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ORIGINAL ARTICLE

Less Invasive Surfactant Administration Via Tracheal Catheterization Versus Tracheal Intubation in Preterm Infants with Respiratory Distress Syndrome admitted to neonatal intensive care unit at zagazig university

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ABSTRACT

Background: Respiratory distress syndrome (RDS) is a common neonatal condition in premature infants. Its treatment requires the use of surfactants. This study aimed to assess the effectiveness and safety of less invasive surfactant administration (LISA) via tracheal catheterization compared with intubation. **Methods:** this was a clinical trial study carried out in Zagazig University, in neonatal intensive care unit (NICU), carried on 68 patients that were divided into two groups according to the technique of surfactant administration. **Results**: results revealed that there was a highly statistically difference between LISA and INSURE(intubation surfactant instillation extubation) group regarding CPAP and need for mechanical ventilation; there was a statistically significant difference between LISA and INSURE group regarding the possible complications as INSURE group has a higher possibility for ventilator-associated pneumonia, pneumothorax, Symptomatic PDA, Pulmonary hemorrhage and retinopathy of prematurity screening, but there was no statistically significant difference between LISA and INSURE group regarding the duration of O2 therapy, hospital stay and death before discharge. **Conclusions:** LISA technique for surfactant delivery results in a lesser need for mechanical ventilation and lesser complications in preterm infants with RDS. This method can be a promising and effective step, which is feasible, cost-effective to be standardized.
Keywords: less invasive surfactant administration, respiratory distress syndrome, clinical trial.

INTRODUCTION

Neonatal respiratory distress syndrome (ARDS) due to surfactant deficiency is associated with high morbidity and mortality in preterm infants **[1].** Two-thirds of preterm infants born before 33 weeks gestational age develop RDS after birth and require surfactant therapy. **[2]**

Respiratory distress is one of the most common reasons an infant is admitted to the neonatal intensive care unit **[3].** Fifteen percent of term infants and 29% of late preterm infants admitted to the neonatal intensive care unit develop significant respiratory morbidity; this is even higher for infants born before 34 weeks 'gestation **[4].**

Certain risk factors increase the likelihood of neonatal respiratory disease. These factors include prematurity, meconium-stained amniotic fluid (MSAF), caesarian section delivery, gestational diabetes, maternal chorioamnionitis, or prenatal ultrasonographic findings, such as oligohydramnios or structural lung abnormalities **[5].**

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However, the INSURE technique requires intubation of the trachea, positive pressure ventilation, and sedation, and several negative side effects have been associated with the technique. Attempts to achieve surfactant delivery while avoiding the need for intubation for even a brief period have been further studied using less invasive surfactant administration (LISA), also known as minimally invasive surfactant therapy (MIST) **[1].**

There are four different MIST methods, i.e., pharyngeal surfactant administration, aerosolized surfactant administration, laryngeal mask guided surfactant administration, and surfactant administration via a thin catheter**.**

Surfactant administration through tracheal catheterization was first described by **verder et al**.**[6]**, who used it as an alternative to the INSURE technique**. Kribs et al. [7]** performed and published the first feasibility study using the Cologne method, in which a 4 to 5FG feeding tube and Magill forceps are used to introduce a thin catheter past the vocal cords. This procedure is part of a complete intervention aimed at avoidance of tracheal intubation and positive pressure ventilation during the first 72 hours after birth **[8].**

This study conducted to assess the effectiveness of less invasive surfactant administration (LISA) via tracheal catheterization compared with intubation

METHODS

This study was a Prospective randomized interventional clinical trial Study, That was carried out at the NICU of the pediatric department, Faculty of Medicine, Zagazig University, It had been conducted on 68 preterm infants. It included the following 2 groups: **Group A**: preterm with RDS needing Surfactant Administration Via tracheal catheterization (LISA). **Group B**: preterm with RDS needing Surfactant Administration Via Tracheal Intubation **(INSURE**). Infants with major congenital anomalies, Infants who required mechanical ventilation or intubation in the delivery room were excluded from the study. The participants were chosen by systematic random sampling Serial numbers from 1-100 were randomized divided into two groups using a web-based randomization tool. All pre- terms were first stabilized in the delivery room and then shifted to the neonatal intensive care unit. RDS was diagnosed based on prematurity, tachypnea with respiratory rate >60/minute, subcostal or intercostal chest recession, grunting, nasal flaring, and cyanosis. Radiological findings of RDS were bilateral diffuse reticular granular (ground glass) appearance, air bronchograms and poor lung expansion **[9]**. Blood gases are estimated in all the cases before and after the procedure. Both groups were placed on n CPAP withFiO2 adjusted to maintain O2 saturations of 88-92%. They were given surfactant if they needed FiO2of >0.4during the first 12 hours of life. in the LISA group, a sterile orogastric tube is inserted through the vocal cords through the desired length from the vocal cords under direct visualization using standard direct laryngoscope After insertion, the laryngoscope is removed and the nasogastric tube is manually held in place. A pre-warmed surfactant (Survanta) at a dose of100 mg/kg (ml/kg) is then administered in 30–45 s and the orogastric tube is then at once withdrawn In the second group, i.e. the INSURE group, the infants were intubated and surfactant was administered successfully in 2-3 aliquots with an endotracheal tube with the same dose as in LISA group, while they received positive pressure ventilation. After a brief period of positive pressure ventilation for15-20 minutes, the endotracheal was removed and the infants were placed on n CPAP. The criteria for a subsequent dose of surfactant and mechanical ventilation were the same as in the LISA group. All the data variables were recorded for both groups.

