bebeklerde BPD ve ROP gelişme riski anlamlı olarak daha yüksekti (sırasıyla p=0,0003 ve p=0,03).

Sonuç: Daha az invaziv LISA ve INSURE yöntemlerinin karşılaştırması, tedavi sonuçları veya komplikasyonlar açısından istatistiksel olarak anlamlı bir fark ortaya koymadı. Yeni yaklaşımları ve tedavi biçimlerini, bunların uygulanabilirliğini ve daha fazla sayıda vakayı içeren daha fazla prospektif çalışmaya artık ihtiyaç duyulmaktadır.

Introduction

Respiratory distress syndrome (RDS) is a condition deriving from alveolar surfactant deficiency accompanying structural immaturity in the lungs. Despite major advances in treatment, it is still a major cause of severe morbidity and mortality in premature infants.. Early surfactant administration is widely employed in the treatment of RDS in preterm infants (1). The most widely employed technique for surfactant therapy is endotracheal intubation and short-term mechanical ventilation (INSURE, INtubation SURfactant and Extubation). However, premature babies' lungs are highly susceptible to mechanical ventilation-associated damage (2). A systematic review study reported that Less Invasive Surfactant Administration (LISA) reduced mechanical ventilation requirements and represented a better alternative compared to surfactant administration with mechanical ventilation via an endotracheal tube (3). Feeding tubes are easily available in all neonatal intensive care units (NICUs) and have been shown to be more reasonably priced than special catheters (4).

This study was planned to assess the effect of surfactant application via the INSURE and LISA methods on treatment and complications.

Materials and Methods

Preterm babies born at less than 36 weeks, administered surfactant by the two methods, and followed up between June 1, 2018, and October 1, 2019 in the NICU were included in this prospective study. Babies receiving surfactant via the INSURE method were classified as group I and those receiving surfactant via the LISA method as group II. Ninety-three babies were enrolled, 44 in Group I and 49 in Group II. Approval for the study was granted by the Atatürk University Medical Faculty ethical committee, Türkiye (decision no. 12, session 14, dated 30.05.2019). Informed consent was obtained from all individual participants included in the study.

Patients exhibiting postnatal tachypnea, grunting, retractions, and cyanosis, with hypoaeration, widespread reticulogranular opacity and air bronchograms on chest radiographs, were diagnosed with RDS. Surfactant was applied to patients with RDS when fraction of inspired oxygen (FiO_2) requirements were ≥40%. Babies with no regression in their clinical RDS findings and FiO_2 requirements persisting at ≥40% received repeat surfactant therapy at the intervals specified for each preparation.

Surfactant Preparation and Dosage

Three surfactant types were used;

1. Poractant (Curosurf®, Chiesi Farmaceutici SpA, Parma, Italy): Pharmaceutical type 80 mg/ml. Since studies have shown that an initial Poractant dose of 200 mg/kg is associated with lower mortality than a 100 mg/kg dose of the same preparation. The first dose was administered at 200 mg/kg, and when second and third doses were required, 100 mg/kg was given.
2. Beractant (Survanta®, AbbVie Inc. North Chicago, IL, USA): administered at a dosage of 100 mg/kg (25 mg/ml). The same dose was repeated when necessary.
3. Calfactant (Infasurf®, ONY Inc. Amherst, NY, USA): administered at 100 mg/kg (35 mg/ml). The same dose was repeated when necessary.

Methods of Application

Application Using the INSURE Method

Three different surfactant preparations were administered using the INSURE method to the babies in Group I. Endotracheal intubation was first performed, and the surfactant was then administered gradually through the tube in approximately one minute. Self-inflating balloon positive pressure ventilation was then applied for 30 seconds, after which the intubation tube was withdrawn and the baby was placed on continuous positive airway pressure (CPAP). In the INSURE method, surfactant preparations for a dose of 100 mg/kg were randomly selected from all three preparates.

