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Original article

Surfactant replacement in preterm infants with respiratory distress syndrome

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Abstract. Surfactant treatment has been demonstrated to decrease pneumothorax and mortality in preterm infants (with RDS). In many neonatal intensive care units NCPAP is used immediately after birth, while surfactant is given as early rescue in infants who develop RDS. This approach has been found safe and effective in several studies and a recent meta-analysis demonstrated a decreased risk of bronchopulmonary dysplasia or death in infants following this strategy. (www.actabiomedica.it)

Key words: surfactant, CPAP, respiratory distress syndrome, preterm infant

Artificial respiratory support and surfactant are the cornerstone of respiratory distress syndrome (RDS) treatment in preterm infants. In particular, it has been demonstrated that surfactant decreases pneumothorax and mortality rate (1-3). Although many studies investigated the effectiveness of this drug in preterm infants and many questions were answered, other issues are not yet cleared and may deserve considerations such as the timing of the treatment, and its role in relationship with other respiratory support, such as nasal continuous positive airway pressure (NCPAP)

Several studies confirmed that surfactant prophylaxis performed before the clinical onset or worsening of RDS is followed by a better outcome than the surfactant administration after RDS is firmly established (rescue treatment) (4). However, surfactant instillation requires tracheal intubation and positive pressure ventilation for its distribution, and it is well known that even a very short period of vigorous manual ventilation can induce a significant lung injury in immature lambs (5). In addition, many Neonatologists are uncomfortable intubating and ventilating preterm infant for surfactant prophylaxis in the current era of increased antenatal steroid usage and NCPAP, mainly considering that a number of patients would be treated without a true need. Otherwise, it is not definitively recognized whether prophylaxis is superior to an early rescue treatment with surfactant. Therefore, in many neonatal intensive care units (NICUs) NCPAP is used frequently and immediately after birth, while surfactant is given as early rescue in infants who develop RDS.

We previously demonstrated that preterm infants with RDS who did not require mechanical ventilation (MV) and were treated with NCPAP and surfactant administration followed by the immediate re-institution of NCPAP have a better short-outcome than infants receiving MV after surfactant administration (6). In fact, this procedure, commonly referred to as INSURE (*IN*tubatio-*SUR*factant-*E*xtubation), reduced the need for MV, the duration of respiratory support, and the need for surfactant in our population (6), and thereafter was extensively applied in our center. However, we observed that INSURE cannot be given to all infants and is unsuccessful in others, and, therefore, we carried out an observational prospective analysis of

the hospital course of inborn preterm infants at our institution with the aim of identifying clinical characteristics which could differentiate infants who need initial treatment with MV from those who can be managed with INSURE and which could predict INSURE success or failure (7).

This study evaluated the effect of the extensive application of INSURE strategy in a cohort of extremely preterm infants (mean gestational age 27 weeks, range 23-29) who required a FiO_2 >30% without need for MV during the first hour of life. We demonstrated that, despite the low gestational age of our population, only 24% of studied infants needed MV in the delivery room, while the majority of them (76%) could be managed for their respiratory failure with INSURE (60%) or NCPAP alone (16%) (7). The large majority (91%) of our patients were successfully treated with the INSURE method. Infants in the success group had :less severe RDS and less occurrence of sepsis and pneumothorax; lower mortality and shorter duration of stay in the NICU than infants in the failure group. Moreover, a birth weight <750 grams and severe RDS (pO_2/FiO_2 <218, a/ApO_2 <0.44 at the first blood gas analysis) were independent risk factor for INSURE failure (7).

In reviewing the literature we observed that in previous studies the INSURE procedure was performed only once, and in case of its failure patients started MV; differently, in our center INSURE may be repeated in selected patients. Thus, we wondered whether multiple INSURE procedures could affect infants' outcome compared to a single procedure and whether it is possible to identify some infants' clinical characteristics which distinguish these different categories of patients. To answer this question we studied 75 infants <30 weeks of gestation with RDS: 71% received single INSURE (with FiO_2 >0.30 without need of MV) and 29% received multiple INSURE (FiO_2 >0.40 without need of MV) procedures. Infants in the single and multiple groups had similar rates of need of MV (15 vs. 23%) and the occurrence of BPD (9 vs. 9%), although the latter were more immature and affected by more severe RDS than the former (8). Thus, we concluded that multiple INSURE procedure can be made safely and can contribute to decrease the need of MV in preterm infants.