Ethical consideration: Informed consent was obtained from written informed consent was taken from parents for participation in the study. The study was approved by the research ethics committee of the faculty of medicine, Zagazig University. The work has been carried out by the code of ethics of the world medical association (declaration of Helsinki) for studies involving humans.

Statistical Analysis: Descriptive statistics: Data were checked, entered, and analyzed

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using SPSS version 23 for data processing. The following statistical methods were used for the analysis of the results of the present study. Data were expressed as number and percentage for qualitative variables and mean ± standard deviation (SD) for quantitative ones.

Analytical statistics: Kruskal-Wallis test was used to assess the statistical significance of the difference of a non-parametric variable between more than two study groups.

RESULTS

There was no significant difference between LISA and INSURE groups regarding gender, age, gestational age, birth weight, APGAR score, and prenatal risk factors as presented in table(1).

There was a statistically significant difference between LISA and INSURE group regarding heart rate (higher in LISA than INSURE group) and respiratory rate (higher in INSURE than the LISA group) while there was no significant difference regarding blood pressure, SO2, and chest X-ray after as presented in table(2).

There was a statistically significant difference between before and after for the LISA group regarding PH, PCO2, and PO2. (PH, Po2 are higher and Pco2 is lower before than after the procedure) . Also, there was a statistically significant difference between before and after for INSURE group regarding PH and PO2 (PH, Po2 are higher before than after procedure) while there was no significant difference regarding PCO2 as presented in table(3)

There was a highly statistically significant difference between LISA and INSURE group regarding CPAP and need for mechanical ventilation (LISA group has higher CPAP hours than INSURE group, but INSURE has a higher need for MV than LISA group) while there was no significant difference regarding CPAP FiO2 and mechanical ventilation duration between the two groups as presented in table(4).

There was no statistically significant difference between LISA and INSURE group regarding the duration of O2 therapy, hospital stay, need for vasopressors, and death before discharge as presented in table (5)

There was a statistically significant difference between LISA and INSURE group regarding Ventilator-associated pneumonia, Pneumothorax, Symptomatic PDA, Pulmonary hemorrhage, and ROP screening INSURE has a higher possibility for this complication and association than LISA) while there was no statistically significant difference regarding NEC, IVH, BPD, early and late-onset sepsis as presented in table(6).

Table (1): Comparison between the studied groups (LISA & Insure) regarding the baseline characteristics and prenatal risk factors.

Baseline characteristics and prenatal risk factors	LISA	INSURE	P-value
	(n=34)	(n=34)	
Gender			
Female	16 (47.1%)	20 (58.8%)	0.331
Male	18 (52.9%)	14 (41.2%)	
Age (hours)			
Median (IQR)	5 (4 – 7)	6 (4.75 – 8.5)	0.159
Gestational age (weeks)			
Median (IQR)	32 (30 – 34.25)	32 (32 – 35.25)	0.073
Birth weight (gm)			
Median (IQR)	1500 (1300 – 1600)	1450 (1137.5 – 1762.5)	0.640

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Baseline characteristics and prenatal risk factors	LISA	INSURE	P-value
APGAR			
Median (IQR)	6 (5.75 – 7)	6 (5 – 7)	0.231
Prenatal risk factors			
CS	24 (70.6%)	28 (82.4%)	0.253
Antenatal steroids	8 (23.5%)	4 (11.8%)	0.203
PROM	22 (64.7%)	14 (41.2%)	0.052

• Mann Whitney U test.
‡ Chi-square test.
p< 0.05 is significant.
Sig.: significance.

Table (2): Comparison between the studied groups(LISA & Insure) regarding the vital signs, So2 during the procedure, Xray before and after.