Application Using the LISA Method

Poractant was administered to all the babies in Group II using the LISA method. The surfactant was administered by passing the vocal cord gap using a laryngoscope with the help of a LISAcath (130 mm long, 1.7 mm thick, Chiesi Farmaceutici SpA, Parma, Italy) with the baby on CPAP.

Mechanical ventilator requirements were classified as invasive and non-invasive mechanical ventilation . CPAP was defined as non-invasive, and endotracheal intubation as invasive mechanical ventilation.

Demographic data, type of delivery, birth weight, sex, APGAR score, surfactant administration method (INSURE or LISA), repeated surfactant administration requirements, pulmonary air-leak, whether or not intraventricular bleeding, BPD, and ROP developed, Clinical Risk of Babies (CRIB) score, duration of ventilator and oxygen therapy, and length of hospital stay were recorded.

Complications developing during observation were identified based on diagnostic criteria. Pulmonary air-leak was evaluated based on clinical and pulmonary findings, BPD using radiological National Institute of Child Health and Human Development criteria, intraventricular bleeding based on cranial ultrasonography and computed tomography/magnetic resonance imaging if required, ROP based on the international ROP classification, and CRIB scoring based on physiological parameters obtained in the first 12 hours (birth weight, birth week, presence of congenital malformation, the highest base deficit value in blood gas and the highest and lowest amount of FiO_2 administered). APGAR scores were calculated based on the baby's skin color, heart rate, muscle tone, and respiration in the first and fifth minutes after birth.

Statistical Analysis

Statistical analyses were carried out on SPSS version 22 software. The data were expressed as mean, standard deviation, mean (minimum-maximum), number, and percentage values. Normality of distribution by groups was assessed using the One-Sample Kolmogorov-Smirnov test. $p > 0.05$ was regarded as representing normal distribution. Normally distributed data were analyzed using the One–Way ANOVA test, and non-normally distributed data with the Mann-Whitney U and chi-square tests. p values <0.05 were considered statistically significant.

Results

Ninety-three babies were included in the study, 49 randomly assigned to the LISA group and 44 to the INSURE group for surfactant administration. The babies in both groups were delivered via cesarean section. Birth weights in the babies in group II were significantly lower than in group I ($p=0.02$). No difference was observed between the groups in terms of frequencies of multiple births ($p=0.08$). Fifth-minute APGAR scores were lower in group I ($p=0.01$). The groups' demographic characteristics are shown in Table 1.

The surfactant preparations applied are shown in Table 2.

Twenty-five (56.8) babies in Group I received two doses of surfactant and 23 (46.9%) of those in group II. Three doses were administered to two (4.5%) patients in group 1 and seven (14.3%) in group II. No statistically significant difference was determined between the two groups in terms of repeat surfactant requirements ($p>0.05$) (Table 3). The babies receiving a first surfactant dose of 200 mg/kg and those given 100 mg/kg were compared within and between the groups. Nineteen (59.45) of the 32 babies receiving 100 mg/kg surfactant in group I required repeat surfactant administration compared to 23 (46.9%) of the 449 babies receiving surfactant at 200 mg/kg in group II. The difference was not statistically significant ($p=0.27$). Six (50%) of the 12 babies in Group I receiving an initial surfactant dosage of 200 mg/kg required repeat application, while 17 (51.3%) of the 32 babies beractant+calfactant at 100 mg/kg required repeat application. The difference was also not statistically significant ($p=0.85$) (Table 4).

No significant differences were determined between the groups in terms of duration of mechanical ventilation, duration of nasal CPAP, length of oxygen hood use, or length of hospital stay ($p=0.44$, $p=0.53$, $p=0.41$, and $p=0.59$,

respectively). The groups receiving surfactant by the LISA and INSURE methods were also analyzed in terms of complications developing during follow-up. No statistically significant differences were determined between the groups in terms of pneumothorax, pulmonary hemorrhage, BPD, intraventricular bleeding, or ROP (Table 3).

