

Abstract

This meta-analysis evaluated the efficacy of less invasive surfactant administration (LISA) versus INSURE in preterm infants with or at risk of respiratory distress syndrome (RDS). 21 randomized controlled trials (2,656 infants) were included. LISA was associated with lower odds of bronchopulmonary dysplasia, death, intubation within 72 hours, and severe intraventricular hemorrhage. Subgroup analyses suggested greater benefits in infants ≤ 34 weeks gestational age and antenatal steroid exposure for bronchopulmonary dysplasia (BPD) and the composite outcome of death/BPD. These findings support LISA as a less invasive alternative to INSURE, with heterogeneity in clinical advantages.

Introduction

Less invasive surfactant administration (LISA) is increasingly used for preterm infants with respiratory distress syndrome (RDS) in the last two decades¹. Compared to INSURE (Intubation-Surfactant-Extubation), LISA enables spontaneous breathing during surfactant delivery and is endorsed by European guidelines². While prior meta-analyses have demonstrated LISA's overall efficacy^{3,4}, subgroup-specific effects remain insufficiently characterized. This meta-analysis evaluates LISA versus INSURE across clinically relevant subpopulations to provide more tailored evidence for treatment decision-making.

Methods

A systematic literature search was conducted in MEDLINE, EMBASE, and CENTRAL to identify randomized controlled trials (RCTs) comparing LISA and INSURE in preterm infants with or at risk of RDS. Pairwise comparisons were conducted for seven predefined outcomes: bronchopulmonary dysplasia (BPD) at 36 weeks PMA, death during first hospitalization, composite outcome of BPD or death, need for intubation within 72 hours, severe intraventricular hemorrhage (IVH), pneumothorax, and need for additional surfactant. Meta-analyses were performed using generalized linear mixed models (GLMM) with random-effects as the primary model to account for heterogeneity. Analyses were conducted in R (v4.4.3) using the metabin package, with results reported as odds ratios (OR) with 95% confidence intervals (CI). Subgroup analyses explored clinical factors including gestational age ≤ 34 weeks, surfactant product type, and antenatal steroid exposure.

Results

A total of 21 RCTs (2,656 infants) were included. Compared with INSURE, LISA significantly reduced the risk of BPD, death, intubation/mechanical ventilation, and severe IVH (Figure 1). Subgroup analyses suggested greater benefits of LISA in infants ≤ 34 weeks gestational age and antenatal steroid exposure, particularly for reducing BPD and the composite outcome of BPD or death. While efficacy estimates varied across other subgroups, differences were not statistically significant, likely due to limited sample sizes (Table 1).

Figure 1. Pairwise Meta-Analysis of Efficacy Outcomes Comparing LISA vs INSURE in Preterm Infants

