

Comparative efficacy of methods for surfactant administration: a network meta-analysis

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ABSTRACT

Objectives To compare surfactant administration via thin catheters, laryngeal mask, nebulisation, pharyngeal instillation, intubation and surfactant administration followed by immediate extubation (InSurE) and no surfactant administration.

Design Network meta-analysis.

Setting Medline, Scopus, CENTRAL, Web of Science, Google-scholar and Clinicaltrials.gov databases were systematically searched from inception to 15 February 2020.

Patients Preterm neonates with respiratory distress syndrome.

Interventions Less invasive surfactant administration.

Main outcome measures The primary outcomes were mortality, mechanical ventilation and bronchopulmonary dysplasia.

Results Overall, 16 randomised controlled trials (RCTs) and 20 observational studies were included (N=13 234). For the InSurE group, the median risk of mortality, mechanical ventilation and bronchopulmonary dysplasia were 7.8%, 42.1% and 10%, respectively. Compared with InSurE, administration via thin catheter was associated with significantly lower rates of mortality (OR: 0.64, 95% CI: 0.54 to 0.76), mechanical ventilation (OR: 0.43, 95% CI: 0.29 to 0.63), bronchopulmonary dysplasia (OR: 0.57, 95% CI: 0.44 to 0.73), periventricular leukomalacia (OR: 0.66, 95% CI: 0.53 to 0.82) with moderate quality of evidence and necrotising enterocolitis (OR: 0.67, 95% CI: 0.41 to 0.9, low quality of evidence). No significant differences were observed by comparing InSurE with administration via laryngeal mask, nebulisation or pharyngeal instillation. In RCTs, thin catheter administration lowered the rates of mechanical ventilation (OR: 0.39, 95% CI: 0.26 to 0.60) but not the incidence of the remaining outcomes.

Conclusion Among preterm infants, surfactant administration via thin catheters was associated with lower likelihood of mortality, need for mechanical ventilation and bronchopulmonary dysplasia compared with InSurE. Further research is needed to reach firm conclusions about the efficacy of alternative minimally invasive techniques of surfactant administration.

INTRODUCTION

Respiratory distress syndrome (RDS) is the major cause of respiratory insufficiency, mortality and morbidity in preterm neonates. RDS results from surfactant deficiency and its frequency increases with the decrease in the gestational week.¹ According to the Vermont Oxford Network, in 2017 the incidence of RDS was approximated at 80% of neonates born at 28 weeks, increasing up to 90% at

What is already known on this topic?

- Continuous positive airway pressure along with surfactant are the key components for managing respiratory distress syndrome.
- There are various methods of surfactant administration described in literature.

What this study adds?

- Among the already described methods of surfactant delivery, surfactant delivery via thin catheters seems presently the most feasible and useful of all.

the gestational age of 24 weeks.² Exogenous surfactant is the most effective evidence-based therapy in the management of RDS due to its capacity to improve pulmonary gas exchange in preterm infants by maintaining the functional residual capacity and decreasing the work of breathing.³ Surfactant replacement therapy is required in over 50% of very low birth weight neonates.² In intubated preterm newborns diagnosed with RDS, surfactant administration is proposed to be offered within the first 2 hours of life,⁴ whereas in preterm neonates that switch successfully on continuous positive airway pressure (CPAP), surfactant replacement therapy is deemed necessary when babies are worsening on CPAP pressure of ≥ 6 cm H₂O and requires Fio₂ >0.30 to maintain saturation target.⁵ Importantly, together with mechanical ventilation (MV), RDS plays a pivotal role in the pathophysiology of bronchopulmonary dysplasia (BPD), which is diagnosed in preterm infants with oxygen requirements at 36 weeks' postmenstrual age.⁶ BPD is nowadays one of the greatest burdens of prematurity, affecting approximately half of neonates with gestational age ≤ 29 weeks^{7 8} also as a result of the improved survival of even the smallest babies (23–24 weeks' gestation).⁹ Thus, the clinical management of RDS aims towards the maximisation of survival and minimisation of adverse events, especially BPD.