The mean duration of mechanical ventilation among the babies in group I was 0.42±1.44 days for those receiving Poractant, 0.96±3.68 days for those given Beractant, and 1.75±4.2 days for those given Calfactant. Durations of stay were 32.6±17.7 days for the babies receiving Poractant, 42.1±32.4 days for those given Beractant, and 32.5±20.28 days for those given Calfactant. The differences were not statistically significant (p=0.68, p=0.18, and p=0.51, respectively). BPD developed in three (25%) of the babies in group I given Poractant, eight (33.7%) of those given Beractant, and one (12.5%) of the eight babies receiving Calfactant. This was also not statistically significant (p=0.64). While no ROP developed in any of the babies given Poractant and Calfactant, it was observed in one (4%) of those receiving Calfactant. The difference was not significant (p=0.58) (Table 5).

Respiratory distress syndrome is a neonatal disease frequently seen in preterm babies. However, the risk of mortality and BPD decreased with the entry into use of surfactants in treatment (5). The present study investigated the effects on treatment and development of complications of surfactant administration using the INSURE and LISA methods in preterm babies born at less than 36 weeks. Recent studies have shown that LISA represents the best approach in preterm babies with surfactant requirements. However, our results revealed no superiority of LISA over INSURE. High-dose surfactant administration can reduce repeat surfactant requirements and potential complications in babies with RDS.

Table 1. The Patients' Demographic Characteristics

			n (%)	p
Gender	Group 1 (n=44)	Female	19 (43.2%)	0.23
		Male	25 (56.8%)	
	Group 2 (n=49)	Female	18 (36.7%)	
		Male	31 (63.3%)	
Multiple pregnancy	Group 1 (n=44)	No	38 (86.4%)	0.08
		Yes	6 (13.6%)	
	Group 2 (n=49)	No	39 (79.6%)	
		Yes	10 (20.4%)	
			Mean ± SD	**p**
Birth weight (g)	Group 1 (n=44)		1727.39±455.25	0.04
	Group 2 (n=49)		1506.33±668.96	
Birth week	Group 1 (n=44)		31.32±2.79	0.57
	Group 2 (n=49)		30.33±3.26	
1st minute APGAR	Group 1 (n=44)		4.66±1.14	0.62
	Group 2 (n=49)		5.06±1.19	
5th minute APGAR	Group 1 (n=44)		6.39±0.86	0.01
	Group 2 (n=49)		6.94±0.62	

SD: Standard deviation

Table 2. The Surfactant Preparations Applied in the Groups

	Poractant n(%)	Beractant n (%)	Calfactant n (%)
Group 1 (n=44)	12 (27.3)	24 (54.5)	8 (18.2)
Group 2 (n=49)	49 (100)	-	-

Table 3. The Two Groups' LISA and INSURE outcome variables				
		Single dose	Second dose	P
Surfactant	Group 1 (n=44)	19 (43.2%)	25 (56.8%)	0.34
	Group 2 (n=49)	26 (53.1%)	23 (46.9%)	
Days of mechanical ventilation Mean±SD	Group 1 (n=44)	6±6.5		0.44
	Group 2 (n=49)	5.6±4.8		
Days of nasal CPAP Mean±SD	Group 1 (n=44)	6.5±6.2		0.53
	Group 2 (n=49)	6.2±7.2		
Days of O_2 via hood Mean±SD	Group 1 (n=44)	7±6.2		0.41
	Group 2 (n=49)	9.8±5.7		
Length of admission Mean±SD	Group 1 (n=44)	37.8±27		0.59
	Group 2 (n=49)	41.5±30.3		
CPAP: Continuous Positive Airway Pressure				

Table 4. The Comparison of Repeat Dose Requirements among Babies Receiving Initial Surfactant Doses of 200 mg/kg and 100 mg/kg			
	Repeat surfactant administration not required n (%)	Repeat application required n (%)	P
Group 1, initial dose 100 mg/kg (n=32) (Beractant + Calfactant)	13 (40.6)	19 (59.4)	0.27
Group 2, initial dose 200 mg/kg (n=49) (Poractant)	26 (53.1)	23 (46.9)	
Group 1, initial dose 100 mg/kg (n=32) (Beractant + Calfactant)	15 (46.9)	17 (53.1)	0.85
Group 1, initial dose 200 mg/kg (n=12) (Poractant)	6 (50)	6 (50)	

