

**Do we really know when to administer surfactant in preterm infants with RDS managed
on non-invasive respiratory support?**

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Surfactant replacement therapy, a major breakthrough in the care of preterm neonates, remains an exciting and extensively researched field. From the initial days of routine intubation and prophylactic surfactant administration coupled with ongoing invasive mechanical ventilation, to the present-day predominant approach of less invasive surfactant administration, practices have evolved considerably. However, the pertinent question neonatologists often ponder is – “At what threshold shall I be deciding on surfactant therapy in a preterm neonate with RDS who is managed on non-invasive respiratory support such as CPAP?”, where the threshold is commonly defined by the fraction of inspired oxygen (FiO_2), level of CPAP and, to a lesser extent clinical factors like work of breathing.

Historical landmark trials such as the SUPPORT trial were instrumental in tilting the practice from routine prophylactic surfactant administration in neonates at risk of RDS to rescue treatment for symptomatic ones stabilized on early CPAP. The Cochrane review and meta-analysis indicates that ‘early rescue’ is better than ‘late rescue’.¹ However, it is important to note that the evidence behind this conclusion stems from trials in which infants were mechanically ventilated. Generalizing evidence from infants who were managed with mechanical ventilation to those who are now predominantly cared with non-invasive respiratory support may be inappropriate. Further, most of the trials included in the meta-analysis used lower oxygen saturation cut-offs than the currently advocated target of 90-95%. ‘Early’ in its true sense, as understood by clinicians nowadays, may not only relate to the timing of surfactant administration, but also to the FiO_2 requirement while being treated with CPAP.. Till date, there are no prospective RCTs comparing the routinely used thresholds of surfactant administration (for example, FiO_2 0.3 versus 0.4 or CPAP level of 6 cm H_2O versus 7 cm H_2O) in preterm neonates with RDS who are on non-invasive respiratory support. This is true as well for the aspect of repeat surfactant administration for ongoing moderate to severe RDS. While there is only one RCT that had evaluated a lower versus higher threshold for further doses of

surfactant in neonates requiring invasive mechanical ventilation,² there is none that had evaluated the different thresholds in neonates managed with non-invasive respiratory support.² The paucity of high-quality evidence for early surfactant administration as adjudged based on parameters such as FiO₂ or different levels of CPAP is well reflected in the differing recommendations, put forward by national and international clinical practice guidelines. Whilst the European Consensus Guidelines on the Management of Respiratory Distress Syndrome – 2019 Update recommends giving surfactant if the FiO₂ requirement is more than 0.30 on CPAP ≥ 6 cm H₂O³, the Canadian Paediatric Society (CPS) 2021 advocates an FiO₂ cut-off of 0.50 with no specific recommendation for CPAP threshold.⁴ Furthermore, the strength of recommendation varies between the two guidelines with it being B2 (moderate certainty of evidence with a weak recommendation) by the European 2019 consensus and Grade A (consistent level 1 studies) by the CPS 2021. Though the European 2019 consensus and the CPS 2021 recommendations give a strong recommendation for repeat surfactant dosing in neonates with moderate to severe RDS or those with persistent high oxygen requirement based on evidence from the aforementioned RCT evaluating ventilated infants², no objective criteria are spelled out for neonates on non-invasive respiratory support.

Delving further into the evidence-base guiding the recommendations for early surfactant administration reveals significant differences. Whilst the CPS 2021 relied on two systematic reviews, one RCT and two observational studies, the European consensus 2019 based its recommendation on one observational study.^{3,4} The certainty of evidence from the two systematic reviews evaluated by CPS 2021 were limited by indirectness related to the patient population enrolled.⁴ While one review had compared two groups of neonates who were on invasive ventilation, the other had studied intubate-surfactant-extubate (INSURE) versus surfactant followed by continued invasive ventilation.⁴ Further, the only RCT (Verder et al.) considered by the CPS 2021 had compared two groups of preterm infants with RDS who were

managed on CPAP and in whom surfactant was given at FiO_2 of 0.37-0.55 versus 0.57-0.77.⁴ The observational study by Dargaville et al. on which the European 2019 consensus was based upon had indicated that an $\text{FiO}_2 > 0.30$ in the initial hours of postnatal life predicted future CPAP failure in preterm infants with RDS.⁵ Though there is good certainty of evidence from Verder et al.'s RCT that administering surfactant at an FiO_2 threshold range of 0.37-0.55 might be beneficial, it is unclear as to whether the lower FiO_2 threshold of 0.30 as recommended by the European consensus 2019 or the higher one of 0.50 advocated by CPS 2021 is better. Isayama et al. in their meta-analysis evaluating 'early INSURE' versus 'CPAP alone followed by surfactant when intubated or when CPAP failure occurs' concluded that there was a trend towards decreased risk of bronchopulmonary dysplasia (BPD) and combined outcome of BPD or mortality favoring 'Early INSURE'. It is to be noted that barring one study by Verder et al., none of the included studies in this meta-analysis had used a FiO_2 threshold for deciding on 'early INSURE', which was predominantly based on timing the surfactant administration within the first hour of life. The FiO_2 threshold for intubation and delayed surfactant administration in CPAP alone group varied significantly as well. While Dilmen et al., Reininger et al. and Sandri et al. had used a FiO_2 threshold of >0.30 - 0.40 for surfactant administration in the CPAP only group, Kandraju et al. had used >0.50 , Dunn et al. utilized >0.60 and Rojas et al. a cut off of >0.75 .⁶

Despite decades of research and rapid strides in the care of preterm infants with RDS, the precise decision threshold guiding surfactant administration still remains largely unanswered. Widely varying recommendations by different academic bodies based on contrasting evidence further adds to the existing chasm. While it is plausible that the use of a lower FiO_2 threshold might result in surfactant overuse and the added procedure related risks, the higher threshold might be associated with worsening disease severity and requirement of higher levels of respiratory support, including heightened and prolonged oxygen exposure. It is to be noted that

there may be other considerations apart from FiO_2 and CPAP levels which may be taken into account while deciding on surfactant administration. These may include adjudging the severity of RDS with chest radiography and lung ultrasound severity score, both of which might aid in earlier prediction of surfactant requirement. We believe that the ambiguity regarding the ideal threshold for surfactant administration aiming at maximizing its benefits in conjunction with preventing its over usage is a subject of important clinical significance and needs further clarification. We suggest comprehensive, adequately powered multi-centric RCTs with robust designs evaluating the different FiO_2 and CPAP level thresholds for surfactant administration in preterm neonates with RDS. These RCTs need to ensure that other plausible confounding factors such as the type of surfactant used (porcine 200 mg/kg versus bovine 100 mg/kg) and the modality of its administration (INSURE versus less invasive surfactant administration) are similar in both the groups. This might be challenging in multi-centric studies where the protocols related to surfactant use for the aforementioned practices may vary between the centers.

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