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"Comparison of NCPAP and INSURE Strategy in Management of Preterm VLBW Neonates with RDS in A Tertiary Care Setting".

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Abstract:
Background: *Respiratory distress syndrome (RDS) is a frequent cause of concern in neonates, more so if the baby is born premature. Evidence suggests that INSURE strategy (INtubate-SURfactant administration and Extubate to nasal continuous positive airway pressure or NCPAP) is superior to mechanical ventilation (MV) with rescue surfactant for the management of RDS in very low birth weight (VLBW) neonates. There is limited evidence, however, to assess whether INSURE is superior to NCPAP alone. We aimed to compare these two strategies regarding early and late outcomes.*
Methodology: *We randomized 40 preterm VLBW neonates of 28-32 weeks gestation with RDS into NCPAP (n=20) & INSURE group (n=20) Primary outcome was the need for intubation and mechanical ventilation; secondary outcomes were mortality & other complications.*
Results: *The mean age at admission in our NICU was 3.96 hours in NCPAP group and 4.1 hours in INSURE group. The mean age at surfactant therapy in INSURE group was 4.4 hours. There was no significant difference in the requirement of mechanical ventilator as well as mortality or other complications between the two groups.*
Conclusion: *Not all preterm VLBW neonates with RDS require exogenous surfactant. After the first few hours of life, routine use of exogenous surfactant in babies already on NCPAP support provides no additional benefit.*
Abbreviations: *BPD: Brocho pulmonary dysplasia; NCPAP: Nasal continuous positive airway pressure, INSURE: Intubation-surfactant therapy followed by extubation; EONS: Early onset neonatal sepsis; GA: Gestational age; MV: Mechanical ventilation; PT: Preterm; PMA: Post menstrual age; RDS: respiratory distress syndrome; VLBW: Very low birth weight;*

Keywords: *Bronchopulmonary dysplasia, respiratory distress syndrome, nasal continuous positive airway pressure, INSURE therapy, Surfactant, Mechanical ventilator, Neonatal intensive care unit*

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I. Introduction

RDS is a very common cause of neonatal mortality and morbidity due to structural immaturity[1] of the lungs leading to surfactant insufficiency, especially in premature babies. The incidence of this important condition inversely correlates to the gestational age at birth, from about 50% in babies born at 26-28 weeks, to about 25% at 30-31 weeks[2]. Because of their immature respiratory system, most premature neonates with RDS require some form of respiratory support. Introduction of newer modes of mechanical ventilation has failed to demonstrate any significant decrease in the rate of bronchopulmonary dysplasia (BPD) and mechanical ventilation is still considered as perhaps the most important risk factor for the development of BPD[3]. The American Academy of Pediatrics recommends that: (1) preterm VLBW infants in need of mechanical ventilation due to severe RDS should be given surfactant after initial stabilization; and (2) that continuous positive airway pressure (CPAP) immediately after birth with selective surfactant administration be used as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants[4]. The widely accepted INSURE technique, which consists of INtubation-SURfactant-Extubation sequence followed by NCPAP therapy, has been reported to result in a decreased need for mechanical ventilation, duration of respiratory support and the need for rescue surfactant therapy in preterm infants with RDS[5]. However, many studies on the INSURE strategy have shown no additional benefit compared to NCPAP alone and the benefits claimed were inconsistant.[6] Interestingly, some researchers have reported that approximately 10% of those babies who were intubated solely for surfactant administration could not be extubated in next 1 hour[7]. In addition, intubation of the trachea with an endotracheal tube is an invasive procedure and is not without its own

risks. Most of the trials comparing the effects of INSURE with early NCPAP have been conducted in well-equipped NICUs in western world where the treatment (NCPAP/surfactant) was started very early. Whereas, in our country, facilities for CPAP or surfactant administration are scarce, thereby forcing transportation of the patient to an equipped NICU, leading to a delay of several hours in treatment. Though surfactant therapy is costly, it is also true that in most of the resource limited settings a mechanical ventilator is not always available should an infant on NCPAP subsequently require ventilator support. So, through this study we tried to find out whether addition of surfactant to standalone NCPAP therapy actually decreased the need of mechanical ventilator, which is mostly already occupied, & additional risks, if any, are associated with this strategy.