Table 5. Risk Factors and Complication Development According to Surfactant Types in Group I				
		Mean ± SD		P
Days of mechanical ventilation	Poractant (n=12)	0.42±1.44		0.68
	Beractant (n-=24)	0.96±3.68		
	Calfactant (n=8)	1.75±4.2		
Length of stay	Poractant (n=12)	32.6±17.7		0.51
	Beractant (n=24)	42.1±32.4		
	Calfactant (n=8)	32.5±20.28		
		None n(%)	Present n(%)	P
BPD	Poractant (n=12)	9 (75)	3 (3)	0.64
	Beractant (n=24)	16 (66.7)	8 (33.7)	
	Calfactant (n=8)	7 (87.5)	1 (12.5)	
ROP	Poractant (n=12)	12 (100)	-	0.58
	Beractant (n=24)	23 (95.8)	1 (4.2)	
	Calfactant (n=8)	8 (100)	-	

SD: Standard deviation; BPD: Bronchopulmonary Dysplasia; ROP: Retinopathy of Prematurity

The groups administered surfactant via the LISA and INSURE methods were evaluated in terms of complications developing during follow-up. No significant differences were observed between the two groups in terms of development of pneumothorax, pulmonary hemorrhage, BPD, intraventricular bleeding, or ROP (Table 6)

Table 6. Complications Developing in the Study Groups				
		None(n,%)	Present(n,%)	p
Pneumothorax	Group 1 (n=44)	43 (97.7%)	1 (2.3%)	0.36
	Group 2 (n=49)	46 (93.9%)	3 (6.1%)	
Pulmonary hemorrhage	Group 1 (n=44)	44 (100%)	0	0.34
	Group 2 (n=49)	48 (98%)	1 (2%)	
Bronchopulmonary dysplasia	Group 1 (n=44)	32 (72.7%)	12 (27.3%)	0.59
	Group 2 (n=49)	38 (77.6%)	11 (22.4%)	
Intraventricular bleeding	Group 1 (n=44)	44 (100%)	0	0.34
	Group 2 (n=49)	48 (98%)	1 (2%)	
Retinopathy of prematurity	Group 1 (n=44)	43 (97.7%)	1 (2.3%)	0.21
	Group 2 (n=49)	45 (91.8%)	4 (8.2%)	

Although the treatment outcomes and complication rates were similar between the LISA and INSURE groups, it should be noted that the mean birth weight was significantly lower in the LISA group (1506 g vs. 1727 g, p=0.04). This difference might have influenced the comparability of clinical outcomes despite the lack of statistical significance in gestational age. Therefore, this heterogeneity should be considered as a potential limitation of our study.

Studies have shown that surfactant administration using the INSURE method significantly reduces patients' mechanical ventilation requirements(6,7). This method involving endotracheal intubation requires the use of sedation, and complications such as decreased SpO_2 and trauma may develop. In addition, this method requires positive pressure ventilation, albeit for a short period, following surfactant administration. A need for surfactant administration methods that do not require endotracheal intubation has therefore been reported (8). Less invasive surfactant administration techniques have been described for reducing intubation and associated complications (9-11). Studies have shown that surfactant use with non-invasive ventilation causes less alveolar damage than mechanical ventilation via an endotracheal tube (12). In their multi-center study, Kribs et al. (13) recorded a significant decrease in mechanical ventilation requirements and in the incidence of BPD in the first 72 hours in their LISA group. A randomized, controlled study comparing LISA and INSURE in babies with RDS born at 26-34 weeks reported no significant difference in total respiration support, but that invasive mechanical ventilation requirements were lower in the LISA group (14). In the present study, the length of stay in the mechanical ventilator was shorter in Group II than in Group I. However, no significant differences were observed between LISA and INSURE in terms of length of stay in the mechanical ventilator, duration of nasal CPAP, length of hood use, or length of hospital stay. The youth of the study population may very likely have affected the significance level of the findings.

