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Less invasive surfactant administration in preterm neonates with respiratory distress syndrome: a network meta-analysis

Ioannis Bellos¹, Georgia Fitrou¹, Aakash Pandita²

¹National and Kapodistrian University of Athens, Greece, ²Department of Neonatology, Sanjay Gandhi PGIMS, Lucknow, U.P, India

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Ioannis Bellos

ABSTRACT

Preterm birth is often associated with respiratory distress syndrome, which may lead to bronchopulmonary dysplasia and high rates of morbidity and mortality. The current treatment approach is the initial use of nasal continuous positive airway pressure (nCPAP), followed by surfactant administration in neonates with worsening respiratory distress. The aim of the present network meta-analysis is to simultaneously assess the effects of less invasive methods for administering surfactant on clinical outcomes and compare them to the conventional InSurE (Intubation, Surfactant administration and Extubation) method.

- 1 Review title: Less invasive surfactant administration in preterm neonates with respiratory distress syndrome: a network meta-analysis 2: Review question: The meta-analysis aims to compare adverse clinical outcomes in neonates treated with less invasive surfactant administration compared to those treated with the InSurE (Intubation, Surfactant administration and Extubation) method or solely with nasal CPAP without surfactant administration. Population: Preterm neonates with respiratory distress syndrome Intervention: Less invasive surfactant administration Comparison: InSurE or no surfactant Outcome: Need for mechanical ventilation, bronchopulmonary dysplasia, mortality
- 2 Searches: MEDLINE, Scopus, CENTRAL, ClinicalTrials.gov, Google Scholar will be systematically searched from inception. No date or language restrictions will be used. The following terms will be applied: less invasive; surfactant; minimally invasive; lisa; mist; insure; sure; intubation; preterm; respiratory distress; rds; mechanical ventilation
- 3 Condition or domain being studied: Preterm birth is often associated with respiratory distress syndrome, which may lead to bronchopulmonary dysplasia and high rates of morbidity and mortality. The current treatment approach is the initial use of nasal continuous positive airway pressure (nCPAP), followed by surfactant administration in neonates with worsening respiratory distress. More specifically, neonates are intubated and ventilated for surfactant administration through the InSurE procedure; however, less invasive techniques for surfactant administration have been developed in order to prevent intubation, although their efficacy and safety remains still under investigation.
- 4 Participants/population: Inclusion criteria: preterm infants with respiratory distress syndrome, requiring continuous positive airway pressure Exclusion criteria: need for mechanical ventilation at birth, any congenital malformation or cardiac abnormality
- 5 Intervention(s), exposure(s): Intervention: less invasive surfactant administration (LISA) via thin catheter, laryngeal mask, nebulisation or pharyngeal deposition
- 6 Comparator(s)/control: Comparators: Intubation, Surfactant administration and Extubation (InSurE) or nasal CPAP alone
- 7 Types of study to be included: Both randomized controlled trials and observational studies (prospective/retrospective) will be held eligible. Studies will be included if they report the efficacy and safety of LISA in preterm infants with respiratory distress syndrome, comparing it to InSurE or no surfactant administration.
- 8 Main outcome(s): Need for mechanical ventilation, incidence of bronchopulmonary dysplasia, mortality rates

- 9 Additional outcome(s): Need for repeat dose of surfactant, patent ductus arteriosus requiring treatment, intraventricular hemorrhage (\geq grade 2), periventricular leukomalacia, pneumothorax
- 10 Data extraction (selection and coding): Studies will be held eligible if they report any of the outcomes of interest among preterm neonates with respiratory distress syndrome treated with any LISA method. The extracted data will include the following: name of first author, year of publication, country, study design, eligibility criteria, type of intervention, patient gender, gestational age, antenatal steroid administration, delivery with cesarean section, apgar score, time to surfactant administration, respiratory distress score and the outcomes of interest. Data extraction will be independently conducted by two reviewers and any disagreements will be resolved through the consensus of all authors.
- 11 Risk of bias (quality) assessment: Randomized controlled trials will be assessed with the Jadad scale and the score of the Cochrane Collaboration, taking into account the domains of randomization, blinding, allocation concealment, withdrawals and dropouts. Observational studies will be evaluated with the ROBINS-I tool, which assesses the domains of confounding, selection of participants, classification of interventions, deviation from intended intervention, missing data, measurement and reporting of the outcomes. Both tools will be independently implemented by two researchers, while any potential disagreements will be resolved by their consensus. The credibility of outcomes will be evaluated on the grounds of within-study bias, across-studies bias, indirectness, imprecision, heterogeneity and incoherence.
- 12 Strategy for data synthesis: A random-effects frequentist network meta-analytic model will be fitted in order to provide pooled estimates of odds ratio (OR) and 95% CI, taking into account both direct and indirect comparisons. Forest plots will be constructed to visualize the estimated effect sized for all comparisons. Heterogeneity will be measured by calculating the between-study variance (τ^2) and its impact on the outcomes will be evaluated by estimating the 95% prediction intervals (PI). The plausibility of the transitivity assumption will be tested through the evaluation of distributions of possible confounding factors across studies grouped by comparison. The consistency of network will be statistically assessed with a global (design-by-treatment interaction) test and a local (Separating Indirect from Direct Evidence-SIDE splitting) test. Meta-regression analysis will be performed to evaluate the potential influence of study design, sample size, type of surfactant, administration of premedication and use of forceps during surfactant administration via thin catheter.
- 13 Keywords LISA; surfactant; INSURE; respiratory distress syndrome; meta-analysis



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