Original Article
Surfactant Therapy in Preterm Infants with Respiratory Distress Syndrome in Two Treatment Modalities. (A Single-Center Experience)
Madiha S. Abdallah *1; Al shaima G. Hasan2
DOI: 10.21608/ANJ.2021.111306.1042
*Correspondence: Lecturer, Pediatric Department, Faculty of Medicine, Minia University, Egypt
Email: madi-ali@aun.edu.eg
Full list of author information is available at the end of the article.

Abstract

Background: Surfactant therapy represents the cornerstone in treating respiratory distress syndrome (RDS). Different methods have been implicated for surfactant administration in the last few years.

Objective: This study aimed to compare the use of surfactant therapy in the intubate, surfactant, extubate (INSURE) technique with surfactant- conventional mechanical ventilation (CMV) modality.

Patients and methods: A retrospective comparative study conducted between January 2015 and January 2021 at Minia university hospital for obstetrics and children included 68 preterm infants with respiratory distress syndrome treated with surfactants. They are categorized into two groups: group I included 34 preterm neonates treated by INSURE technique then continuous positive airway pressure (CPAP) and group II: included 34 preterm neonates treated by (surfactant- CMV) using mechanical ventilation. Preterm infants’ demographic data, arterial blood gases, oxygen indices, response to treatment, duration of ventilation, hospital stay, and the number of surfactant doses were analyzed and compared. Results: Treatment was successful in 85.29% of INSURE-CPAP compared to 79.42% in the surfactant-CMV group. Respiratory indices such as arterial/alveolar oxygen ratio(a/APO2) were significantly low and alveolar /arterial gradient (AaDo2) was significantly high in surfactant- CMV group, Down’s score, the number of surfactant doses, duration of ventilation, and hospital stay all were significantly reduced in INSURE-CPAP group. Conclusions: INSURE- CPAP technique is a reliable and effective method for the treatment of RDS, especially in cases with high arterial alveolar ratio (a/APO2) and low arterial oxygen gradient (AaDO2).

Key words: INSURE Technique, mechanical ventilation, surfactant therapy, preterm.
**Introduction**

In preterm infants, respiratory distress syndrome develops due to impaired surfactant synthesis and secretion, leading to atelectasis, ventilation-perfusion (V/Q) inequality, and hypoventilation with resultant hypoxemia and hypercarbia. Blood gases show respiratory and metabolic acidosis, resulting in pulmonary vasoconstriction, which leads to impaired endothelial integrity, leakage of proteinaceous exudate, and development of respiratory distress syndrome [1]. Neonatal respiratory failure is a serious complication associated with high morbidity and cost. For the best management of RDS, coordination between different teams, including neonatologists, nurses, respiratory therapists, nutritionists, and pharmacists is required [2].

Selecting the optimal mode of respiratory support remains a daily challenge for the practicing neonatologist; there is increasing enthusiasm for non-invasive respiratory support of preterm infants [3]. The sequential application of the least invasive treatment to achieve the relevant therapeutic goals with the re-evaluation of the neonate's condition for possible escalation of requirements and support as needed, coupled with the application of lung-protective strategies of respiratory support, appears to offer the best chance of minimizing adverse pulmonary and neurodevelopmental outcome [4,5].

INSURE describes a surfactant administration after endotracheal intubation, followed by brief ventilation, timely extubation (within 60 min), and reinstitution of non-invasive ventilation (NIV) [6]. The purpose of this study was to compare outcomes between INSURE method (intubate, surfactant administration, and extubation to CPAP and use of surfactant followed by continued mechanical ventilation.

**Methods**

This retrospective study was carried out at the Neonatal Intensive Care Unit (NICU) at Minia university hospital for
obstetrics and children between January 2015 and January 2021. All preterm infants with respiratory distress syndrome with a Down’s score system five or more were enrolled in this study. Preterm infants with congenital heart disease, diaphragmatic hernia, tracheo-esophageal fistula, cleft lip/palate also cases with respiratory distress secondary to severe birth asphyxia (Apgar score ≤ 3 at 1 and 5 minutes) were excluded from the study. Enrolled preterm infants were categorized into two groups: Group I: included 34 babies treated with INSURE-CPAP method. Group II: included another 34 babies treated surfactant with conventional mechanical ventilation (surfactant-CMV) method.

