JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.712931
J Contemp Med 2020;10(4):493-498

Orjinal Araştırma / Original Article

Comparison Of Less Invasive Surfactant Delivery Techniques In Respiratory Distress Syndrome

Solunum Sıkıntısı Sendromunda Daha Az İnvazif Sürfaktan Verme Tekniklerinin Karşılaştırılması

Yasemin Çoban[1], Erdal Taskin[2]

[1]Department of Pediatrics, Fırat University, Elazığ, Turkey
[2]Department of Neonatal Intensive Care Unit , Fırat University, Elazıg, Turkey

Abstract

Background: This study was conducted to evaluate and compare the effectiveness of newly developed minimal invasive methods for surfactant administration (LISA by using Magill forceps, INSURE)

Methods: The research was conducted on 15 patients between 685-2100 gr weight, requiring surfactant administration. Poractant alpha, dose 200 mg/kg, was administered to patients with spontaneous breathing on continuous positive airway pressure support. LISA was used to administer surfactant to 7 of 15 patients, whereas 8 of them had surfactant administered using the INSURE method.

Results: The data regarding the delivery method, birth weight, gender, prenatal history, usage of steroids, APGAR scores and other data about the patients until hospital discharge were recorded. Desaturation and bradycardia for 3-4 minutes were observed in 71% (5/7) of LISA and 87.5% (7/8) of INSURE cases. Bradycardia was observed in 4 of 8 patients from the INSURE group and positive ventilation was needed. From the INSURE group, 3 patients died; one of 15 had ROP and this patient was from the INSURE group. No difference was found among the groups regarding required duration of O_2 and days of hospital stay ($p<0.05$). The thin catheter group had significantly fewer median days on mechanical ventilation and lower rate of mortality ($p<0.05$).

Conclusions: When there is no need for mechanical ventilation, intubation for surfactant administration was determined not to be necessary in the present study. LISA was observed to be the best method for surfactant administration among the methods without intubation.

Keyword: Respiratory distress syndrome, surfactant, complications, new method, CPAP

Öz

Giriş: Bu çalışmada; RDS'li bebeklerde yeni geliştirilen ve daha az invaziv surfaktan uygulama yöntemlerinin (ince kateter yöntemi ve INSURE) etkinliğini değerlendirmesi ve bu yöntemlerin birbiriyle karşılaştırılması amaçlandı.

Gereç ve Yöntem: Spontan soluyan ve surfaktan ihtiyacı olan 685-2100 gr arasında 15 hasta çalışmaya alındı. Hastaların 7'sine ince kateter yöntemi, 8'ine ise INSURE yöntemi ile surfaktan uygulandı.

Bulgular: Hastaların doğum şekli, kilo, cinsiyeti, prenatal öyküleri, steroid kullanımları, APGAR skorları ve hasta taburcu edilinceye kadar tüm veriler kaydedildi. Minimal invaziv sürfaktan tedavisi uygulanan grupta %71 (5/7), INSURE uygulanan grupta %87,5 (7/8) 3-4 dakika süren desaturasyon ve bradikardi gözlendi. INSURE grubunda 8 hastanın 4' ünde bradikardi gözlendi ve pozitif basınçlı ventilasyona ihtiyaç duyuldu. Entübasyon-Sürfaktan-Ekstübasyon grubundan 3 hasta hayatını kaybetti; 15 hastanın birinde, ROP gelişti ve bu hasta da INSURE uygulanan gruptaydı. Gruplar arasında, MV'de kalış süresi ve mortalitede istatistiksel açıdan anlamlı idi ($p<0.01$). Hastanede kalış süresi ve O2 ihtiyaç süreleri arasında farklılığın olmadığı belirlendi ($P<0.05$). İnce kateter yönteminde mekanik ventilatörde kalış süresi ve mortalite oranları daha düşük olarak belirlendi ($p<0.05$).

Sonuç: Spontan soluyan ve surfaktan ihtiyacı olan prematüre bebekler surfaktan tedavisi için entübe edilmesine gerek yoktur. Uygulanan her iki yöntem surfaktan verilişi açısından uygundur. Bu çalışmada entübe edilmeden surfaktan uygulama metotları içerisinde, hasta sonuçları açısından en uygun ve başarılı metotun ince kateter yöntemi olduğu sonucuna varıldı.

