META-ANALYSIS OF LESS INVASIVE SURFACTANT ADMINISTRATION (LIDA) VS STANDARD THERAPY OF MECHANICAL VENTILATION

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**Introduction**

RDS is a dangerous syndrome which principally attacks premature babies causing deficiency, inactivation or dysfunctionality of the surfactant. It is due to the deficiency of the surfactant which causes lung ventilation-perfusion ratio mismatch and ultimately lung collapse or closure. Providing surfactant gives a chance of amelioration by reducing the surface tension of alveoli. Since the 1990s, ventilation practices and surfactant therapy has improved the health status of premature babies with relevance to RDS. Endotracheal tubes were conventionally employed for surfactants which had associated complications with its delivery and now been replaced with more gentle and less invasive delivery protocols. One such method is INSURE which is used to avoid the use of ventilation procedure for infants which causes alveolar injury and chances of dysplasia incidence. It is less invasive as compared to mechanical ventilation but still requires brief ventilation procedure after surfactant administration.[[1]](#footnote-1)

LISA method is preferable and even less invasive which helps in maintaining continuous and positive airway pressure and without any breathing interruption. Previous research studies and surveys have indicated lesser associated risks with LISA, this is one of the significant reasons for preference by the majority of the practitioners and neonatologists. Many tubing devices exist which are employed in LISA administration like gastric tubes, angiography catheters, vascular catheters etc. The surfactant is delivered into the tracheal tube via laryngoscopy by using a thin tube through vocal cords. After the surfactant is administered, the feeding tube is immediately removed. LISA administration has indicated positive results.[[2]](#footnote-2) Currently, the data on LISA technique with relevance to premature infants is scanty and mostly combination procedures are employed for RDS patients. LISA appears to provide promising results for the future care of premature ones with RDS.[[3]](#footnote-3) With the advancement in neonatal care practices, the survival rate of premature infants can be significantly improved and may also contribute to reducing the rate of bronchopulmonary dysplasia significantly. [[4]](#footnote-4)

**Methodology**

A literature study on LISA versus mechanical ventilation was performed using PubMed and Google Scholar from the beginning of the research on it to 2019. The last research was conducted on April 3, 2019. Majorly, the data was extracted from the sources using the keywords 'less invasive', LISA procedure, premature babies with RDS, and treatment in RDS etc. In the case of two similar publications, the recent one was preferred for including in the present study. The data from all the selected research studies were then evaluated with relevance to LISA procedure via a thin catheter, clinical results of using LISA, mechanical ventilation cases and overall improvement ratio as well as notifying the complications emerged during the procedure.

**Results**

In the present study, 10 RCTs were identified, total subjects of study out of all the selected research articles were 1820. The general identification characters and clinical attributes were variant as mentioned in the table.