Preterm babies demographic data: included gestational age, birth weight, Apgar score at 1 and 5 minutes, total duration of ventilation (in hours), whether invasive or non-invasive, duration of oxygen supplement until discharge, O₂ saturation with the target (89%-94%), arterial blood gases on admission, 6, 12 and 24 hours, number of surfactant doses and duration of hospital stay (in days), all these variables were compared between both groups. In this study, two types of Surfactant therapy (alveofact and survanta) were used and Fisher-Paykel CPAP and MECK ventilator for non-invasive and invasive ventilation. Five neonatology and pediatric nursing experts tested the validity of the tools at Minia university hospital for obstetrics and children and affirmed its validity. Official permissions were obtained from the director of the NICU. Data were gathered from the neonates' sheets, which met the inclusion criteria and were admitted to the NICU during the period from January 2015 to January 2021. INSURE-CPAP was considered successful if babies were eligible for weaning with no or mild retraction, the respiratory rate between 30-60/ breaths per minute, spo2 >90 on fio2 <30%, and a PEEP of <5 cm water. Failure of the
INSURE method was considered when there was a need for mechanical ventilation based on clinical deterioration like severe retraction on PEEP more than 7 cm water, significant apnea lasting more than 20 seconds, and associated with pallor or bradycardia or recurrent apnea (> 2 episodes in 24 hours) requiring bag and mask ventilation. Also, blood gases abnormalities such as pH < 7.25, Paco₂ more than 65, or increased O₂ requirements more than 50%. Failure in mechanical ventilation is defined as requiring PIP 26 or more, shifting to HFOV, or developing pneumothorax.

The nursing staff monitored and evaluated the baby's reaction to treatment with continuous monitoring and close observation for both groups. The nurse withdrew arterial blood gases obtained from the umbilical arterial catheter at admission, 6 and 24 hours, after each change of the ventilator settings or with clinical deterioration of the babies.

**Ethical considerations:** The study was conducted, revised, and agreed upon by the scientific ethical committee in both faculties of medicine and nursing, Minia University.

**Statistical analysis**

All data were typed and analyzed using SPSS version 22. Numerical data were expressed as means, while non-numerical data were expressed as frequencies. The comparison between two numerical variables was made using the Student t-test, while the chi-square test was used to compare two categorical variables. Data were expressed in tables using Microsoft word program while figures were presented by using Excel.

**Results**

There was no significant difference between the 2 studied groups regarding gestational age (p=0.4), APGAR score at one and 5 minutes (p=0.1), gender (p=0.1), mode of delivery (p=0.7), and birth weight (p=0.3) however the number of babies with birth weight from 800-1400 were significantly high in Surfactant- CMV group (p<0.036) and babies weighted from 1401-1900 gm.
were significantly high in INSURE-CPAP group (p<0.023), while Down’s score is significantly lower in CMV-Surfactant group (p<0.04*) (Table 1).

PH is significantly lower in the Surfactant-CMV group initially on admission and at 6 hours (p=0.03* and p=0.04* respectively), while no significant difference between the 2 groups after 24 hours of admission (p<0.61). Regarding PaO2, there was a significant difference between the 2 studied groups on admission and after 24 hours (p=0.04, p=0.006**). O2 saturation showed a significant difference between the 2 studied groups on admission (p=0.019*) and after 24 hours (p=0.04*) while no significant difference between the 2 groups after 6 hours of admission (p<0.32). Regarding PaCO2, a significant difference between the 2 studied groups was found on admission (p=0.014*) and after 24 hours (p=0.02*) while no significant difference was detected between the two groups after 6 hours of admission (p=0.61) (Table 2).

The arterial alveolar ratio (a/A ratio) was significantly higher in INSURE-CPAP group on admission (p<0.01*) after 24 hours the a/A ratio was improved in both groups (Figure 1).

Alveolar arterial oxygen gradient (A/aDO2) was significantly high at the time of admission and after 24 hours in the Surfactant-CMV group when compared to INSURE-Surfactant group (p<0.001**) (Figure 2).

