Acta Biomed 2014; Vol. 85, Supplement 1: 35-38

Original article

Surfactant administration in spontaneous breathing with N-CPAP for RDS

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

Abstract. Surfactant administration in spontaneous breathing with N-CPAP seems to be a promising approach in the management of neonatal RDS. Both recent RCTs and single centre experience have shown feasibility and good respiratory outcomes with this approach even in extremely preterm infants with respiratory failure. The results of these studies seem to demonstrate that avoiding mechanical ventilation and manual inflation (therefore the risk of high positive pressure and inappropriate tidal volume) it is possible to reduce the risk of VILI and the evolution towards BPD. Further large clinical studies are needed to confirm this hypothesis. (www.actabiomedica.it)

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

Introduction

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

A transient intubation for surfactant administration, followed by a brief ventilation (less than 30 minutes) with final extubation to restore the non-invasive respiratory support (N-CPAP or NIV) in spontaneous breathing preterm infants has been used in some recent RCTs (4-6). This procedure (IN-SU-RE) 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 the following section we will describe the most important experiences (Germany, Australia and Turkey) related to the use of this "less or minimal" invasive modality for surfactant replacement therapy in spontaneously breathing infants in NIV.

LISA and MIST experiences in the literature

Angela Kribs and her NICU team (Cologne, Germany) have the largest single centre experience in term of LISA procedure since 2001. At first, she published an observational study (2001-2002 years) (8) on the feasibility of this new procedure on 29 preterm infants (mean GA 25.3 wks) and compared their outcome with an historical control (34 neonates with a simi-

lar mean GA, intubated for receiving surfactant and ventilated). In case of severe respiratory distress and a FiO_2 >0.4 the surfactant was given by LISA procedure using a feeding tube with an orifice at the tip and a permanent marker 1.5 cm above the tip; the catheter was connected with a syringe and filled with the surfactant; in laryngoscopy, after visualization of the glottis, the feeding tube was inserted in the trachea by a Magill forceps (premedication with Atropine 0.025 mg/Kg i.v) and the surfactant was pushed in 1-3 minutes with the baby always in N-CPAP, under SpO_2 and HR monitoring to detect desaturation (SpO_2 < 80%) and bradycardia (< 100 bpm) or tachycardia (> 200 bpm). The procedure, performed by highly experienced senior neonatologists, was well tolerated in the majority of the treated group with no increasing of morbidity or mortality compared with the historical control. The Authors concluded that" *Surfactant administration during nCPAP is feasible with rare early complications and this warrants a prospective randomized trial*".

One year later, Kribs published a 4-year observational single centre study on 196 preterm babies with a mean GA of 26 wks, treated with the new less invasive approach, compared with an historical group of 51 babies managed with the INSURE procedure with the same clinical characteristics (9). Primary respiratory support and respiratory outcomes were studied. The rate of N-CPAP failure decreased from 46% to 25% with an increased survival rate (from 76% to 90%) and survival without BPD (from 65% to 80%). In those years the procedure became routine care and performed by all the neonatologists team who were adequately trained.

The less invasive modality for exogenous surfactant replacement was part of a gentle delivery room approach aiming to avoiding mechanical ventilation in ELGA neonates without increase of neurological impairment when compared with the historical control group (10-11).

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

The intervention group had significantly fewer median days on mechanical ventilation, (0 days. IQR 0–3 *vs* 2 days, 0–5) and a lower need for oxygen therapy at 28 days (30 infants [30%] *vs* 49 infants [45%], p=0·032) compared with the standard treatment group. 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). The thin catheter used (diameter 5 french) was always inserted with the Magill forceps.

In Australia, Dargaville (13) 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 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 FiO_2 and pressure. An open feasibility study for the use of MIST was then organized (14), including stable preterm neonates (61 neonates of 25-32 wks' GA) with a N-CPAP level above 7 cm H_2O and need of FiO_2 > 0.3-0.35 (according to GA). In this case the MIST procedure was given maintaining the baby with the CPAP prongs in situ and the administration of surfactant lasted about 15-30 seconds. Oxygenation improved rapidly after MIST 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 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

Table 1. Different approaches for surfactant administration in spontaneously breathing infants

Author	Type of catheter	Length of surfactant administration	Setting
Kribs A.(8-9)	Feeding tube 5-6 F	60-180 seconds	Premedication; Magill
Dargaville P.(14)	Vascular catheter 5 F	15-30 seconds	No premedication nor Magill
Gopel W. (12)	Thin Catheter 2.5-5 F	60-180 seconds	Magill; eventual premedication
Gozde Kanmaz H (15)	Feeding tube 5 F	30-60 seconds	No premedication nor Magill
Lista G. (unpublished data)	Tracheal tube 5-6 F	60-120 seconds	Eventual premedication and Magill

procedure) or with INSURE procedure (100 neonates per group). Mean duration of both nCPAP and MV were significantly shorter in the Take Care group (P values 0.006 and 0.002, respectively). BPD rate was significantly lower in Take Care group (relative risk –0.27, 95% confidence interval –0.1 to –0.72).