Aiims and objectives:

Aiim: TO compare NCPAP alone and INSURE strategy in preventing morbidity and mortality in preterm VLBW babies with RDS.

Primary objective: Failure of NCPAP support requiring mechanical ventilation.

Secondary objective: to compare the incidences of sepsis, air leak, BPD & mortality.

II. Material And Methods

Study design: Randomized control trial.

Study setting: NICU of N.M.C.H Patna.

Study period: 1 year (April 2018 to March 2019).

Inclusion criteria: Spontaneously breathing outborn neonates with-

1) Gestational age 28- 32 weeks, and
2) Birth weight 1- 1.5 kg, and
3) Age less than 12 hours, and
4) RDS with DOWNE'S score 4-7

Exclusion criteria:

1. Gasping or no spontaneous breathing at birth OR
2. Major Congenital anomalies OR
3. DOWNE'S score ≥8

Sample size consideration: Based on a previous study of Verder et al[8] showing benefit of surfactant therapy in significantly reducing the need for mechanical ventilator, we estimated that with an α value of 0.05 and a β value of 90%, sample size of 28 infants was necessary.

Gestational age (GA) was estimated from mother's 1st trimester USG report; if that was'nt available, then GA was estimated from new Ballard scoring[9]. After obtaining written informed consent, we enrolled 40 neonates in this study. Participants were randomized into two groups using computer-generated random numbers and allocation was concealed by using sealed, consecutively numbered opaque envelopes. Group 1 (NCPAP group) as well as Group 2 (INSURE group) were immediately started on NCPAP support using short binasal prongs with starting PEEP of 5 cm H_2O and 40% FiO_2. INSURE group additionally underwent short period of intubation for surfactant therapy @5ml/kg of Neosurf (Cipla Ltd) followed by extubation and again NCPAP support as in group 1. Settings were optimized to maintain SpO_2 in the range of 88-92%.

EONS was defined as growth of a pathogen in blood culture, sample been sent after 12 hours of admission & repeated if sepsis was suspected. Chest X-ray was done at the time of admission and repeated if needed to rule out pneumothorax, pneumonia etc. Other supportive measures as required were given. Post discharge they were followed up till 36 weeks PMA. BPD was defined as requirement of supplemental O_2 at 36 weeks PMA.

Indication of mechanical ventilation support:

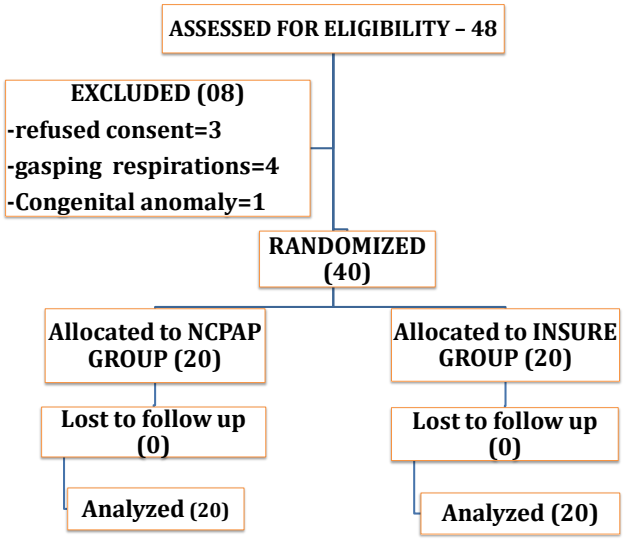
A neonate of either group with one or more of following was labeled as treatment failure and started on mechanical ventilation support:

(1)Apneic spell requiring BMV resuscitation or more than 2 episodes of significant apnea in one hour despite the baby being on NCPAP (2) pH < 7.20, PCO2 > 60, and PaO2 < 50 on arterial blood gas, with a maximum FiO2 of 0.7 & PEEP of 7 cmH2O (3)worsening respiratory distress with Downe's score 8 or more. They were furthered managed as per standard protocol.