Anahtar Kelimeler: Respiratuar Distres Sendromu, surfaktan, komplikasyon, veriliş yöntemi, CPAP

Corresponding *(İletişim)*: Yasemin Çoban, Department of Pediatric Intensive Care, Hatay State Hospital, Hatay, Turkey
E-mail *(E-posta)*: yasemincoban83@gmail.com
Received *(Geliş Tarihi)*: 06.04.2020 **Accepted *(Kabul Tarihi)*:** 13.09.2020

INTRODUCTION

Respiratory distress syndrome (RDS) is observed in premature neonates and is basically a disease caused by surfactant deficiency. In recent times, many immature neonates have begun to survive and development of secondary complications linked to RDS has numerically increased in these neonates. As a result, new studies are continuously being performed about approach and treatment stages for RDS.[1]

To avoid intubation in the delivery room and early postnatal life, NCPAP is commonly used for preterm neonates. In patients only monitored with NCPAP, outcomes are not at desired levels especially in premature neonates below 29 weeks.[2] The failure of NCPAP and especially change to intubation in the first 24 hours was observed and it was identified that pneumothorax, IVH and BPD rates increased in these patients. The results of studies determined some demographic risk factors in groups with CPAP failure. These demographic risk factors were small gestational age, low birth weight and male sex. The risk factors and developing complications identified for CPAP failure overlap with the risk factors and complications of RDS. Thus, it appears the main reason for CPAP failure is RDS.[3-5] After these results, administering surfactant to these patients came to the agenda again. To benefit from the efficacy of NCAP and to be able to administer surfactant, patients were intubated for a short time, surfactant was administered and then they were extubated and NCPAP continued. Many studies have been performed comparing only NCPAP or intubation+surfactant treatment related to this method and these studies still continue. In developing countries at the moment, of patients monitored with NCPAP, only moderate-severe RDS patients are administered surfactant with this method (INSURE).

The INSURE method partially fulfilled the desired outcomes. The BPD rates still not falling to desired levels, inability to wean immature neonates intubated for surfactant from MV, administration of PPV during the procedure and thus exposure of the lungs to barotrauma has led researchers to search for new methods. As a result, first Kribs et al.[6] attempted a thin catheter method, then Dargaville[7] developed this method further and attracted the attention of many clinicians. Research is still being performed on this topic and attempts are made to make this method more useable.

Studies about minimal invasive methods generally only use NCPAP, the traditional method for the control group. However, the numbers of studies published comparing these two minimal invasive methods are limited.

The aim of our study is to determine and discuss the advantages and disadvantages of these two new methods and to present our experience ensuring ease of administration noted during administration with the thin catheter method.

MATERIAL AND METHOD

Permission was granted by Fırat University Non-Interventional Research Ethics committee (30.10.2013/Decision no: 04) and the parents of every patient were informed before the study and consented.

The patient material that formed the topic of the study was obtained from premature patients with gestation less than 34 weeks with RDS diagnosis from May 2013 to March 2014 at Fırat University Faculty of Medicine Tertiary Neonatal Intensive Care Unit.

Respiratory distress syndrome diagnosis was placed for neonates with less than 34 weeks gestation requiring FiO_2 of 0.40 to keep SaO_2 from 90-95%, tachypnea, retraction, moaning and nasal wing respiration, and clear RDS appearance on lung radiography. Acidosis tableau identified with blood gases supported the diagnosis.

Those requiring PPV in the delivery room, intubated within the first 24 hours, who died within the first three days and those with congenital anomalies were excluded from the study dataset.

All patients had surfactant administered as early survival treatment. Groups were divided randomly. Patients included in the first group had surfactant administered with the INSURE method (intubation-surfactant-extubation), while the second group had surfactant administered with the thin catheter method.

All complications observed during surfactant administration were recorded (bradycardia, saturation falls, choking, coughing). Desaturation criteria were accepted as a fall below 10% of the initial saturation value.

Patient follow-up and monitoring

Patients were monitored in the neonatal ward with pulse oximetry and were transported in previously-warmed transport incubators with T-piece revival support.