Changes during the procedure and follow up	LISA	INSURE	P-value
	(n=34)	(n=34)	
HR (beat/min)			
Median (IQR)	115 (104 – 120)	108 (95 – 116)	0.016 *
RR (breath/min)			
Median (IQR)	68.5 (62 – 74.5)	78.5 (69 – 81.5)	<0.001**
BP (mmHg)			
Median (IQR)	52.5 (46.75 – 55)	50.5 (45 – 56)	0.363
SO_2 (%)			
Median (IQR)	89 (86.4 – 91)	89 (86.3 – 91)	0.882
Chest X-ray before			
White lung	34 (100%)	34 (100%)	-
Normal	0 (0%)	0 (0%)	
Chest X-ray after			
Aerated	24 (70.6%)	28 (82.4%)	0.253
Improved	10 (29.4%)	6 (17.6%)	

• Mann Whitney U test.
‡ Chi-square test.
p< 0.05 is significant.
Sig.: significance.

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Table (3): Comparison between the studied groups(LISA & Insure) regarding ABG parameters before and after.

ABG	LISA	INSURE	P-value
	(n=34)	(n=34)	(Sig.)
PH			
Before (Mean ± SD)	7.25 ± 0.07	7.28 ± 0.06	0.083
After (Mean ± SD)	7.30 ± 0.07	7.32 ± 0.05	0.203
Test	-4.276 ₱	-6.829 ₱	
P-value (Sig.)	<0.001 (HS)	<0.001 **	
PCO_2 (mmHg)			
Before (Mean ± SD)	48.6 ± 9.9	51.8 ± 11.2	0.227
After (Mean ± SD)	38.9 ± 9.2	49.6 ± 7.9	<0.001 **
Test	8.517 ₱	1.005 ₱	
P-value (Sig.)	<0.001 (HS)	0.332	
PO_2 (mmHg)			
Before (Mean ± SD)	59.3 ± 13.5	56.1 ± 12.3	0.306
After (Mean ± SD)	86.5 ± 25.5	69.1 ± 12.3	0.001 *
Test	-7.370 ₱	-4.376 ₱	
P-value (Sig.)	<0.001 (HS)	<0.001 **	

Table (4): Comparison between the studied groups(LISA & Insure) regarding the CPAP and MV data.

CPAP and MV data	LISA	INSURE	P-value
	(n=34)	(n=34)	(Sig.)
CPAP (hours)			
Median (IQR)	192 (138 – 252)	96 (48 – 168)	<0.001 **
CPAP FiO_2 [Median (IQR)]			
At 0 hours	87 (82.75 – 88.5)	88 (82 – 90)	0.412
At 6 hours	90 (87.5 – 90.5)	89 (88 – 90.25)	0.822
At 12 hours	92 (90 – 92.25)	90 (87.5 – 93)	0.136
At 24 hours	92 (90 – 92.25)	92 (88 – 93)	0.409
MV data			
Need for MV	16 (47.1%)	30 (88.2%)	<0.001 **
MV duration (days) [Median (IQR)]	5 (3.5 – 6.75)	5 (4 – 7)	0.886

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Table (5): Comparison between the studied groups(LISA & Insure) regarding the follow-up and outcome.

Outcome	LISA	INSURE	P-value
	(n=34)	(n=34)	(Sig.)
Duration of O_2 therapy (hours)			
Median (IQR)	336 (240 – 390)	264 (210 – 406.75)	0.313
Hospital stays (days)			
Median (IQR)	16 (11.75 – 19.25)	14 (9.75 – 19.25)	0.376
Need for vasopressors			
			0.622
Yes	13 (38.2%)	15 (44.1%)	
Death before discharge			
			0.567
Yes	7 (20.6%)	9 (26.5%)	

Table (6): Comparison between the studied groups(LISA & Insure) regarding the possible complications and associations.

The possible complications and associations	LISA	INSURE	P-value
	(n=34)	(n=34)	(Sig.)
Outcome			
VAP	8 (23.5%)	24 (70.6%)	<0.001 **
NEC	14 (41.2%)	8 (23.5%)	0.12
IVH	9 (26.5%)	8 (23.5%)	0.779
Pneumothorax	8 (23.5%)	18 (52.9%)	0.013 *
Symptomatic PDA	8 (23.5%)	20 (58.8%)	0.003 *
Pulmonary hemorrhage	12 (35.3%)	24 (70.6%)	0.004 *
BPD	4 (11.8%)	6 (17.6%)	0.493
Early-onset sepsis	24 (70.6%)	22 (64.7%)	0.604
Late-onset sepsis	28 (82.4%)	28 (82.4%)	1
ROP screening	18 (52.9%)	34 (100%)	<0.001 **

DISCUSSION

Neonatal respiratory distress syndrome due to surfactant deficiency is associated with high morbidity and mortality in preterm infants, and the use of less invasive surfactant administration (LISA) has been increasingly studied **[10].**

The aim of the present study is to assess the effectiveness and safety of Less invasive surfactant administration (LISA) via tracheal catheterization compared with intubation.