Table 1: Downe's Score

Parameter	Score 0	Score 1	Score 2
Respiratory rate	<60/min	60-80/min	>80/min
Grunting	Absent	Heard only with Stethoscope	Heard with unaided ear
Air Entry	Bilateral Good	Mild Decrease	Greatly diminished
Retractions	None	Mild	Moderate/ Severe
Cyanosis	Absent	In room air	In 40% FiO2

Table 2: The consort diagram



Data Analysis:

Pertaining data was entered in Microsoft excel sheet and analyzed using SPSS Software version 18. Chi-square test for discrete variables and Student t–test for continuous variables was used. Confidence limit was set at 95% and a P value <5% was considered significant.

III. Results

Mean gestational age was 29.7± 1.2 weeks in NCPAP group and 29.5± 1.3 weeks in INSURE group. Mean birth weight was 1314 ± 129 gram in group 1 and 1288 ± 118 gram in group 2. The mean Downe's score was 5.6 ± 0.92 in NCPAP group and 5.5 ± 0.86 in INSURE group. There was no statistically significant difference in gestational age, birth weight or Downe's score between the two groups with respective p values of 0.6161, 0.5100 & 0.7245. So, the baseline characteristics were comparable between the two groups. The mean age at admission was 3.96 ± 2.1 hours in NCPAP Group and 4.1 ± 2.3 hours in the INSURE group with no statistically significant (P = 0.8417). NCPAP support was started within 5 minutes of admission in all such babies. In the INSURE group, surfactant was administered at mean age of 4.4 ±2. 2 hours.

Table 3: Comparison of secondary outcomes between the two groups

Study parameter	**NCPAP group**	**INSURE group**	**Chi sq value**	**P value**
ventilator support	35% (7/20)	20% (4/20)	1.100	0.2942
EONS incidence	20% (4/ 20)	30% (6/20)	0.520	0.4708
Air leak syndrome	10% 2 /20)	5% (1/20)	0.351	0.5533
BPD incidence	15% (3/20)	10% (2/20)	0.223	0.6369
Moratlity	10% (2/20)	15% (3/20)	0.223	0.6369

From table 3, it is clear that there was no statistically significant difference between the groups in terms of requirement of mechanical ventilation, EONS, air leaks, BPD & mortality.

IV. Discussion

In the present study involving preterm VLBW babies of 28-32 weeks with RDS, application of the INSURE method as compared to NCPAP alone, resulted in no significant advantage for reducing the further need of intubation and mechanical ventilation or even rate of death, BPD, EONS or air leaks. However it should be noted that in our study, INSURE technique could be employed only after the first few hours of life (after a mean period of 4.4 hours).

CPAP is recognized as an effective and noninvasive method in the treatment of RDS[10]. The use of early CPAP prevents the progression of RDS, and it decreases the need of exogenous surfactant as a routine practice[11]. It is also true that some, but not all premature neonates with RDS on NCPAP do require intubation and surfactant administration[12] when the optimal time for early surfactant has already passed. The INSURE method has the advantage of early administration of surfactant in infants on NCPAP; however, the dangers of intubation as well as the burden of cost are important considerations in making decisions about surfactant administration[13].