In the neonatal ward NCPAP treatment (PEEP 6 cmH_2O) used an SLE 5000 mechanical ventilator (SLE Ltd., London, England) with binasal short prongs and PEEP values were fixed for patients during monitoring. Those younger than 26 weeks gestational age had prophylactic surfactant administered. Those older than 26 weeks gestational age or all nonintubated premature cases had RDS diagnosis with lung radiography findings, clinical assessment (Silverman-Anderson score) and FiO_2 above 40% to keep oxygen saturation form 90-95% had surfactant administration within 2 hours of birth after the first 15 minutes of life.

During NCPAP monitoring of patients, if oxygen saturation was below 90% in spite of FiO_2 60%, CPAP value 6 cmH_2O, and blood pH was <7.20, the patient was intubated. This situation was accepted as NCPAP failure.

Criteria for weaning from continuous nasal positive air way pressure was standardized as FiO_2 <30% to keep SaO_2 >90%, mean airway pressure <6 cmH_2O and blood gas $PaCO_2$ <55 mmHg.

The surfactant preparation was natural poractant alpha (Curosurf; Chiesi Farmaceutici, Parma SPA, Italya) with dose

of 200 mg/kg. For all patients, if FiO_2 requirements were >0.50 12 hours later, a 2nd surfactant dose of 100 mg/kg was administered.

INSURE method

Patients in this group with continuous nasal positive airway pressure and requiring surfactant treatment were briefly separated from the nasal prongs. The routine endotracheal intubation procedure was performed and the tube was fixed. Poractant dose of 200 mg/kg was administered within the endotracheal tube once and then positive pressure ventilation was applied with the balloon for a short time to prevent reflux. When surfactant was not observed within the endotracheal tube and the patient was stabilized, they were extubated. Patients were immediately administered nasal CPAP again and ventilation continued until values before surfactant administration were reached. In necessary situations, changes were made to FiO_2 values according to oxygen saturation. Due to monitoring patients with CPAP, stomach orogastric drainage was applied. However, stomach lavage was not performed after the procedure. In situations where the intubation procedure lasted longer than 30 seconds, the procedure was stopped until the patient's general status regulated (mean 1-2 minutes). PPV was administered if desaturation (saturation <80%) lasted longer than 20 seconds or bradycardia was observed (peak heart rate <100) during surfactant administration.

LISA method

While on NCPAP, patients had a number 6 feeding probe inserted in the trachea to the vocal cord level with the aid of a Magill forceps. The surfactant (poractant), previously warmed by a second assisting health worker and placed in an injector, was inserted behind the catheter and administered slowly. Later, to send the surfactant remaining in the catheter into the lungs, air was taken into the injector and pushed through after the surfactant. This procedure lasted nearly 3 minutes. With this method, orogastric drainage was taken from the patient. This method does not require stomach lavage because the pharyngeal region was observed at intervals during surfactant administration and surfactant regurgitation was not identified. During the procedure, severe coughing or choking was not experienced. The greatest problem during application was using the Magill forceps. Attempts were made to complete the procedure without Magill forceps; however, insertion could not be completed due to the softness of the catheter. If desaturation (saturation <80%) or bradycardia were observed (PHR <100) to occur while inserting the catheter, the procedure was stopped until the patient's values returned to previous levels. During the process, the patient continued to use NCPAP.

All patients had MV mode, respiratory count, PIP, PEEP, inspiratory duration, FiO_2, SaO_2, blood gases and significant developments during patient monitoring recorded at 0, 1, 6, 12, 24, 48, and 72 hours.

With the aim of evaluating blood gases, patients had arterial, venous or capillary blood samples taken. An SLE 5000 (SLE Ltd., London, England) was used as mechanical ventilator. For nasal prongs, Hudson bilateral short nasal prongs (Hudson-RCI, United States of America) were used.

Statistical Analysis

Analysis of parameters with normal distribution used the student t test, while parameters with discontinuous variation used the nonparametric Mann-Whitney U test. When calculating the MV duration, O_2 treatment duration and hospital stay of patients, patients progressing to mortality were removed from the statistical calculations. Analysis of measurements until 72 hours after birth used a General Linear Model repeated measures procedure.

RESULTS

Parameters used as diagnostic criteria for respiratory distress syndrome were lung radiography and Silverman-Anderson scoring. There were no differences identified between the groups on 1-hour lung radiography findings and no differences in Silverman-Anderson scores (p>0.05).

