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Original article

LISA: Surfactant administration in spontaneous breathing. Which evidence from the literature?

G. Lista, A. La Verde, F. Castoldi
NICU «V. Buzzi» Ospedale dei Bambini, ICP, Milan, Italy

Summary. Recent human and animal studies demonstrated that surfactant can be delivered intratracheally without traditional intubation and bagging, but using a fine catheter inserted into the trachea of spontaneously breathing preterm infants on CPAP. This strategy, known as LISA (less invasive surfactant administration) or MIST (minimal invasive surfactant therapy), seems to reduce failure of non-invasive respiratory approach. Avoiding mechanical ventilation and manual inflation it is possible to reduce lung injury due to baro-volutrauma. Moreover leaving the infants supported by N-CPAP during the maneuver, it is possible to reduce the risk of lung derecruitment. Further studies are needed to confirm the promising effects due to this strategy to deliver surfactant. (www.actabiomedica.it)

Key words: surfactant, spontaneous breathing, preterm infants, RDS

Introduction

Surfactant administration is a well recognized management for respiratory distress syndrome (RDS) (1); N-CPAP and Non Invasive Ventilation (NIV) are often used to reduce the occurrence of mechanical ventilation (2-3) and so to minimize the risk of lung injury and the evolution towards bronchopulmonary dysplasia (BPD) .

INSURE procedure (transient intubation for surfactant administration, followed by a brief ventilation with final extubation to restore the non-invasive respiratory support in spontaneous breathing preterm infants) used in some recent RCTs (4-6), it has been recognized to reduce the need of mechanical ventilation (MV) (7).

Anyway in order to reduce the potential risk of tracheal intubation and lung injury due to the ventilation even if for a short period during INSURE procedure, a new method to give exogenous surfactant without tracheal intubation and MV has been studied since 2001; this method leaves the baby spontaneously breathing on CPAP during the procedure. The glottis is visualized with the laryngoscope and the surfactant is introduced in the trachea using different thin catheters. The procedure is called LISA (less invasive surfactant administration) or MIST (minimal invasive surfactant therapy).

In literature many important experiences are described about the use of this "less or minimal" invasive modality for surfactant replacement therapy in spontaneously breathing preterm infants on non-invasive respiratory support.

In Germany, Angela Kribs documented as a single center experience that this procedure is feasible with rare early complications and able to reduce the rate of N-CPAP failure (from 46% to 25%) with an increased survival rate (from 76% to 90%) and survival without BPD (from 65% to 80%) (8-11)

After this single center experience, in Germany was planned the "AMV trial" (Avoiding Mechanical Ventilation): a RCT (19 NICUs) that enrolled 220 preterm infants (26.0-28.6 wks'GA) who were randomized to standard treatment (INSURE) or to inter-

vention (LISA). Premedication was used at discretion of operator.

The LISA group showed significantly fewer median days on mechanical ventilation, (0 days. IQR 0–3 *vs* 2 days, 0–5) and a lower need for oxygen supplementation at 28 days (30 infants [30%] *vs* 49 infants [45%], p=0·032) compared with the INSURE group. The thin catheter used (diameter 5 french) was always inserted with the Magill forceps. They recorded no differences between groups in terms of mortality (7 deaths in the intervention group *vs 5* in the standard treatment group) and serious adverse events (21 *vs* 28 respectively) (12).

