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The Impact of Surfactant Administration Techniques (LISA vs INSURE) on the Outcomes of Respiratory Distress Syndrome in premature babies.

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ABSTRACT… Objective: We aimed this study to find out the Impact of Surfactant Administration Techniques (LISA vs INSURE) on the Outcomes of RDS in premature newborns. **Study Design:** Retrospective study. **Setting:** Children's Hospital and The institute of Child Health Multan. **Period:** October 2018 to March 2020. **Material & Methods:** 159 premature babies reported with RDS at Institute of child health, Multan were evaluated. Out of these 87 infants were given surfactant through LISA technique and 72 were given through INSURE. The surfactant used for all these babies was proractant alpha. **Results:** The duration of oxygen (O_2) therapy was significantly less in LISA group (14.87 ± 11.21 days) as compare to INSURE (19.67 ± 9.79 days), $p < 0.001$. Number of patients who require mechanical ventilation was (23% vs 44%, $p < 0.05$) and median days of nCPAP was (10.74 ± 3.07 vs 15.12 ± 8.79, $p < 0.05$). Our analysis shows that no significant difference in mortality, incidence of air leak and bronchopulmonary dysplasia (BPD) between the two groups. **Conclusion:** Patients administered surfactant through LISA technique requires significantly less duration of oxygen therapy and need of mechanical ventilation as well as duration of nCPAP. We conclude that LISA technique is preferable method for surfactant administration in premature infants.

Key words: Bronchopulmonary Dysplasia, Mortality, Necrotizing Enterocolitis, Oxygen Therapy.

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INTRODUCTION

In Pakistan, mortality under the age of 5 years is estimated to be 69.3 per 1000 live births for the year 2019 while premature birth is the leading contributing factor contributing to neonatal mortality.[1] Respiratory distress syndrome (RDS) due to deficiency of pulmonary surfactant is the commonest cause of morbidity and mortality in premature infants worldwide. American academy of pediatrics (AAP); strongly endorses that premature infants born prior to 30 weeks of gestation needing mechanical ventilation (MV) because of RDS must be provided surfactant after initial stabilization.[2] Conventional methods of surfactant administration involved endotracheal intubation and MV for a short period, this method is known as "Intubation-surfactant administration extubation (INSURE)" and linked with higher chances of barotrauma and volutrauma.[1,2] To prevent mechanical lung damage alternative techniques to administer surfactant was developed which includes "nasal continuous positive airway pressure (nCPAP)".[2,3]

A new method which combines the advantages of nCPAP and surfactant administration was developed in 2007 by Kribs et al, referring it as a "less invasive surfactant administration (LISA)" technique.[4] LISA is the favored way of surfactant administration for spontaneous breathing babies on nCPAP if neonatologists are used to this technique. The latest clinical evidences showed LISA technique to reduce the adverse effects of routinely used ways of surfactant administration and it is safe and effective.[5,6] LISA can reduce chances of mortality among premature infants and might result in improvement of lung outcomes, reducing the incidence of bronchopulmonary dysplasia (BPD) and MV along with shortening the duration of oxygen supplementation while

minimizing risks of death.[7-10] LISA is also known as "minimally invasive surfactant therapy (MIST)" when surfactant is given by thin catheter which is stiff enough to be placed in trachea. In our settings we started using LISA technique of surfactant administration since last year and our objective was to evaluate the impact of surfactant administration techniques LISA vs INSURE in terms of safety and efficacy.

MATERIAL & METHODS

It was a retrospective study in which 159 premature infants admitted over a period of 18 months from October 2018 to March 2020 at The Children's Hospital and The institute of Child Health, Multan were evaluated for treatment outcomes of RDS. Approval from ethical research committee was taken and data of all the patients were used after the informed consent from parents or guardians. All the infants were given surfactant proractant alpha. All the premature babies with gestational age < 34 weeks were included. Diagnosis of RDS was made on the basis of clinical examination and was confirmed by chest X-ray evaluated by pediatric radiologist. Babies with respiratory functions effected by congenital developmental abnormalities, congenital lung malformation, congenital heart disease and family members of infant who did not give consent to use the data were excluded from study.

LISA was done under direct laryngoscopy, a vascular catheter of size 6F was inserted below the vocal cords. Once the correct position of catheter was confirmed surfactant was administrated slowly by keeping saturation >90%. After administration, catheter was immediately removed and nCPAP was started. Cases in ISNURE group were treated with tracheal intubation, artificial positive pressure ventilation and extubation on nCPAP.

Prophylactic or preventive surfactant therapy is given within 15-30 mints after birth to prevent development of RDS. Rescue surfactant therapy within 4-6 hours of birth with established RDS (EARLY RESCUE within in 1-2 hours, late rescue within in 4-6 hours).

INSURE (Intubate-surfactant-extubate to n-CPAP). After giving surfactant through ETT MV is done followed by weaning and Extubation to n-CPAP within 1-2 hours when spontaneous breathing has resumed. Surfactant is administered through Cather that is stiff enough to be positioned in the trachea under direct laryngoscopy. In LISA, thin catheter are used so chances of lung damages are less.[11]

We noted duration of oxygen therapy (Days), duration of nCPAP (Days) and number of patients who require MV (n). In addition to the above following complications were recorded to evaluate the safety of both the techniques, bronchopulmonary dysplasia, intraventricular hemorrhage, pulmonary Hemorrhage, air leak (Pneumothorax), necrotizing enterocolitis and mortality rate.

SPSS version 26.0 was used for data analysis. Comparison of the general data like distribution of gender and indicators of safety of both treatment groups were compared using Chi square test. Qualitative variables like age, gestational age, birth weight, duration of oxygen therapy, duration of nCPAP and MV were compared using independent sample t-test between both study groups. P value<0.05 was considered as statistically significant.