While the procedure was successful on the first attempt with the INSURE method, with the thin catheter method the procedure was successful for 42.85% on the first attempt, 42.85% on the second attempt and 14.20% on the third attempt. After every failure, the patient was left until saturation and PHR reached normal intervals. At the same time, during the procedure PHR falls and amount and duration of falls in saturation were recorded. When patients with the INSURE and LISA methods were compared for SaO_2, desaturation duration and proportion of SaO_2 fall compared to initial value during administration, differences were not observed (p>0.05) (**Table 1**). In both groups, choking, respiratory and cardiac arrest were not observed during administration.

Table 1. Desaturation amounts during administration

		Patient number	Mean	Minimum	Maximum	p
SaO_2 levels during administration (%)	INSURE	8	78.50±4.32	60.0	95.0	0.980
	LISA	7	78.29±7.55	45.0	98.0	
Desaturation duration (seconds)	INSURE	8	69.38±19.42	0.0	120.0	0.587
	LISA	7	85.71±22.13	0.0	120.0	
Fall from initial SaO_2 during administration (%)	INSURE	8	17.75±12.27	0.00	33.00	0.944
	LISA	7	18.33±18.69	0.00	50.00	

The difference between groups shown by different letters in the same column are statistically significant (p<0.05).

With the intubation-surfactant-extubation (INSURE) method, 1/8 patients (12.50%) required surfactant administration a second time, while 2nd surfactant administration was not required with the LISA method. Within the first 72 hours, 1 patient required intubation in the INSURE group and this patient had CPAP failure in the 72nd hour.

The FiO_2 values recorded in patients reduced over time in all groups ($p<0.01$) (Table 2). In the INSURE and LISA groups, FiO_2 values were determined to be mean 61.25±2.26 and 57.71±4.28, respectively, before surfactant with the difference between the groups being statistically insignificant ($p>0.05$) (Table 7). The time when FiO_2 fell below 40% was determined as the 24th hour with the INSURE method and the 12th hour with the LISA method.

With the LISA and INSURE methods for surfactant administration, there were no statistically significant differences for the mean values of FiO_2, blood pH and PaO_2 parameters ($p>0.05$). The FiO_2 value in both groups showed a linear reduction over time from the 0 hour to 72 hours ($p<0.01$). Blood pH increased from 0 (7.31) to 6 hours to reach highest value (7.46) with the thin catheter method, while with the INSURE method after the highest value was reached (7.42) there was a reducing trend in both groups with a quadratic pattern ($p<0.01$) (**Table 2**).

Blood pH increased for the first 6 hours in all groups and then showed a slight fall ($p<0.01$). The initial blood gas pH values were determined as 7.33±0.03 in the 1st group and 7.31±0.02 in the 2nd group. All blood pH levels were observed to improve within the first hour. All these values were within physiologic levels.

The change in PaO_2 value over time was found to be statistically insignificant ($p>0.05$) (**Table 2**). Similarly, differences were not found between the groups ($p>0.05$) (**Table 2**).

Table 2. FiO_2 and blood gas levels with time in the groups

	Time	INSURE	LISA	P	
				Method	Time
FiO_2	0 hour	61.25±3.19	55.71±3.41	0.29	0.00
	1st hour	55.00±4.48	47.86±4.79		
	6th hour	46.25±3.71	38.71±3.97		
	12th hour	41.88±4.14	35.29±4.43		
	24th hour	38.88±4.05	31.14±4.33		
	48th hour	33.00±5.69	33.29±6.08		
	74th hour	29.25±3.76	27.57±4.02		
pH	0 hour	7.33±0.02	7.31±0.02	0.44	0.01
	1st hour	7.38±0.03	7.41±0.03		
	6th hour	7.41±0.03	7.46±0.03		
	12th hour	7.42±0.01	7.44±0.02		
	24th hour	7.41±0.03	7.43±0.03		
	48th hour	7.40±0.02	7.41±0.02		
	74th hour	7.39±0.01	7.43±0.02		
PaO_2	0. hour	58.13±8.05	57.90±8.60	0.67	0.58
	1st hour	53.13±8.24	66.66±8.81		
	6th hour	55.19±3.32	54.30±3.55		
	12th hour	57.75±4.98	55.87±5.33		
	24th hour	56.13±5.87	59.09±6.28		
	48th hour	58.38±5.47	61.14±5.854		
	74th hour	60.13±4.98	63.00±5.323		

P values given for mean values at all times

Additionally, considering all patients received NCPAP or free oxygen (in hood or incubator) in this period, and knowing the mechanical ventilator is set to keep patient saturation from 90-95%, blood gases were kept at appropriate levels and respiratory failure was not observed.

