Recruitment: the best way to IN-SUR-E surfactant delivery?

APHP-Cochin-Voisin/Phanie/Science Photo Library

Lancet Respir Med 2020

Published Online
July 17, 2020
https://doi.org/10.1016/S2213-2600(20)30242-3

See Online/Articles
https://doi.org/10.1016/S2213-2600(20)30179-X

Surfactant therapy is a well established treatment for neonates with respiratory distress syndrome. However, the ideal method for delivery of surfactant remains under investigation. In *The Lancet Respiratory Medicine*, Giovanni Vento and colleagues report the results of a prospective, multicentre, randomised trial of a technique to improve surfactant delivery in 218 extremely premature neonates in 35 centres across Italy.[1] This unblinded study compared the approach of intubation-surfactant-extubation (IN-SUR-E) with intubate-recruit-surfactant-extubate (IN-REC-SUR-E), a technique which involved a lung recruitment manoeuvre after intubation before the administration of surfactant.

This novel approach, first described by De Jaegere and colleagues,[2] involves the use of high-frequency oscillatory ventilation (HFOV) to perform a lung recruitment manoeuvre. The intervention involves increasing the mean airway pressure every few minutes based on pulse oximetry (SpO_2) values as the amount of supplemental oxygen is reduced. Subsequently, the mean airway pressure is reduced every few minutes until the SpO_2 deteriorates. Lastly a chest radiograph is obtained.[2] This procedure is intricate and, in Vento and colleagues' trial, somewhat prolonged (median 30 min, IQR 20–45), exposing infants to very elevated mean airway pressures, as high as 17–18 cmH_2O. The safety of such a manoeuvre in a population of extremely low birthweight infants has not been tested aside from this study, and although the authors did not report any increase in air leaks or deaths, this manoeuvre needs to be tested in a larger sample size. The approach requires an experienced team, the addition of an HFOV ventilator, and very careful monitoring, which the results suggest was delivered by the treatment teams in this study.

The primary outcome—the need for mechanical ventilation in the first 72 h—was reduced for the IN-REC-SUR-E group (43 [40%] of 107) compared with the IN-SUR-E group (60 [54%] of 111; adjusted RR 0·75, 95% CI 0·57–0·98; p=0·037). Although this outcome has been used in several pilot studies,[3,4] it does not provide power for important neonatal outcomes such as bronchopulmonary dysplasia or death. Although there were fewer deaths in the IN-REC-SUR-E group, the difference was only significant in per-protocol analyses. Other outcomes were similar, including the occurrence of air leaks. The unblinded study design could have allowed for potential biases, possibly mitigating some of these outcomes such as detection of difference of air leaks or bronchopulmonary dysplasia.

The authors suggest that the IN-SUR-E technique might be associated with lung de-recruitment. Both IN-SUR-E and IN-REC-SUR-E involve laryngoscopy without positive end-expiratory pressure. There are less invasive techniques that might prevent such de-recruitment by maintaining positive end-expiratory pressure, including the use of higher continuous positive airway pressure (CPAP) levels, the delivery of surfactant as an aerosol during continued CPAP,[5] and the method of least invasive surfactant administration (LISA) as originally described by Kribs and colleagues.[6] In this technique, a small catheter is passed through the vocal cords to administer surfactant while the infant receives substantial CPAP pressures.[6] LISA has been reported in a meta-analysis to be associated with less bronchopulmonary dysplasia or death in premature infants when compared with IN-SUR-E and CPAP.[7]

For IN-REC-SUR-E to be considered as an equivalent approach to LISA we should see a similar or greater reduction in some of these neonatal morbidities, as reported for the LISA techniques. In addition to lung recruitment, the timing of caffeine should also be considered. Very early caffeine, given immediately at birth, can have different effects than when given even hours later. Caffeine has been shown to improve minute ventilation and tidal volumes in spontaneously breathing infants when given in the delivery room compared with administration in the neonatal intensive care unit, often at several hours of life.[8] It is unclear whether early caffeine was always given before IN-REC-SUR-E. The LISA approach is simple enough to be done in the delivery room and was preceded by caffeine.[9]

Maintenance of lung recruitment during surfactant administration can be essential for the very preterm (<32 weeks) infant with respiratory distress. We agree with the authors' conclusions that further studies are required. There are potential complications associated with the use of high airway pressures such as those used in the current study, as well as the time, equipment, and

personnel required for lung recruitment, and the absence of any substantial longer-term benefit (eg, a lowered overall occurrence of bronchopulmonary dysplasia, death, and other outcomes). Therefore, we believe that the next logical step would be the comparison of IN-REC-SUR-E with LISA in a larger study powered for such important outcomes.

We declare no competing interests.

Neil N Finer, Anup Katheria
nfiner@ucsd.edu

School of Medicine, University of California, San Diego, San Diego, CA, USA (NNF); and Sharp Mary Birch Hospital for Women and Newborns, San Diego, CA 92123, USA (NNF, AK)

1 Vento G, Ventura ML, Pastorino R, et al. Lung recruitment before surfactant administration in extremely preterm neonates with respiratory distress syndrome (IN-REC-SUR-E): a randomised, unblinded, controlled trial. *Lancet Respir Med* 2020; published online July 17. https://doi.org/10.1016/S2213-2600(20)30179-X.

2 De Jaegere A, van Veenendaal MB, Michiels A, van Kaam AH. Lung recruitment using oxygenation during open lung high-frequency ventilation in preterm infants. *Am J Respir Crit Care Med* 2006; **174:** 639–45.

3 Lista G, Boni L, Scopesi F, et al. Sustained lung inflation at birth for preterm infants: a randomized clinical trial. *Pediatrics* 2015; **135:** e457–64.

4 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.

5 Finer NN, Merritt TA, Bernstein G, Job L, Mazela J, Segal R. An open label, pilot study of Aerosurf® combined with nCPAP to prevent RDS in preterm neonates. *J Aerosol Med Pulm Drug Deliv* 2010; **23:** 303–09.

6 Kribs A, Pillekamp F, Hünseler C, Vierzig A, Roth B. Early administration of surfactant in spontaneous breathing with nCPAP: feasibility and outcome in extremely premature infants (postmenstrual age </=27 weeks). *Paediatr Anaesth* 2007; **17:** 364–69.

7 Isayama T, Iwami H, McDonald S, Beyene J. Association of noninvasive ventilation strategies with mortality and bronchopulmonary dysplasia among preterm infants: a systematic review and meta-analysis. *JAMA* 2016; **316:** 611–24.

8 Dekker J, Hooper SB, van Vonderen JJ, Witlox RSGM, Lopriore E, Te Pas AB. Caffeine to improve breathing effort of preterm infants at birth: a randomized controlled trial. *Pediatr Res* 2017; **82:** 290–96.

9 Kribs A, Hummler H. Ancillary therapies to enhance success of non-invasive modes of respiratory support - approaches to delivery room use of surfactant and caffeine? *Semin Fetal Neonatal Med* 2016; **21:** 212–18.