In this regard, the use of antenatal steroids, gentler ventilation modes that favour non-invasive respiratory support rather than MV and less invasive surfactant administration techniques are all interventions that offer an advantage against adverse effects.⁵ Historically, surfactant administration has been performed via the endotracheal tube (ETT) either in mechanically ventilated neonates or in babies supported with non-invasive ventilation (NIV) by



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means of the Intubation-Surfactant-Extubation (InSurE) technique. Nonetheless, the InSurE technique requires a brief intubation of the trachea with provision of positive pressure ventilation (PPV), which may be accountable for acute and chronic complications, including BPD.¹⁰ Hence, over the last three decades, much effort has been put in developing alternative and less invasive surfactant administration techniques, aiming principally at providing an adequate dose of surfactant without the recourse to intubation and PPV. Nowadays, multiple alternative surfactant administration methods are available. They are better classified according to the grade of invasiveness into two main groups.¹¹ More precisely, the acronym 'SURE' refers to all the methods that still require direct laryngoscopy, but replace the ETT with a thin catheter (either a flexible feeding tube or a semirigid angiocath), namely LISA (less invasive surfactant administration),¹² MIST (minimally invasive surfactant therapy)¹³ and Take Care.¹⁴ Other least invasive methods which are coming up include laryngeal mask airway,^{15 16} nebulisation^{17–22} and pharyngeal installation.²³ Despite the growing number of randomised controlled trials (RCTs) and observational studies assessing the feasibility and effectiveness of these novel methods in comparison with the standard of care, currently there are no data derived from the direct comparison of these new techniques between them. A network meta-analysis aims to simultaneously compare multiple intervention, by taking into account both direct and indirect evidences, enabling the ranking of treatments.¹⁵ The present network meta-analysis aims to compare the efficacy of all techniques of less and minimally invasive surfactant administration with InSurE and no surfactant administration, thus offering to the clinicians and neonatal proceduralists a complete overview of current evidence in order to gain a better understanding of evidence-based effectiveness of each method.

MATERIALS AND METHODS

This network meta-analysis was designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁶ The protocol of the study has been prospectively registered ([dx.doi.org/10.17504/protocols.io/bcbmisk6](https://doi.org/10.17504/protocols.io/bcbmisk6)).

Eligibility criteria

Both RCTs and non-randomised studies (prospective or retrospective cohort studies) were planned to be included. Observational studies were included in order to complement the findings of RCTs, increase precision and provide evidence based on real-world data. Studies were considered as eligible if they assessed clinical outcomes among preterm neonates with respiratory distress syndrome treated with less and minimally invasive methods of administering surfactant without intubation, such as via thin catheter (nasogastric tube or angiocath), laryngeal mask, nebulisation or pharyngeal instillation, comparing them with neonates treated with either the InSurE method or with no surfactant administration. Preterm neonates born at <37 weeks were included. Single-arm studies without control group were not included. Studies examining neonates with major congenital structural/chromosomal abnormalities or neonates requiring intubation for resuscitation were excluded.

Literature search

The primary literature databases were: Medline, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Clinicaltrials.gov. Subsequently, the Google Scholar database was searched in order to provide grey literature

coverage, as well as to find records that were not identified by primary search. Screening for additional papers was performed with the 'snowball' method (search of the full reference list of included studies and previous systematic reviews). The date of the last search was 15 February 2020. The search strategy relied on algorithms including combinations of the following key terms: 'less invasive, minimally invasive, LISA, MIST, SURE, INSURE, surfactant, intubation, extubation, respiratory distress, RDS bronchopulmonary dysplasia, BPD, preterm, premature, neonate, infant, newborn'. The main search algorithm was the following: '(minimally invasive OR less invasive OR LISA OR MIST OR SURE OR INSURE OR intubation OR extubation) AND surfactant AND (preterm OR premature OR neonate OR infant OR newborn)' (online supplemental appendix 1).