Since december 2013, after these interesting results, we have introduced this approach also in our NICU for infants assisted in N-CPAP in order to avoid manual ventilation and mechanical ventilation, always maintaining the baby in N-CPAP (to reduce the risk of lung derecruitment during surfactant administration). In 5 months, we treated 10 preterm infants < 35 wks'GA, with moderate RDS, in N-CPAP. All the preterm babies before the procedure showed a need of FiO_2 > 0.35-0.4 in N-CPAP at 6-7 cmH20; the bolus of surfactant was given by a " less invasive procedure" (in 60-120 seconds), generally without pre-medication, with or without Magill forceps, using a thin tracheal catheter (5-6 F) inserted through the vocal cords under direct vision. The procedure was well tolerated, with only transient bradycardia (only in 1 out of 10 patients the HR was less than 100 bpm for 5-10 seconds) and minimal surfactant reflux in some cases. No severe adverse effects (e.g. pneumothorax or pulmonary haemorrhage were registered). In the majority of the babies (80%) the oxygenation improved rapidly after the procedure. In the future we wish to understand the real benefits of this procedure in comparison with standard procedure (INSURE). In Table 1, the different approaches are reported.

Conclusions

Surfactant administration to spontaneously breathing preterm infants seem to be safe, well tolerated and associated with improved short and long term-respiratory outcomes.

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 NIV, indipendently from the GA and birth weight, whenever the surfactant administration is considered necessary.

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

References

1. Seger N, Soll R. Animal derived surfactant extract for treatment of respiratory distress syndrome. Cochrane Database Syst Rev 2009; 2: CD007836.
2. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008; 358: 700-8.
3. Support Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 2010; 362: 1970-79.
4. Rojas MA, Lozano JM, Rojas MX, et al. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. Pediatrics 2009; 123: 137-42.
5. Sandri F, Plavka R, Ancora G, et al, for the CURPAP study group. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics 2010; 125: e1402-09.
6. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Dunn MS,

Kaempf J, de Klerk R, Reilly M, Howard D, Ferrelli K, O'Conor J, Soll R; VON DRM study group. Pediatrics 2011; 128 (5): e1069-76
7. Stevens TP, Harrington EW, Blennow M, Soll R. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database Syst Rev 2007; 4: CD003063.
8. Kribs A, Pillekamp F, Nseler CH,Vierzig A, Roth B. Early administration of surfactant in spontaneous breathing with nCPAP: feasibility and outcome in extremely premature infants (postmenstrual age <27 weeks). Pediatric Anesthesia 2007; 17: 364-9
9. Kribs A, Vierzig A, Hunseler C, et al. Early surfactant in spontaneously breathing with nCPAP in ELBW infants - a single centre four year experience. Acta Paediatr 2008; 97: 293-98.
10. Porath M, Korp L,Wendrich D, Dlugay V, Roth B, Kribs A. Surfactant in spontaneous breathing with nCPAP: neurodevelopmental outcome at early school age of infants < 27 weeks. Acta Paedaitrica 2011; 100: 352-359.
11. Meheler K, Grimme J, Abele J, Huenseler C, Roth B, Kribs A. Outcome of extremely low gestational age newborns after introduction of a revised protocol to assist preterm infants in their transition to extrauterine life. Acta Paediatrica 2012; 101: 1232-9.
12. Göpel W, Kribs A, Ziegler A, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet 2011; 378: 1627-34
13. Dargaville PA, Aiyappan A, Cornelius A, et al. Preliminary evaluation of a new technique of minimally invasive surfactant therapy. Arch Dis Child Fetal Neonatal Ed 2011; 96: F243-8.
14. Dargaville PA, Aiyappan A, De Paoli AG, et al. Minimally-invasive surfactant therapy in preterm infants on continuous positive airway pressure. Arch Dis Child Fetal Neonatal Ed 2013; 98: F122-F126
15. Gozde Kanmaz H, Erdeve O, Emre Canpolat F, Mutlu B, Dilmen U. Randomized Controlled Trial Surfactant Administration via Thin Catheter During Spontaneous. Pediatrics 2013; 131: e502-e508

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