The patients' MV durations were found to be longer in patients with the INSURE method compared to the LISA method ($p<0.05$) (**Table 3**). There were no differences for oxygen treatment duration and hospital stay between the two methods ($p>0.05$) (**Table 3**).

Table 3. Mechanical ventilator requirements, oxygen treatment duration and hospital stay in the groups

	INSURE	LISA	P
MV duration (days)	6.75±1.56	2.57±0.57	0.03
Oxygen treatment duration (days)	11.25±2.90	5.43±0.43	0.09
Hospital stay (days)	22.00±5.50	26.00±3.80	0.57

MV: Mechanic Ventilator

Mortality rates were 38% with the INSURE method and 0% for the LISA method.

In terms of complications, most complications were observed with the INSURE method. BPD was not observed in any group. With the INSURE method, 12.50% developed IVH, 12.50% had pulmonary hemorrhage, 25% had NEC, 12.50% had PDA and 25% developed sepsis. Only 1 of the patients developing complications required intubation within the first 24 hours. One of these patients developed both PDA and NEC, and later sepsis. One had sepsis and secondary to sepsis pulmonary hemorrhage developed. One developed IVH. These 3 patients had mortality as outcome. The other patient developing NEC survived. With the INSURE method complications developed in 4 patients and 3 resulted in mortality.

With the LISA method, 14.20% sepsis and 14.20% PDA were identified. Complications were observed in two different patients. Mortality was not observed with this method.

DISCUSSION

In this study based on simultaneous patient groups in a single center, the thin catheter method for infants with RDS was observed to clearly reduce BPD, pulmonary hemorrhage, hospital stay, and mechanical ventilatory requirements duration compared to the INSURE method and was determined to be successful.

Our INSURE group was compared with INSURE groups from previous studies.[8-10] When examined in terms of statistics, the study by Dani et al.[8] about outcomes of the SURF-NCPAP group with standardized parameters were determined to have similar MV requirements and 2nd surfactant requirement rates similar to our study. There were differences in terms of hospital stay and NCPAP or MV durations. We obtained better rates than the study by the Oxford Study group and Colombia study.[9,10] The BPD, ROP and NEC incidence rates in our study were lower than the other studies.[8-10]

The LISA method used in our study was similar to previous studies but there were some differences in administration.

The thin catheter method (LISA) was begun by Kanmaz[11] and Dargaville[12] and given its final form by Kribs.[14] When explaining the LISA method, the Kribs[14] study did not take the patient off NCPAP, inserted the 4f catheter with Magill forceps and then administered 100 mg/kg poractant over 30-120 s.

In our study, as we did not have a 4f catheter, so a 6f catheter was used, and slower infusion duration of 200 mcg/kg surfactant was administered. However, again, PPV was not required and no repeated doses of surfactant were required. We could not compare with our study as this data was not included in the study by Kribs.[14]

The thin catheter method in our study was modified from the methods applied by Kanmaz[11] and Dargaville[12] and used a number 6 feeding probe and ensured better management of surfactant administration due to the long catheter. However, contrary to both methods, the catheter was inserted with a Magill forceps because the soft nasogastric probe used could not be directed by hand. Additionally, in our study, as the tip of the catheter was made with the property of not harming mucosa, we did not think it appropriate to shorten the catheter. In fact, the length of the catheter was useful, and ensured easier control while the 2nd person administered surfactant.

During administration by Dargaville,[12] the patient was taken off NCPAP, while during administration in the Kanmaz[11] and Kribs[14] studies, the patient continued to benefit from NCPAP during administration. In our study, no patient was taken off NCPCP during all procedures.