This study shows that there was no significant difference between groups regarding gender, age, gestational age, birth weight, APGAR score, and prenatal risk factors, We found that the Median (IQR) ages of the LISA group and Insure Group were 32 (30 – 34.25) weeks (GA) and 32 (32-35.25) weeks (GA), respectively. There was no significant difference between groups regarding age. Also, there was no significant difference between groups regarding birth weight. The Median (IQR (weight of the LISA group and Insure Group were 1500 (1300 – 1600) grams and 1450 (1137.5 – 1762.5) grams.

There were no significant differences between the two groups in terms of birth weight, gender, mode of childbirth, gestational age, Silverman respiratory distress score before treatment, and receiving steroids before childbirth (P>0.05).

This coped with the study of **Halim et al [9]** who reported that Median birth weight was 1300 grams(IQR 600) in LISA, while 1400 grams (IQR 400) in INSURE infants with no

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significant difference between groups regarding age

Also coped with the study of **Kazemian et al** [11] there was no significant difference between groups regarding APGAR. The Median (IQR) APGAR of the LISA group and InSure Group were (6 (5.75 – 7) and 6 (5 – 7).

This observation was found to be in agreement with that reported by **Bao et al** [12] who reported that During the whole procedure of PS administration, there was less fluctuation of FiO2 and oxygen saturation in an infant receiving LISA. The final effects of providing PS using the two methods were similar. However, cases of surfactant reflux were more frequent in the LISA group (17 out of 47 vs. 5 out of 43, p=0.01).

On another hand, **Aguiar et al** [13] reported that while there was no significant difference regarding FiO2 before surfactant administration before the procedure.

In contrast to the above findings, **Ramos and colleagues** [14] showed a non-significant difference between the LISA and standard groups, 73.3% vs. 86.6%.

The present study showed that there was a highly statistically significant difference between LISA and INSURE groups regarding CPAP and the need for mechanical ventilation while there was no significant difference regarding CPAP FiO_2 and mechanical ventilation duration.

This coped with the study of **Halim et al** [9] who reported that the duration of mechanical ventilation was also significantly higher in INSURE group with a median of 71(IQR 62) vs. 40 (IQR 75) hours, p <0.05 as compared with LISA group. Duration of respiratory support (CPAP)was noted significantly (p <0.05) greater in the LISA group , having a median of 48 hours (IQR 42) as compared with INSURE group median of 29.5 hours (IQR 43)

Regarding Comparison between the studied groups regarding the possible complications and associations. there was a statistically significant difference between LISA and INSURE group regarding VAP, Pneumothorax, Symptomatic PDA, Pulmonary hemorrhage, and ROP screening while there was no statistically significant difference regarding NEC, IVH, BPD, early and late-onset sepsis.

Also, there was no statistically significant difference between LISA and INSURE group regarding the overall survival rates along the hospital follow up duration using Kaplan Meier Survival Curve

This coped with the study of **Halim et al** [9] who reported that an improved survival ratio of babies was found in the LISA group (62% discharged, 38% died) as compared to INSURE group (44% discharged, 56% died), without statistical significance. A recent meta-analysis did not show any significant difference in mortality or risk of complication between LISA or INSURE (RR=1.13; 95%CI=0.603, p=.691).

Halim et al [9] also reported that no significant difference was observed in both groups based on complication rate (pneumothorax, PDA, pulmonary hemorrhage). In INSURE group 5 patients (10%) developed pneumothorax compared to 2 (4%) in LISA group (p=0.625).

This finding was also seen in previous studies. According to a meta-analysis of less invasive surfactant administration at St. Barnabas Medical Center, NJ, USA, few patients in the LISA group developed pneumothorax as compared to INSURE group, 17.6% reduction but was not significant **[10].**

Kribs et al[15] had also observed less risk of pneumothorax and severe IVH in the LISA group, survival without BPD was67.3% vs. 58.7% (p=0.20).13With the use of the LISA technique, the outcome of the premature infants with RDS can be improved, reducing the cost of hospital stay and complications of mechanical ventilation by avoiding intubation.

A study conducted by **Naseh et al** [16] showed that post-injection use of INSURE can significantly reduce the mortality rate in preterm infants with respiratory distress. In their study, **Verder et al** [6] argued that using INSURE instead of a mechanical ventilator on the first day of life reduces the risk of pulmonary dysplasia.

LIMITATION

• There were some limitations in the study as a small sample size that to be increased to emphasize our conclusion.

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• The side effects commonly associated with the technique, such as bradycardia, apnea, or desaturation, were not systematically collected.

CONCLUSION

LISA technique for surfactant delivery results in a lesser need for mechanical ventilation and lesser complications in preterm infants with RDS. This method can be a promising and effective step, which is feasible, cost-effective to be standardized.

RECOMMENDATIONS

For widespread use of the LISA technique as it is more effective and has fewer complications than INSURE technique.

Further studies and research for implementation of this technique on a wider number of preterm infants with RDS.

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