Table (3) showed that the duration of assisted ventilation (in-hours) was significantly lower in INSURE-CPAP group (p=0.04*), also the length of hospital stay has been found to be significantly shorter in INSURE-Surfactant group (p=0.03*). The response to treatment was detected in 85.29% of the INSURE group compared to 79.42% in the Surfactant-CMV group, also there was a significant difference between the two studied groups regarding the time required for the first
dose (longer in INSURE-CPAP group) (p=0.007**) awhile the number of surfactant doses required was found to be less in the same group (p=0.04*).

**Discussion**

Nearly half of the preterm infants (<34 weeks) with respiratory distress syndrome (RDS) managed on continuous positive airway pressure (CPAP) require surfactant administration via endotracheal intubation [7]. In the last few years, there has been marked advancement of surfactant administration which utilizes the least invasive technique through the catheter while the baby is on CPAP without interruption of ventilation; however, these methods require well-trained personnel with updating education on theory and mannequin simulation plus the provision of video laryngoscopy [8].

This technique is not available in our unit currently; INSURE technique and surfactant followed by mechanical ventilation are still the only two methods used. The present study showed that extremely low birth weight babies comprised 13 (38.24%) in the Surfactant-CMV group compared to 4 (11.76%) in ENSURE-CPAP, no other differences in the rest of the demographic data this in accordance with one previous study, which reported no gender predominance or significant demographic differences between the two studied groups [9].

a/APO$_2$ ratio (PaO$_2$/PAO$_2$) is known as an index of gas exchange function, it was 0.35 ± 0.07 in the Surfactant-CPAP group compared to 0.18 ± 0.08 in the group of mechanical ventilation (P value=0.0045*), this significant high ratio may be one of the factors for success in the INSURE group. It was reported that initial a/APO$_2$ less than 0.22 is one of the indicators of INSURE failure [10-12].

Figure (2) showed that the initial alveolar-arterial oxygen gradient was 263.74 ± 98.43 in the group of mechanical ventilation (group II), which is significantly higher than that of the INSURE group (group I) 173.51 ± 32.33,
(P-value 0.001). These results give the evidence that if a/A ratio is low or /AaDo₂ is high, it is appropriate to start with mechanical ventilation without a trail of INSURE as these two indices were involved with CPAP failure. Many previous studies strongly support our suggestion as Koh et al. [13] who reported that an initial or pre surfactant low a/APO₂ ratio was a significant risk factor for INSURE failure, which suggested that INSURE was more likely to fail in infants if gas exchange in the alveoli was severely impaired due to severe RDS. Also, Dani et al. [14] reported birth weight < 750 g, PO₂/FiO₂ < 218, and a/APO₂ < 0.44 at the first-blood gas analysis as the independent factors of INSURE failure in infants less than 30 weeks. It was postulated that the multiple INSURE techniques might decrease the failure in those infants and increase the effectiveness of preventing mechanical ventilation [15, 16].

In the same direction, interpretation of arterial blood gas showed that the CMV group had the lowest PH and Pao₂ and high Paco₂, which gave the importance of selecting cases candidate for intubation and continued mechanical ventilation from the beginning.

It was reported that it might be appropriate to differentiate in the first hours of life those infants who have a good chance of succeeding in the INSURE procedure from those who have a high risk of failing it and, therefore, those infants should preferably be intubated electively for surfactant administration and continued MV [17]. Similarly, De Bisschop et al. reported that infants with high gestational ages were associated with the success of INSURE technique in contrast to those with low gestational age in whom INSURE should be considered cautiously [18]. The results of the present study showed that INSURE technique was a successful method in treating respiratory distress syndrome in 85.29% compared to 79.42% in Surfactant- CMV group. It had been reported that the failure of
INSURE is a matter of controversy. Cherif at al., reported that the rate of INSURE failure was 32.1% in a study of 109 neonates with 27–34 weeks of gestation [19], another study Najafian et al., reported a failure rate of 43.8% for INSURE technique [20]. Many studies have suggested that the early application of nasal continuous positive airway pressure (nCPAP) for RDS treatment is effective and can reduce the occurrence of lung injury [7, 21]. Due to an expected synergistic effect, surfactant administration with nCPAP has been an ideal non-invasive treatment of RDS [7].