Some studies reduced the amount of surfactant or completed the procedure in two sessions to protect against desaturation.[11,12] However, previous studies have shown that when poractant is administered at 200 mg/kg doses mortality and repeated surfactant requirements clearly reduce.[13] As a result, in our study all patient groups were administered 200 mg/kg poractant, surfactant infusion rate was slowed to 2-3 minutes and continuous NCPAP was used in an attempt to protect against desaturation. Our successful desaturation levels are present in the table. As this data is not included in the study by Kribs,[14] we could not compare with our study.

In our study, while inserting the catheter and administering surfactant, sedation was not administered to patients as in the TAKE-CARE[11] and LISA[14] methods and no patient was taken off NCPAP. Thus, patients were protected from the side effects of sedation and did not require PPV.

Additionally, all patients had caffeine loading before the procedure.

The pharynx was observed while administering surfactant and thus regurgitation was prevented and administration of surfactant as infusion protected patients from apnea.

The LISA method uses Magill forceps. During the study, attempts were made to insert the feeding probe without Magill forceps; however, this was not successful as the catheter is too soft. As proposed by Kanmaz[11] and Dargaville,[12] it is considered that the use of a hard and narrow tube is appropriate for this procedure.

Metaanalysis of many datasets compared the INSURE method and the LISA (thin catheter) method. One of these studies determined the LISA method had less complications (BPD development, mortality, serious intraventricular hemorrhage, NEC and MV requirements) to a clearly low degree compared to the INSURE method.[15] Another observational cohort study compared INSURE and LISA methods and determined the LISA method had significantly low levels of BPD and mortality rate. However, this study identified high focal intestinal perforation with the LISA method. This situation should not just be linked to the method as it may occur neonates less than 26 GW in age and they stated more studies are required.[16]

Many metaanalyses and reviews have been published showing the LISA method has less BPD development, NCPAP failure and mortality compared to the INSURE method.[17,18]

Since these studies, the LISA method has begun to enter RDS approach guidelines and the European Consensus Guidelines recommended the LISA method in 2019.[19]

For the first time, 2 minimal invasive method were performed by Kanmaz et al.[11] in a single center and comparisons found no statistical differences between the 2 groups (1st group TAKE-CARE, 2nd group INSURE) in terms of desaturation and bradycardia during administration. In our study, similar to the study by Kanmaz et al.[11] the INSURE and LISA methods were compared. There were no differences observed between the 1st and 2nd groups (1st group INSURE, 2nd group LISA) in terms of desaturation level and duration. These results comply with the desaturation percentage findings of Kanmaz et al.[11]

In our study, there were statistical differences between LISA and INSURE in terms of duration on MV. Complication development and mortality rates were identified to be clearly high with the INSURE method.

In our study, FiO_2 levels reduced over time in both groups, with no statistical significance between the groups. FiO_2 levels were <40% in the LISA group in the 6th hour, while they reached this level in the INSURE group in the 12th hour. The early fall in FiO_2 shows the thin catheter method has better efficacy compared to INSURE. The $PaCO_2$ fall rates were equivalent in both groups.

In our study, 12.5% were identified to require MV within the first 72 hours with the INSURE method. Many studies have linked CPAP failure in the first 24 hours to method (intubated surfactant administration) and patients with INSURE management needed to be intubated at 72 hours. In light of this knowledge, when the thin catheter method is evaluated in terms of MV requirements, it appears to be a very successful method.

In our study groups BPD was not observed. In the study by Kanmaz et al.[11] BPD developed in 9% of the TAKE-CARE group and 17% in the INSURE method group. The lack of observation of BPD in our study may be due to administering poractant at 200 mg/kg and to the lack of PPV administration. There was 38% mortality observed in the INSURE group. This rate was statistically significant between the two groups.

CONCLUSION

The INSURE method was identified to have clearly high duration of stay on mechanical ventilation, MV requirements and mortality rates compared to the thin catheter method. This situation supports previous studies.

Especially in the first hour of life, the LISA method is superior to the INSURE method for administration of surfactant without requiring PPV.

However, there is a need to develop new material for the LISA method. In fact, for the thin catheter method, a cannula may be produced that contains a guide within it and more clear length indications.

New studies about the LISA method will modify the administration form slightly and finally ensure standardization.