**Table 1: Descriptions and Clinical Attributes of Premature infants with RDS**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Study** | **Attributes** | **LISA** | **INSURE** | **p-value** |
|  | **Halim *et al.,* 2019[[5]](#footnote-5)** | Male N  Female N | 28  22 | 31  19 | 0.542 |
|  |  | Gestational age N  32-34 weeks  30-31 weeks  28-29 weeks  <28 weeks | 26  11  8  5 | 24  14  6  5 | 0.87 |
|  |  | Birth weight g | 1300 | 1400 | 0.204 |
|  |  | C-section N  SVD N | 26  24 | 24  26 | 0.689 |
|  |  | Prenatal steroids N  Yes  No | 38  12 | 30  20 | 0.086 |
|  | **Berneau et al., 2018[[6]](#footnote-6)** | Number of preterm infants | 316 | 63 |  |
|  |  | Gestational age N | 28.3 | 27.0 | <0.001 |
|  |  | Birth weight g | 1060 | 910 | 0.007 |
|  |  | Prenatal steroids N | 290 | 49 | 0.002 |
|  |  | C-section N | 208 | 39 | 0.652 |
|  | **Bao et al., 2015[[7]](#footnote-7)** | Preterm infants N | 47 | 43 |  |
|  |  | Male N | 28 | 26 | 0.93 |
|  |  | GA weeks | 29.1 | 29.3 | 0.54 |
|  |  | Birth weight g | 1034 | 1087 | 0.24 |
|  |  | Complete antenatal corticosteroids N | 42 | 40 | 0.54 |
|  |  | C-section N | 35 | 33 | 0.80 |
|  | **Gopel et al., 2015[[8]](#footnote-8)** | Preterm infants N | 108 | 112 |  |
|  |  | Gestational age weeks | 27.6 | 27.5 |  |
|  |  | Birth weight g | 975 | 938 |  |
|  | **Kanmaz et al., 2013[[9]](#footnote-9)** | Preterm infants N | 100 | 100 |  |
|  |  | Gestational age weeks | 28 | 28.2 |  |
|  |  | Birth weight g | 1093 | 1121 |  |
|  | **Mirnia et al., 2013 [[10]](#footnote-10)** | Preterm infants N | 66 | 70 |  |
|  |  | Gestational age weeks | 29.6 | 29.6 |  |
|  |  | Birth weight g | 1339 | 1304 |  |
|  | **Mohammadizadeh et al., 2015[[11]](#footnote-11)** | Preterm infants N | 19 | 19 |  |
|  |  | Gestational age weeks | 30 | 31 |  |
|  |  | Birth weight g | 1289 | 1428 |  |
|  | **Kribs et al., 2015[[12]](#footnote-12)** | Preterm infants N | 107 | 104 |  |
|  |  | Gestational age weeks | 25.3 | 25.2 |  |
|  |  | Birth weight g | 711 | 674 |  |
|  | **Ramos-Navarro et al., 2016[[13]](#footnote-13)** | Preterm infants N | 30 | 30 |  |
|  |  | Gestational age weeks | 28.4 | 29.1 | 0.15 |
|  |  | Birth weight g | 1058 | 1232 | 0.26 |
|  |  | Male N | 12 | 18 | 0.12 |
|  |  | C-section N | 24 | 22 | 0.12 |
|  |  | Prenatal steroids N | 22 | 21 | 0.42 |
|  | **Niknafs et al., 2014** | Preterm infants N | 202 | 184 | 0.08 |
|  |  | Gestational age weeks | 31 | 32 | 0.7 |
|  |  | Birth weight g | 1688 | 1787 | 0.12 |

*N = number; g = grams*

As per data obtained from Halim and colleagues study, out of 148 babies at <34 weeks of gestation, 100 suffered from RDS. An equal number of cases were administered for LISA and INSURE. It was observed that in the case of LISA as well as INSURE, the catheter was easily passed and surfactant was delivered successfully. Though the surfactant was delivered successfully in both cases, FiO2 reduction was observed to be higher in LISA administered patients. Additionally, the need for invasive mechanical ventilation was also required to INSURE patients and not for LISA ones. Hence, LISA was concluded to be a preferred method for surfactant administration because it showed no complications and no need for any mechanical ventilation invasion, yet no reduction in case of BPD was observed.[[14]](#footnote-14) In another study, out of all 379 cases, LISA was found to be associated with lesser tracheal ventilation and no supplementary oxygen was required for patients as well. On the other hand, no reduction in death or BPD cases was observed. The results coincide with those of Halim and co-authors’ work.[[15]](#footnote-15)