In this study, the duration of ventilation in INSURE-CPAP group was 46.85 ± 20.15 days compared to 61.21 ± 33.34 days (P= 0.04*) which is significantly lower than that of the mechanical ventilation group. These results agreed with Koh et al., who reported that the application of INSURE method for treatment of RDS in extremely premature infants is successful at reducing the duration of MV and the occurrence of BPD at 36-week postmenstrual age (P < 0.05). However, they found no difference in mortality of BPD at that age; they added that the duration of oxygen supplement, the need for oxygen at 28 days, and the use of a postnatal steroid were significantly decreased in the INSURE-CPAP group. It was reported that PDA was a significant independent factor for an increase in the duration of MV (P=0.001), presumably because PDA could deteriorate lung function and hence prolong the duration of ventilation in those babies [22].

In the present study, the duration of hospital admission (in days) is prolonged in a mechanical ventilated group. This result was consistent with Chotigeat et al., who reported similar results [23]. The current results showed that the time to give the 1st dose of surfactant is significantly shorter in the surfactant-CMV group (48.97 ± 22.42 minutes) than in the INSURE-CPAP group (66.32 ± 28.66 minutes) (P-value (0.007*), this can be due to the relatively higher
gestational age and birth weight in INSURE group and development of RDS is late in this group in contrast to surfactant-CMV group which usually receives the first dose at delivery room or within 15 minutes after delivery in our unit as a prophylactic treatment. Sweet et al reported that early rescue surfactant should be the standard in most cases; however, intubated babies should be given the first dose of surfactant in the delivery suite, when intubation is needed for stabilization [24].

The number of surfactant doses was significantly greater in the surfactant-CMV group (3.31 ± 0.7 while in INSURE group was 1.25 ± 0.44 (P=0.04*). This can be explained by low birth weight and severity of the disease in the CMV group, as shown by decreased arterial /alveolar ratio and increased AaDo2 and down score. This finding is in accordance with Tsakaldis et al., who reported that an increased number of surfactant doses is associated with lower GA and BW which is considered a risk factor for multiple doses administration [25].

The present study concluded that the INSURE-CPAP technique could be applied to the majority of neonates with RDS, which is followed by a high percentage of success as the A/a ratio improved after 24 hours from therapy and arterial blood gases showed significant improvement at the 24 hours also results in O2 saturation is significantly higher in the INSURE group however it still was in the target range for preterm in addition to reduced duration of ventilation and hospital stay.

Limitation of the study: we have two limitations; the first one is a retrospective study the second is the small number of cases. So, a broad study with multiple centers experience is need

**Conclusions**

INSURE- CPAP technique is a reliable and effective method for the treatment of RDS, especially in cases with high arterial alveolar ratio (a/APO2) and low arterial oxygen gradient (AaDO2).
Author's contributions
MA constructed the research plan, collected the data interpreting statistics, and edited the manuscript to be published in its final format. AH shared in collecting data, interpreting and revising the manuscript. Both authors agreed the final proof of the manuscript.

Conflict of interest
The authors have no conflict of interests to declare.

Funding
This study received no special funding and was totally funded by the authors.

Author's details
1Pediatric Department, Faculty of Medicine, Minia University, Egypt
2Pediatric nursing - College of Nursing - Minia University, Egypt

Date received: 21st November 2021, accepted 30th December 2021

References


13. Koh JW, Kim JW, Chang YP. Transient intubation for surfactant administration in the treatment of


Table (1): Demographic data of the studied groups

<table>
<thead>
<tr>
<th>Demographic Data</th>
<th>Studied groups</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>INSURE-CPAP</td>
<td>Surfactant-CMV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=34)</td>
<td>(N=34)</td>
<td></td>
</tr>
<tr>
<td>Gestational age (hours)</td>
<td>31.8 ± 1.7</td>
<td>32.2 ± 1.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Birth Weight (g)</td>
<td>800-1400</td>
<td>4(11.76%).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13(38.24%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1401-1900</td>
<td>13(38.24%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5(14.70%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1901-2400</td>
<td>17(50%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>16(47.26%)</td>
<td></td>
</tr>
<tr>
<td>Birth Weight (g) Mean (±SD)</td>
<td>1841.2 ± 420.7</td>
<td>1730.2±496.7</td>
<td>0.3</td>
</tr>
<tr>
<td>APGAR score at one min</td>
<td>5.02 ± 1.4</td>
<td>5.5 ± 1.4</td>
<td>0.1</td>
</tr>
<tr>
<td>APGAR score at 5 min</td>
<td>8.2 ± 0.9</td>
<td>8.5 ± 0.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Male (N/%)</td>
<td>19(55.9%)</td>
<td>25(73.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Female (N/%)</td>
<td>15(44.1%)</td>
<td>9(26.5%)</td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery (N/%)</td>
<td>6(17.5%)</td>
<td>5(14.7%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Caesarian section (N/%)</td>
<td>28(82.4%)</td>
<td>29(85.3%)</td>
<td></td>
</tr>
<tr>
<td>Down score</td>
<td>6.2±1.4</td>
<td>8.1±1.1</td>
<td>0.04*</td>
</tr>
</tbody>
</table>
* = Significant (p < 0.05