Anand reported comparable incidences of BPD in the two groups, and a low general incidence of ROP [14]. A meta-analysis comparing surfactant administration using the LISA method and intubation techniques in preterm infants diagnosed with RDS concluded that surfactant therapy with LISA was beneficial since this reduced the combined outcome of BPD and mortality and also mechanical ventilation requirements. Lower pneumothorax rates were also achieved with LISA. Meta-analysis results identified no difference in mortality or other neonatal morbidity outcomes (15). A previous review study reported no significant association between BPD and the LISA technique (16). No significant finding in terms of BPD or ROP emerged between the LISA and INSURE methods in the present research, although a significant increase in BPD development was determined in patients requiring repeat surfactant administration.

Surfactant administration with the LISA technique allows the maintenance of uninterrupted nasal CPAP support and also prevents pulmonary damage that may occur due to loss of functional capacity in the lung and atelectasis (17). The distribution of the surfactant in pulmonary tissue when applied using the LISA technique depends on the infant's efforts to breathe spontaneously. Compared with the INSURE method, in which repeated positive pressure air is applied, the surfactant reaches the lung tissue and is integrated with

it more quickly with LISA (18,19). No significant difference was observed between the two techniques in terms of pneumothorax and pulmonary hemorrhage complication development in the present study.

In their recent systematic review study, Isayama et al. (3) described LISA as reducing the incidence of intraventricular bleeding and BPD in addition to lowering mechanical ventilation requirements. There was no significant difference in terms of the development of intraventricular bleeding between the two groups in the current research.

Recent studies have shown that LISA reduces the need and duration of mechanical ventilation, decreases CPAP failure, and lowers the rates of bronchopulmonary dysplasia, pneumothorax, intraventricular hemorrhage and mortality compared to the INSURE method (14,20). However, our study included different surfactant preparations and doses, which may influence the comparability of LISA and INSURE outcomes.

Augur et al. (11) reported a significantly higher second dose of surfactant requirement in a LISA group compared to an INSURE group (35.6% compared to 6.5%, $p = 0.003$). This may be due to the surfactant dose in the LISA procedure (100 mg/kg) being lower than that in the INSURE group (200 mg/kg). Anand et al. (14) reported no significant difference between the two groups in terms of second dose of surfactant requirements. No significant difference in surfactant requirements was also determined in the present research. Although repeat surfactant requirements were lower in the group receiving 200 mg/kg initially, the difference was not statistically significant. The need for repeated surfactant may be lower with a 200 mg/kg dose applied through a less invasive method 200 mg/kg. A decreased repeat surfactant requirement may be beneficial in terms of a decrease in secondary complications and in terms of lowering costs. Further studies with larger case numbers are now needed to address this.

Study Limitations

Although this study compared both the LISA and INSURE methods, different surfactant preparations and initial doses (poractant alfa 200 mg/kg and other preparations 100 mg/kg) were used. This heterogeneity may have influenced the outcomes and reduced comparability between the two methods. A more homogeneous analysis restricted to infants receiving poractant alfa would likely provide a clearer evaluation of the differences between LISA and INSURE. This study was conducted in a single center with a relatively small sample size, and included heterogeneous surfactant types and initial doses. These factors may have limited the statistical power and generalizability of the findings.

Conclusion

Due to the sensitive state of premature babies and the complications that may develop after any form of invasive intervention, less invasive and interventional procedures are becoming increasingly important. The number of studies comparing the INSURE and LISA techniques in the international literature and in Türkiye is quite low. The present study is one of the few to compare the two. No statistically significant difference was determined in terms of complications with the two techniques. Endotracheal surfactant administration techniques will continue to occupy an important place in premature babies, for whom less invasive interventions are being sought. Further prospective studies evaluating novel approaches and forms of treatment, and the applicability there of, together with larger case numbers, are now needed.

Ethics

Ethical Approval: Approval for the study was granted by the Atatürk University Medical Faculty ethical committee, Türkiye (decision no. 12, session 14, dated 30.05.2019).

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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