RESULTS

A total of 159 premature infants were evaluated out of which 87 (55%) were given surfactant through LISA technique and 72 (45%) were given through INSURE technique.

There was no difference between the general data among both study groups (Table-I)

No significant difference in age of first surfactant use which is defined as time of surfactant use from birth 17.02 ± 2.6 vs 16.34 ± 2.12, p=0.0767 was observed between the two groups. The duration of oxygen therapy and nCPAP use was significantly less in premature infants who were administered surfactant through INSURE technique 14.87 ± 11.21 as compare to those who were given surfactant through INSURE technique 19.67 ± 9.79, p<0.05 and for nCPAP (10.74 ±

3.07 vs 15.12 ± 8.79), p<0.05. In addition to this 20 (23%) infants require MV in the LISA group as compare to 32 (44%) in the INSURE group, which is again statistically significant, p<0.05. (Table-II)

No statistically significant differences were observed in terms of adverse events between the two group during the whole course of administration, the incidence of bronchopulmonary dysplasia and air leak was less in the LISA group as compare to INSURE group (13.7% vs 25.0%) and (5.0% and 9.7%) but it was statistically insignificant. The mortality rate was more in INSURE group as compare to LISA (15.0% vs 10.0%). (Table-III)

	LISA (n=87)	INSURE (n=72)	P-Value
Gestational age in weeks (Mean+SD)	31.46 ± 1.75	30.96 ± 1.54	0.0603
Birth Weight in kilograms (Mean+SD)	1.6 ± 0.65	1.5 ± 0.45	0.6593
Male n (%)	48 (55%)	43 (60%)	0.5638

Table-I. General data in between both study groups.

	LISA (n=87)	INSURE (n=72)	P-Value
Age of first surfactant therapy (Hours)	17.02 ± 2.6	16.34 ± 2.12	0.0767
Duration of Oxygen (O2) therapy (Days)	14.87 ± 11.21	19.67 ± 9.79	<0.0001
Duration of nCPAP (Days)	10.74 ± 3.07	15.12 ± 8.79	<0.0001
Mechanical Ventilation (n)	20 (23%)	32 (44%)	<0.0001

Table-II. Indicators for efficacy among both study groups.

	LISA (n=87)	INSURE (n=72)	P-Value
BPD n (%)	12 (13.7%)	18 (25.0%)	0.0722
Intraventricular Hemorrhage n (%)	11 (12.6%)	9 (12.0%)	0.9783
Pulmonary Hemorrhage n (%)	10 (11.0%)	13 (18.0%)	0.2417
Air Leak n (%)	4 (5.0%)	7 (9.7%)	0.2050
Treatment of PDA n (%)	16 (18.0%)	21 (15.0%)	0.1095
Necrotizing Enterocolitis n (%)	10 (11.0%)	12 (17.0%)	0.3471
Sepsis (+ve Culture) n (%)	35 (41.0%)	33 (46.0%)	0.4771
Mortality n (%)	9 (10.0%)	11 (15.0%)	0.3504

Table-III. Indicators for Safety Among both study groups.

DISCUSSION

Neonatal morbidity and mortality due to RDS has greatly been reduced by using steroids in antenatal period and surfactant in immediate post-natal period. In the recent past with some advancements in in non-invasive methods. Now MV is only indicated for patients who did not respond to the maneuvers. MV in INSURE technique is very short term and did not induce adverse effects associated with intubation.[13-15]

There is an increase in number of infants using nCPAP right after birth while conventional methods of surfactant administration i.e. tracheal intubation are questioned a lot. The objective of introducing the LISA technique is to minimize the use of nCPAP and to avoid failure of mechanical ventilation.[16] LISA technique improves the lungs compliance by ensuring the uniform distribution of pulmonary surfactant.[17] The first study using surfactant administration through thin endotracheal catheter was conducted by Kribs et al, on 42 infants and he reported mortality rate of 12% in comparison to past figures of 35% and established LISA as a feasible technique of surfactant administration.[4]

Researchers have found LISA to have comparative effectiveness when compared to INSURE. Aguar et al, analyzing 44 preterm newborns having

RDS using surfactant through gastric tube place in the trachea and noted no real differences with regards to requirement of MV (25% vs. 33%, p-value>0.05), span of MV (115 vs. 150 hours, p-value>0.05), oxygen supplementation (102 vs. 117 hours, p-value>0.05), BPD (4.5% vs. 6.5%, p-value>0.05), NICU stay (20 vs. 22 days, p-value>0.05), or mortality (4.5% vs. 3.2%, p-value>0.05), when compared with past trends of INSURE technique.[18]

On the other hand, Krajewshki et al evaluating 26 preterm newborns having RDS using surfactant through catheter and found significant decline in terms of requirement of MV (19.2% vs. 65%, p-value<0.05) and BPD (15.4% vs 40%, p-value<0.05) when compared to historical patterns of INSURE technique.[19]

The present retrospective analysis at our institution showed that LISA technique is associated with significant minimization in duration of oxygen therapy and nCPAP as well as need of MV was significantly less in this new method of surfactant administration as compare to INSURE technique. A trend towards reduction of BPD was observed in the LISA group but it failed to reach a statistical significance. The mortality rate in the LISA group was also less and it is safe to adopt having no significant differences in terms of complications when comparing to INSURE technique.

CONCLUSION

We conclude that LISA via thin catheter is an effective technique in premature infants, it significantly reduces the duration of mechanical ventilation, duration of nCPAP oxygen supplementation. There is no apparent adverse effects associated with it which may prevent its use for surfactant administration in premature infants.

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