Table (2): Arterial blood gas parameters in studied groups

<table>
<thead>
<tr>
<th>Demographic Data</th>
<th>Studied groups</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>INSURE-CPAP</td>
<td>Surfactant-CMV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=34)</td>
<td>(N=34)</td>
<td></td>
</tr>
<tr>
<td>PH</td>
<td>On admission</td>
<td>7.27±9.06</td>
<td>0.03*</td>
</tr>
<tr>
<td></td>
<td>At 6 hours</td>
<td>7.33±0.06</td>
<td>0.04*</td>
</tr>
<tr>
<td></td>
<td>At 24 hours</td>
<td>7.35±0.07</td>
<td>0.61</td>
</tr>
<tr>
<td>Pco2 PaCO2</td>
<td>On admission</td>
<td>48.77±7.60</td>
<td>0.014*</td>
</tr>
<tr>
<td></td>
<td>At 6 hours</td>
<td>45.68±13.81</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>At 24 hours</td>
<td>36.26±5.18</td>
<td>0.02*</td>
</tr>
<tr>
<td>Po2 PaO2</td>
<td>On admission</td>
<td>57.24 ± 13.33</td>
<td>0.04*</td>
</tr>
<tr>
<td></td>
<td>At 6 hours</td>
<td>74.06±32.40</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>At 24 hours</td>
<td>80.88±20.34</td>
<td>0.006*</td>
</tr>
<tr>
<td>O2 Saturation</td>
<td>On admission</td>
<td>85.82±4.84</td>
<td>0.019*</td>
</tr>
<tr>
<td></td>
<td>At 6 hours</td>
<td>91.38±4.29</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>At 24 hours</td>
<td>94.06±2.68</td>
<td>0.04*</td>
</tr>
</tbody>
</table>
* = Significant (p < 0.05

Table (3): Patient parameters in the studied groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group II Surfactant - CMV (N=34)</th>
<th>Group I INSURE- CPAP (N=34)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to treatment</td>
<td>Yes 29(85.29%)</td>
<td>27(79.42%)</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>No (failure) 5 (14.71%)</td>
<td>7(20.58%)</td>
<td></td>
</tr>
<tr>
<td>Duration of ventilation (hours) (Mean ±SD)</td>
<td>46.85±20.15</td>
<td>61.21±33.34</td>
<td>0.04*</td>
</tr>
<tr>
<td>Duration of hospital stay (day)</td>
<td>16.22± 1.5</td>
<td>21.11±12.33</td>
<td>0.036*</td>
</tr>
<tr>
<td>Surfactant (Mean ±SD)</td>
<td>Time to 1st dose (minutes) 66.32±28.66</td>
<td>48.97 ± 22.42</td>
<td>0.007*</td>
</tr>
<tr>
<td></td>
<td>Number of dosages 1.25 ± 0.44</td>
<td>3.31 ± 0.7</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

*= Significant (p < 0.05)

Figure (1): Arterial Alveolar Ratio (a/APO2). A: On admission, B: At 24 hours

**Citation:** Madiha S. Abdallah and Al shaima G. Hasan. 2022 This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (4).

**Figure (2):** Alveolar Arterial Oxygen Gradient (AaDO2) A: On admission and B: At 24 hours

Submit your next manuscript to Annals of Neonatology Journal and take full advantage of:
- Convenient online submission
- Thorough and rapid peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- No limit as regards tables or figures.
- Open Access research freely available for redistribution

Submit your manuscript at:
www.anj.journals.ekb.eg

**Copyright:** Madiha S. Abdallah and Al shaima G. Hasan. 2022 This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (4).