Another pilot scale study was performed in Chinese tertiary centre which claimed that the mechanical ventilation and nCPAP was greatly reduced in LISA administered infants in comparison to intubation administered yet no significant impact on the rate of mortality and BPD was seen.[[16]](#footnote-16) One hundred infants were LISA and INSURE administered. The former group had a low BPD incidence and requirement of nCPAP and mechanical ventilation was also significantly reduced. It deduced that LISA is a better technique as compared to INSURE.[[17]](#footnote-17) The research study conducted for comparing the impact of an intratracheal and an endotracheal catheter in surfactant administration revealed that patients who were administered via an intratracheal experienced lesser adverse effects than those via an endotracheal catheter. In general, the health condition of babies improved as per deduction from all the selected works, yet the mortality rate was not reduced in terminally or critically ill babies. By this means that babies with extremely weak immunity or those in early gestational age were difficult to survive and respond to the surfactant administration. As in the case of LISA, the patient needs to continually breathe for spreading the surfactant throughout the lungs and those with extremely weak lungs are unable to do so and they ultimately expire.[[18]](#footnote-18)

**Discussion**

RDS being a serious lung problem of a premature baby is given a lot of significance. These days, most treatment is with nCPAP yet surfactant therapy is still needed. Surfactant therapy is dependent upon spontaneous breathing effort by the baby for avoiding the intrusion of positive pressure ventilation procedure which may cause lungs collapse and closure.[[19]](#footnote-19) Respiratory care is a crucial step regarding care practice for premature infants for which LISA is being practised in several countries. LISA has been reportedly declared a superior treatment strategy and confirmed by GNN (German Neonatal Network) Centres as far as RDS is concerned specifically for infants with <34 gestational age. Lungs and CNS related complications after premature birth are greatly reduced if the patient is administered wisely and efficiently employing LISA.[[20]](#footnote-20)

The current meta-analysis suggests that most of the studies have indicated LISA as a preferable and beneficial approach as far as RDS treatment in preterm infants is concerned. It improves the health condition of the baby and stabilizes it within a few days to weeks’ time span depending upon the criticality and varies with each case. A very important concern in this treatment is the optimized use of a feeding tube which may also impact and influences the treatment outcomes. A European study highlighted this aspect of the treatment and suggests the use of the most appropriate feeding tube in surfactant replacement therapy. LISA Cath is the most preferred one, with better mechanical attributes than any other catheter. Therefore, LISA is surely a better option as compared to any other treatment approach yet it still requires careful administration and intelligent opting of procedural steps, only then can this therapy be successful.[[21]](#footnote-21)

Another important aspect which has emerged due to this meta-analysis and is of consideration is that BPD emergence in RDS cases. It can be reduced by opting various strategies like utilizing a thin catheter which has shown positive and successful outcomes. Though the use of thin catheter comes up with great benefits in relevance to treatment yet it has its own associated flaws as well like it involves laryngoscopy to examine the vocal cords which requires the infant to be awake. It can be difficult and traumatic for an infant. In order to successfully administer surfactant while maintaining the comfort level of an infant and avoid giving sedatives and analgesics still is a clinical challenge in the way of treating premature infants non-invasively and with no to minimal possible side effects. Together with this, another aspect on the treatment of infants with RDS is the amount of surfactant supplied to the amount reaching the lungs is not certain.[[22]](#footnote-22)

The results obtained from this meta-analysis is significant yet there is a limitation to this study because of a lot of variations and heterogeneity of the randomized control trials. Catheters used in each study were also different which impacted the treatment outcomes as well. As a suggestion to evaluating and coming up with best treatment strategies for RDS in babies, placebo-controlled trials can be performed to evaluate the efficacy pattern of LISA with thin catheters and will also help in defining a specific type and dose of surfactant which can be used on the basis of the criticality of cases. **[[23]](#footnote-23)**

**Conclusion**

The use of LISA technique for treating premature RDS infants can reduce the hospital stay and risk factor of mechanical ventilation due to avoiding intubation**.** LISA technique seems a valuable one for preterm babies with RDS. It is a promising procedure but requires additional RCTs which may in future be helpful in further ameliorating the protocol and lessening the undesirable impacts like mortality and morbidity and someday practitioners may proudly state that they have saved all of the infants by administering them through best healthcare strategies and practices.[[24]](#footnote-24)

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