During catheter insertion with the LISA method, oxygen support with continuous NCPAP will prevent desaturation to a certain degree. Additionally, observation of the pharynx during surfactant administration completely prevented regurgitation and it is certain that the administered surfactant was 100% used.

The administration of surfactant with the LISA method as infusion rather than bolus will lower the desaturation rates in patients.

If the LISA method is compared with the INSURE method, the LISA method was observed to be statistically significant in terms of duration on MV and mortality. Additionally, though not statistically significant, the INSURE method was observed to involve more complications during patient surveillance compared to the thin catheter method.

ETHICAL DECLARATIONS

Ethics Committee Approval: Permission was granted by Fırat University Non-Interventional Research Ethics committee (30.10.2013/Decision no: 04).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Hamvas A. Pathophysiology and management of respiratory distress syndrome. Fanaroff & Martın's Neonatal Perinatal Medicine 9th. edition, Elsevier Mosby, 2011:1075-116.
2. Gallimore V. The report of the Australian and New Zealand Neonatal Network, 2007.
3. Fuchs H, Lindner W, Leiprecht A, Mendler MR, Hummler HD. Predictors of early nasal CPAP failure and effects of various intubation criteria on the rate of mechanical ventilation in preterm infants of <29 weeks gestational age. Arch Dis Child Fetal Neonatal Ed 2011; 96: 343-347.
4. Ammari A, Suri M, Milisavljevic V, et al. variables associated with the early failure of nasal CPAP in very loe birth weight infants. J Pediatr 2005; 147: 341-347.
5. De Jaegere AP, Lee JH, Cante C, Kaam AH. Early prediction of nasal continuous positive airway pressure failure in preterm infants less than 30 weeks gestation. Acta Paediatr 2011; 101: 374-379.
6. Kribs A, Pillekamp F, Hünseler 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.
7. Dargaville PA, Aiyappan A, Cornelius A, Williams C, De Paoli AG. Preliminary evaluation of a new technique of minimally invasive surfactant therapy. Arch Dis Child Fetal Neonatal Ed 2011; 96: 243-248.
8. 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: 560–563.
9. Dunn MS, Kaempf J, de Klerk A, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics. 2011;128(5):e1069-e1076.
10. Rojas MA, Lozano JM, Rojas MX, et al. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. Pediatrics 2009; 123: 137-142.
11. Kanmaz G, Erdeve Ö, Canpolat FE, Mutlu B, Dilmen U. Surfactant Administration via thin catheter during spontaneous breathing: randomized controlled trial. Am Pediatrics 2013; 131: 502 -509.
12. Dargaville PA, Aiyappan A, De Paoli AG, et al. Minimally-invasive surfactant therapy in preterm infants on continuous positive airway pressure. Arch Dis Child Fetal Neonatal Ed 2013; 98: 122-126.
13. Ramanathan R, Bhatia JJ, Sekar K, Ernst FR. Mortality in preterm infants with respiratory distress syndrome treated with poractant alfa, calfactant or beractant: a retrospective study. J Perinatol. Feb 2013; 33: 119–125.
14. Kribs A, Roll C, Göpel W, et al. Nonintubated surfactant application vs conventional therapy in extremely preterm infants: a randomized clinical trial. JAMA Pediatrics. 2015; 169(8): 723-730.
15. Isayama, T, Iwami H, McDonald S, Beyene J. Association of noninvasive ventilation strategies with mortality and bronchopulmonary dysplasia among preterm infants: a systematic review and meta-analysis. Jama. 2016; 316(6): 611-624.
16. Härtel C, Paul P, Hanke K, et al. Less invasive surfactant administration and complications of preterm birth. Scientific reports. 2018; 8(1): 8333.
17. Dumpa V & Bhandari V. Surfactant, steroids and non-invasive ventilation in the prevention of BPD. In Seminars in perinatology. 2018, October. WB Saunders.
18. Rigo V, Lefebvre C, Broux I. Surfactant instillation in spontaneously breathing preterm infants: a systematic review and meta-analysis. Eur j pediatr 2016; 175(12): 1933-1942.
19. Sweet DG, Carnielli V, Greisen G, et al. European consensus guidelines on the management of respiratory distress syndrome–2019 update. Neonatology. 2019; 15(4): 432-450.