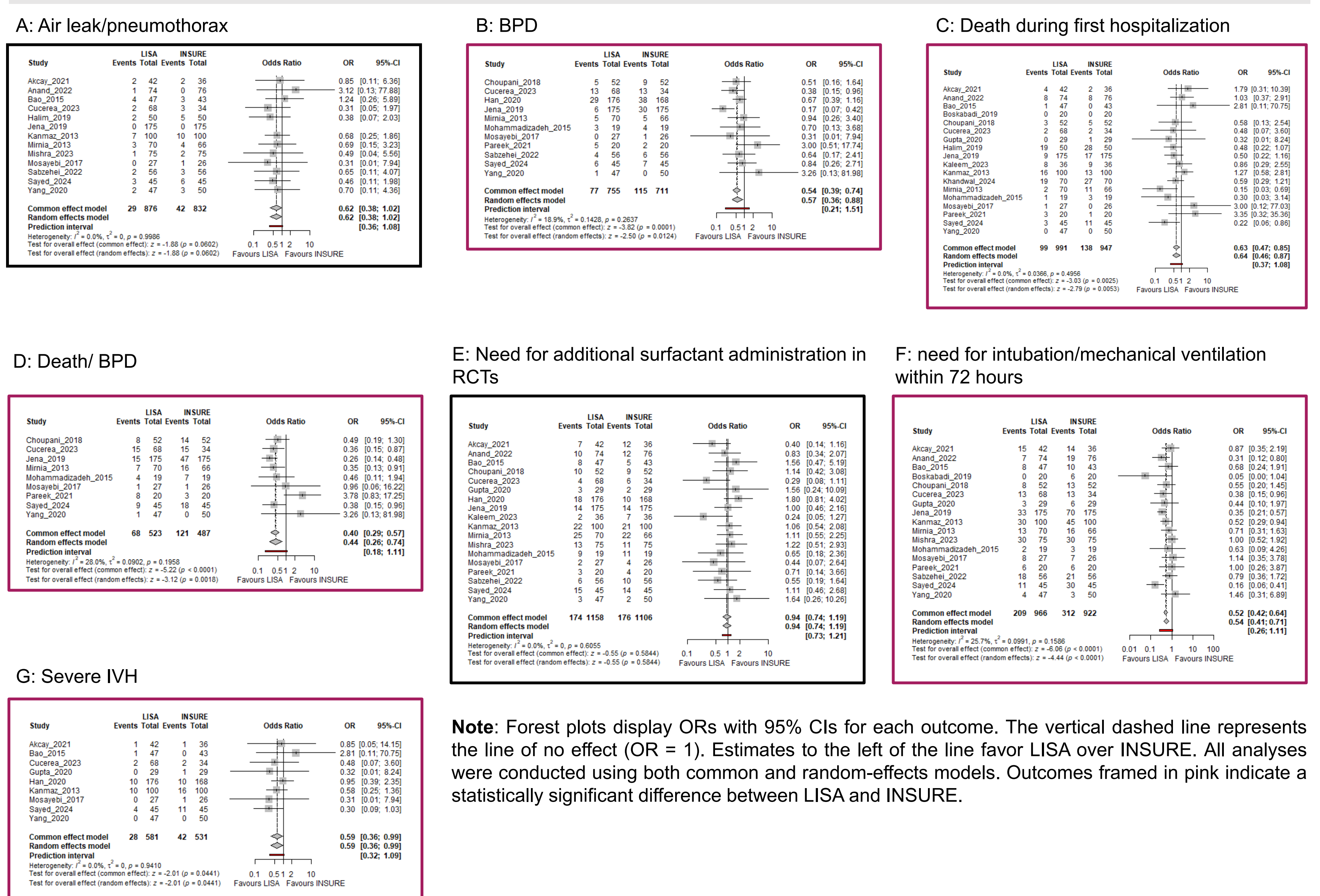


Table 1. Subgroup Analyses of Efficacy Outcomes by Clinical Characteristics

Outcome	No. of studies for base-case*	Overall	Gestational age ≤ 34 weeks	Curosurf [®] as the surfactant product	No mandatory pre-procedural medications	No sedation	Antenatal steroids in $\geq 50\%$ of infants
Number of studies for analysis	-	9 to 18	5 to 14	6 to 12	4 to 13	4 to 11	4 to 8
Air leak/pneumothorax	12 (13)	0.62 [0.38, 1.02]	0.66 [0.36, 1.18]	0.67 [0.38, 1.19]	0.68 [0.38, 1.2]	0.61 [0.29, 1.29]	0.56 [0.3, 1.03]
BPD at 36 weeks PMA	11	0.57 [0.36, 0.88]	0.45 [0.26, 0.76]	0.56 [0.33, 0.96]	0.68 [0.27, 1.73]	0.47 [0.23, 0.99]	0.38 [0.21, 0.71]
Death during first hospitalization	16 (18)	0.64 [0.46, 0.87]	0.66 [0.48, 0.91]	0.72 [0.4, 1.28]	0.7 [0.51, 0.97]	0.92 [0.61, 1.39]	0.6 [0.36, 1]
Death/BPD	9	0.44 [0.26, 0.74]	0.32 [0.21, 0.48]	0.43 [0.26, 0.7]	0.74 [0.2, 2.75]	0.6 [0.2, 1.83]	0.32 [0.21, 0.48]
Need for additional surfactant administration	18	0.94 [0.74, 1.19]	0.91 [0.69, 1.2]	0.81 [0.59, 1.11]	1.02 [0.77, 1.35]	0.87 [0.61, 1.25]	0.78 [0.56, 1.09]
Need for intubation/mechanical ventilation within 72 hours	17	0.54 [0.41, 0.71]	0.47 [0.36, 0.61]	0.61 [0.46, 0.81]	0.49 [0.33, 0.72]	0.55 [0.4, 0.77]	0.55 [0.39, 0.76]
Severe IVH (Grade 3 or 4)	8 (9)	0.59 [0.36, 0.99]	0.7 [0.4, 1.22]	0.57 [0.28, 1.17]	0.62 [0.37, 1.05]	0.66 [0.38, 1.17]	0.55 [0.26, 1.16]

Note: Data is reported as odds ratio [95% confidence interval] for LISA vs INSURE/ETT, where an odds ratio < 1 favors LISA. A 95% CI that does not include 1 indicates a statistically significant difference between LISA and INSURE/ETT, as indicated by pink font. *Studies with 0 events in both arms were not included in the analysis, and the total no. of studies including such studies are presented in parenthesis. **Abbreviations:** BPD: Bronchopulmonary Dysplasia; INSURE: Intubation-Surfactant-Extubation; IVH: Intraventricular Hemorrhage; LISA: Less Invasive Surfactant Administration; PMA: Postmenstrual Age

Conclusion

This meta-analysis found that LISA was associated with lower odds of bronchopulmonary dysplasia, death, intubation within 72 hours, and severe intraventricular hemorrhage compared to INSURE. Subgroup analyses suggest that these benefits may be more evident in infants ≤ 34 weeks gestational age and those without sedation or antenatal steroid exposure. LISA offers a less invasive and effective alternative to INSURE. Its potential advantages in specific subgroups warrant further investigation to refine patient selection and optimize outcomes.

References

- Kakkilaya V, Gautham KS. Should less invasive surfactant administration (LISA) become routine practice in US neonatal units? *Pediatr Res.* Apr 2023;93(5):1188-1198. doi:10.1038/s41390-022-02265-8
- Sweet DG, Carnielli VP, Greisen G, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update. *Neonatology.* 2023;120(1):3-23. doi:10.1159/000528914
- Abdel-Latif ME, Davis PG, Wheeler KI, De Paoli AG, Dargaville PA. Surfactant therapy via thin catheter in preterm infants with or at risk of respiratory distress syndrome. *Cochrane Database Syst Rev.* May 10 2021;5(5):CD011672. doi:10.1002/14651858.CD011672.pub2
- 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.* Aug 9 2016;316(6):611-24. doi:10.1001/jama.2016.10708