In 2014 using the data from the German Neonatal Network (GNN) each infant (below 32 wks'GA) receiving LISA (between 2009 and 2012) was matched with one infant not treated with LISA. All the patients (1103 neonates in each group) were analyzed about their respiratory outcomes. LISA infants had lower rates of mechanical ventilation (41% versus 62%, p < 0.001), postnatal dexamethasone treatment (2.5% versus 7%, p < 0.001), BPD (12% versus 18%, p = 0.001) and BPD or death (14% versus 21%, p < 0.001) than the controls.(13)

In Australia, Dargaville (14) planned a non-randomised feasibility study on two groups of spontaneously breathing babies on N-CPAP (25-28 wks' GA (n= 11) and 29-34 wks'GA (n=14) who received the "minimal invasive surfactant therapy" (MIST). Without any premedication, a 5 F vascular catheter was inserted through the vocal cords under direct vision. Porcine surfactant (~100 mg/kg) was then instilled, followed by reinstitution of N-CPAP. The catheter was prepared by marking a point indicating the desired depth of insertion beyond the vocal cords with a marker pen (the point was different according to different GA). In all cases, surfactant was successfully administered (in 10-20 seconds) and N-CPAP re-established with reduction in FiO2 and pressure. An open feasibility study for the use of MIST was then organized (15), including stable preterm neonates (61 neonates of 25-32 wks' GA) with a N-CPAP level above 7 cmH20 and need of FiO2 > 0.3-0.35 (according to GA). In this case the MIST procedure was given maintaining the infant with the CPAP prongs in situ and the administration of surfactant lasted about 15-30 seconds. Oxygenation improved rapidly after MIST procedure in all patients. Rates of pneumothorax, BPD and other major morbidities were not substantially different between the MIST group and their respective controls managed with INSURE procedure. Duration of respiratory support was similar between MIST and control groups, but the lenght of oxygen therapy was lower in MIST group.

The last relevant clinical experience was published by a Turkish group that planned a RCT on preterm infants < 32 wks'GA. The infants in N-CPAP were randomized to receive surfactant (as a bolus in 30-60 seconds) while spontaneously breathing (using a 5F, flexible, sterile nasogastric tube for the procedure called TAKE CARE procedure) or with INSURE procedure (100 neonates per group). No sedation was used. Mean duration of both N-CPAP and MV were significantly shorter in the Take Care group (P values .006 and .002, respectively). BPD rate was significantly lower in Take Care group (relative risk –0.27, 95% confidence interval –0.1 to –0.72)(16).

The LISA procedure was tested in a spontaneous breathing preterm lamb model. Preterm lambs (n = 12) of 133–134 days of gestational age were randomized to receive : (i) continuous positive airway pressure (CPAP) only, (ii) CPAP + LISA, and (iii) intubation and mechanical ventilation with surfactant administration. Surfactant was labeled with samarium oxide. During the next 180 min after randomization, blood gas analyses were performed. Postmortem, lungs were removed and surfactant distribution was assessed, and pressure–volume curves were performed. LISA improved oxygenation, similar to conventional surfactant application techniques, despite lower surfactant deposition (at the right upper lobe) and lung compliance. (17).

Conclusions

Surfactant administration to spontaneously breathing preterm infants (LISA or MIST procedure) seem to be safe, well tolerated and associated with reduced NIV failure and less need of mechanical ventilation.

Actually there is not a universal consensus about the best choice of the catether to use for the procedure,

the lenght of manoeuvre, the need for Magill forceps and for an eventual pre-medication, the safety for all the spontaneously breathing preterm infants in non-invasive respiratory support, indipendently from the GA and birth weight, whenever the surfactant administration is considered necessary.

Moreover it could be important to evaluate (e.g. in animal experiment) if this procedure could be enhanced by a preliminary maneuver to recruit the lungs and so to allow a better distribution of surfactant in course of spontaneous breathing only supported by N-CPAP.

Anyway, even if BPD is a multifactorial disease, LISA/MIST procedure for surfactant administration because seems to improve short term respiratory outcomes (e.g. need of mechanical ventilation and lenght of respiratory support) could reduce the risk of lung injury and so the evolution towards BPD. More larger RCT are needed to confirm this hypothesis.

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Correspondance:
Gianluca Lista, MD
NICU - "V.Buzzi" Ospedale dei Bambini
Azienda ICP, Milano-Italy
Tel./Fax (39) (02) 57995346
E-mail: g.lista@icp.mi.it