Recently, many randomized controlled studies investigated the issue of the early respiratory management of preterm infants. In the COIN Trial 610 babies born at 25-28 weeks' gestation who were breathing spontaneously at 5 min of age were randomized to either early NCPAP alone or prophylactic intubation with planned early extubation to NCPAP (9). Surfactant treatment, ventilation settings, and extubation and reintubation criteria were not mandated and followed local protocols. Therefore, surfactant was given only to 12% of infants in the NCPAP group and 25% of infants in the intubation group. Forty-six% of infants in the NCPAP group required MV within the first 5 days of life , more babies developed pneumothoraces in the NCPAP group (9% vs. 3%), and there was no significant difference in mortality or BPD occurrence (9). This study suggests that it is possible to initiate CPAP in extremely preterm infants (> 25 wks) and treat them with surfactant only if they require MV. On the other hand, surfactant treatment has been associated with a reduction in the rate of pneumothorax and this could explain its higher rate in the NCPAP group (9). In fact, Rojas et al. demonstrated that surfactant therapy within 1 h of life in 27-31 weeks' gestation infants with RDS managed on NCPAP had less need for MV but also fewer pneumothoraces than infants who were managed on NCPAP alone (10).

A recent European multicentre trial, the CURPAP study, evaluated if the administration of prophylactic surfactant to infants (n=208) born at 25-29 weeks' gestation (who did not need MV at birth) receiving NCPAP within 30 min from birth is followed by better respiratory outcome than NCPAP alone and rescue surfactant treatment. Infants in the NCPAP group received surfactant in case they need MV, in particular when FiO_2 was >0.40. This study demonstrated that prophylactic surfactant does not decrease the need of MV within 5 days of life (31.4 vs. 33.0%) and the incidence of main morbidities of prematurity (11).

In the SUPPORT study 1316 infants born at 24-27 weeks of gestation were randomly assigned to intubation and surfactant treatment (within 1 hour after birth) or to CPAP treatment initiated in the delivery room (12). Infants in the first group were ventilated

for at least 24 hours; infants in the CPAP group who require intubation for resuscitation in the delivery room or later in NICU (when FiO_2 was >0.50) received surfactant treatment. Overall, 67.1% of the infants in the CPAP group received surfactant during their hospitalization. Infants who received CPAP treatment, as compared with infants who received surfactant treatment, had similar occurrence of death and/or BPD, but required fewer days of mechanical ventilation, and were more likely to be alive and free from the need for MV by day 7; the rates of other adverse neonatal outcomes did not differ significantly between the two groups (12). However, this study presents some limitations: since no signs of RDS were evaluated at birth this is a prophylaxis study and the distribution of patients without RDS between the groups could bias the randomization; the study design established that MV had to be continued for at least 24 hours in the surfactant group and this could relevantly favours the development of BPD in these patients; finally, extubation criteria differed between the groups and this could affect the results.

On the basis of the previous considerations, they are particularly important the results of a recent meta-analysis which has finally concluded that "Although the early trials of prophylactic surfactant administration to infants judged to be at risk of developing RDS compared with selective use of surfactant in infants with established RDS demonstrated a decreased risk of air leak and mortality, recent large trials that reflect current practice (including greater utilization of maternal steroids and routine post delivery stabilization on CPAP) do not support these differences and demonstrate less risk of chronic lung disease or death when using early stabilization on CPAP with selective surfactant administration to infants requiring intubation" (13).

Conclusions

In summary, the widespread use of antenatal steroid therapy and post-natal NCPAP treatment have changed the clinical characteristics of preterm infants with RDS and have permitted a less invasive approach to their respiratory failure. Therefore, the use of surfactant as early selective treatment is currently widely diffused in NICUs. On the other hand, many issues remain unexplored, such as mainly the identification of the best criteria for surfactant treatment in the perinatal period, and the effectiveness of new synthetic surfactants both as prophylactic or rescue treatment.

References

1. Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2000; 2: CD000511.
2. Soll RF. Prophylactic synthetic surfactant for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2000; 2: CD001079.
3. Soll RF. Synthetic surfactant for respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev* 2000; 2: CD001149.
4. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2001; 2: CD000510.
5. Bjorklund LJ, Ingimarsson J, Curstedt T. Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. *Pediatr Res* 1997; 42: 348-55.
6. Dani C, Bertini G, Pezzati M, Cecchi A, Caviglioli C, Rubaltelli FF. Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks' gestation. *Pediatrics* 2004; 113: e560-3
7. Dani C, Corsini I, Bertini G, Fontanelli G, Pratesi S, Rubaltelli FF. The INSURE method in preterm infants of less than 30 weeks' gestation. *J Matern Fetal Neonatal Med* 2010; 23: 1024-9.
8. Dani C, Corsini I, Bertini G, Pratesi S, Barp J, Rubaltelli FF. Effect of multiple INSURE procedures in extremely preterm infants. *J Matern Fetal Neonatal Med* 2011; 24: 1427-31.
9. 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.
10. 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.
11. Sandri F, Plavka R, Simeoni U, CURPAP Advisory Board. The CURPAP Study: an international randomized controlled trial to evaluate the efficacy of combining prophylactic surfactant and early nasal continuous positive pressure in very preterm infants. *Neonatology* 2008; 94: 60-2.

12. 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: 1970-9.
13. Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2012; 14: CD000510.

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