When comparing our results with other randomized trials on this subject, in agreement with our study, most studies have also reported that the rates of CLD and mortality were not different when comparing NCPAP to intubation and surfactant administration. In a recent large study on the comparison between three groups of prophylactic surfactant, INSURE, and CPAP alone, no difference was found in the rate of death or CLD between groups.[14] The SUPPORT study on infants with 24–27 weeks of gestation showed that the rate of mortality or CLD did not differ between the CPAP and early surfactant groups[15]. In the study of the Colombian Neonatal Research Network on the comparison of NCPAP with INSURE in infants with a gestational age of 27–31 weeks[16], in their lower gestational age stratum (27–29 weeks), the rate of CLD or mechanical ventilation was not different between the two groups. Escobedo et al[17] showed that routine elective surfactant administration is not recommended for mild-to-moderate RDS.

However, we also came across studies showing that INSURE is superior to NCPAP in reducing the need for intubation and mechanical ventilation, without any significant difference in the rate of CLD. In one study, Rojas et al[16] showed that early administration of surfactant in premature infants with RDS who were on NCPAP decreased the need for mechanical ventilation, the incidence of pneumothorax, and also the need for subsequent rescue surfactant doses. In their study, the INSURE method was performed in the 1st hour of life, but in our study it was delayed by few hours (mean age of administration 4.4 hours); this delay explains the differences between the beneficial effects of INSURE. However, similar to our results, they also didn't find any significant difference in the rates of mortality and CLD between the two groups. Review of available literature demonstrated the superior effect of INSURE in comparison with NCPAP alone in decreasing the need for mechanical ventilation and improving oxygenation in some other studies too.[18,19,20] However, in these studies too the mortality and CLD rates were not significantly altered by the INSURE method, similar to our results. Most of such studies were conducted 15-20 years ago with a lower rate of antenatal steroid coverage than in present scenario, which might explain why neonates on NCPAP alone didn't have poorer outcomes in our study. Although in almost all these studies, INSURE was more successful in reducing the rate of need for mechanical ventilation, it is also equally true that a significant portion of patients on NCPAP did well even without exogenous surfactant. In our study, 65% of infants of the NCPAP group did well without surfactant treatment. In the study of Dunn et al,[14] 48% of neonates on NCPAP did not need to be intubated, and 54% could be managed well without the administration of exogenous surfactant. Similarly, in the study of Escobedo et al[17] only 29 out of 67 infants in the NCPAP group needed intubation. In addition, in the study of Rojas et al[16] only 26% of infants in the NCPAP group needed surfactant administration. Our findings are also in agreement with the study of Nakhshab M et al[21] who advocated against the use of surfactant routinely for every infant with RDS symptoms who is doing well on NCPAP, especially in developing countries. Therefore these findings reasonably reiterate our observation that, more than half of the patients on NCPAP will not require intubation and surfactant treatment. The increasing practice of using antenatal steroids when a preterm delivery is anticipated can also lead to the decreased need for exogenous surfactant administration in cases of mild and moderate RDS[22]. Another concern is the availability of treatment facilities. The majority of all deaths in children <5 years of age occur in developing countries, one-third of which are neonatal deaths.[23] In many centers of the developing world, the facility of CPAP application or surfactant administration early after birth is not available, and the neonates have to be transported to a higher center. In the majority of cases, the transport process is long and imposes delays, so NCPAP and INSURE procedures are started late. Consequently, surfactant administration is delayed, rendering it less effective.[24] In addition, cost of surfactant is an important issue in under-resourced areas, which should be considered[25,26].

V. Conclusions

Although INSURE method is effective for RDS in some infants, the decision to use surfactant routinely for every infant with RDS symptoms who is doing well on NCPAP seems to be unjustified, especially in developing countries where there is delay in reaching NICU.

More studies are needed to characterize which patients would benefit the most from INSURE method and to determine the severity of RDS at which to intervene with which therapy, so as to avoid exposing patients to unnecessary intubation as well as unjustified costly surfactant administration.

Conflicts of interest:
We have no conflicts of interest to declare.

Limations:
- Small sample size
- Lack of proper blinding

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