Study selection

First, the abstracts of all records identified by literature search were screened to assess for potential eligibility. Second, all articles that were considered to be in accordance with the predefined criteria were chosen. At the next stage, all full-text articles that included the outcomes of interest and did not meet any of the exclusion criteria were selected. Small case series (less than 10 patients), case reports, conference proceedings, posters and in vitro studies were excluded. No language or date restrictions were applied. The study selection process was performed independently by two authors (IB and GF) and any discrepancy was resolved through the consensus of all authors.

Outcomes of interest

The primary outcomes of interest were the following: mortality, need of MV and incidence of BPD. The secondary outcomes were the following: incidence of necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), pneumothorax, periventricular leukomalacia (PVL), patent ductus arteriosus (PDA) and need of repeat dose of surfactant. BPD was defined as oxygen requirement at 36 weeks' postmenstrual age⁶ or at 28 days of life for late preterm infants,²⁴ while NEC was staged according to the modified Bell's criteria.¹⁷ The Papile grading system was used for IVH,¹⁸ while cystic PVL was defined following the de Vries grading approach.¹⁹ PDA referred to haemodynamically significant lesions requiring medical or surgical therapy. Studies were excluded in case of significant deviations from the above definitions, aiming to limit the risk of misclassification bias.

Data extraction

The following study parameters were extracted: sample size, study design, eligibility criteria, method of surfactant administration, use of Magill forceps, premedication before the procedure, surfactant dose and use of nasal CPAP. The baseline patients' characteristics that were taken into consideration were gestational age, gender, ethnicity, birth weight, 5 min Apgar score, mode of delivery, antenatal administration of steroids, presence of chorioamnionitis, premature rupture of membranes and time from birth to surfactant administration. Data extraction was conducted by two investigators, and any possible conflicts were dissolved through their discussion.

Statistical analysis

Statistical analysis was performed in RV.3.6.3 ('netmeta' package²⁰). Statistical significance was defined as $p < 0.05$. The network meta-analysis nodes were specified to be the following: thin catheter administration, administration by laryngeal mask, nebulisation, pharyngeal instillation, InSurE and no surfactant

administration. A random-effects frequentist network meta-analytic model was implemented, which provided pool estimates of OR and 95% CIs by combining both direct and indirect evidences. Analysis was conducted based on the reported event counts of each study. Forest plots were constructed to visualise the estimated effect sized for all comparisons. In the network meta-analysis, it was assumed that the amount of heterogeneity was equal for all treatment comparisons. Heterogeneity was measured by calculating the between-study variance (τ^2) and its influence on the outcomes was evaluated by the 95% prediction intervals (PIs). The 95% PIs express the effects to be expected by a new study in the same population and were estimated according to the methodology proposed by IntHout *et al.*²¹ The 95% PIs provide a wider range than the 95% CI in the presence of heterogeneity and aim to provide a clinically interpretable estimate of what effects can be anticipated by future settings. Regarding the primary outcomes, treatments were ranked based on their estimated p scores, which ranged from 0 to 1, with higher values indicating better interventions.²² To assess the presence of publication bias, the symmetry of comparison-adjusted funnel plots was examined for evidence of small study effects.²³

The validity of the transitivity assumption was examined through the evaluation of distributions of possible confounding factors across different interventions.²⁵ The following potential confounders were assessed: gender, median gestational age, birth weight, 5 min Apgar score, mode of delivery, administration of antenatal steroids, chorioamnionitis, premature rupture of membranes (PROM) and time from birth to surfactant administration. The comparison of distributions was performed by the non-parametric median test. Missing data were handled by pairwise deletion aiming to exploit all the available information from the included studies. The network consistency was statistically evaluated globally with the design-by-treatment interaction test²⁶ and locally with the Separating Indirect from Direct Evidence (SIDE) splitting test,²⁷ provided that closed loops were present. Network meta-regression analysis was 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. The network meta-regression analysis was used as a tool to assess the possible interaction of these covariates with treatment effects aiming to examine whether they may act as effect modifiers. All covariates referred to study-level characteristics and were shared among non-control treatment arms. Treatment with InSurE was set as the control treatment for which the effect is considered a neutral and then β coefficients were introduced for the other nodes.²⁸ As a result, meta-regression was based on the following model:

$$\theta_{ik} = \mu_{ia} + \delta_{iak} + \beta x_i \quad (1)$$

with θ_{ik} is the effect of treatment k in study i , μ_{ia} is the baseline treatment effect of intervention a , δ_{iak} is the treatment effect of intervention k relative to the treatment a in study i and x_i is the covariate level observed for study i .

As a sensitivity analysis, studies including exclusively neonates with gestational age <28 weeks were separately pooled. Pairwise meta-analysis was solely performed for the comparison of thin catheter administration and InSurE since inadequate data were available for the remaining treatment arms.

Design-adjusted analysis

Subgroup analysis was performed by separately pooling the outcomes of RCTs and observational studies. Moreover, a design-adjusted analysis was performed to assess the influence

of the inclusion of non-randomised studies on the estimated outcomes. To achieve this, the amount of confidence placed on observational studies was reduced by dividing the variance of their mean effect by a factor w ($0 < w \leq 1$). The w values of 0.2, 0.5, 0.8 and 1 were used, with $w=1$ denoting naive pooling of randomised and non-randomised studies.²⁹

Quality assessment

The methodological quality of RCTs was appraised using the Cochrane Risk of Bias tool³⁰ and was categorised as low, high or unclear by judging the domains of random sequence generation, blinding, allocation concealment, incomplete outcome and selective reporting. Moreover, the risk of bias in observational studies was assessed with the Risk Of Bias In Non-Randomised Studies of Interventions (ROBINS-I) tool.³¹ Specifically, studies were evaluated to be at low, moderate, high or critical risk of bias concerning the domains of confounding, selection of participants, classification of interventions, deviation from intended intervention, missing data, measurement and reporting of the outcomes. In case of high risk of bias detection in at least a domain, the whole study was judged to be at high risk of bias.

The credibility of outcomes was evaluated following the Confidence In Network Meta-Analysis (CINeMA) approach,³² which is constructed on the context of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework and takes into consideration the possible presence of within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence. In particular, the risk of within-study bias was evaluated as low, uncertain or high depending on the ROBINS-I or Cochrane risk of bias assessments. The evaluation of reporting bias was performed by inspecting the symmetry of comparison-adjusted funnel plots, while the domain of indirectness took into account the similarity of the research question of studies with that of the meta-analysis. Both within-study bias and indirectness were evaluated based on the risk of the majority of the included studies. In order to test for imprecision, a range of equivalence was defined as OR from 0.9 to 1.1, since a 10% change in the incidence of the outcomes of interest was judged as clinically important, based on prior publication in the field.^{33 34} Heterogeneity was quantified by the 95% predictive intervals, while incoherence referred to the statistical analogue of intransitivity and was examined using the SIDE test.

RESULTS

Search strategy

The outcomes of the literature search are summarised in online supplemental appendix 1 (online supplemental figure 1). In particular, the search of literature databases combined with the 'snowball' method identified 1600 records, of which 1182 were screened after removal of duplicates. Subsequently, the majority of them was excluded for not meeting the predefined criteria and thus 43 articles were retrieved to assess for eligibility. Then, seven seven articles were excluded after reading the full-text. Specifically, four studies did not report the outcome of interest as two of them were descriptive epidemiological surveys^{35 36} and two studies aimed merely to describe minimally invasive techniques for surfactant administration.^{37 38} Moreover, one study evaluated exclusively the effects of sedation,³⁹ while another one assessed only intubated patients.⁴⁰ Finally, the study of Plavka *et al.*⁴¹ was excluded as it was a single-arm one since it did not contain a control group. As a result, the present meta-analysis was based on a cohort of 36 studies,^{12 14 42-75} comprising a total of 13 234 neonates.

Included studies

The baseline characteristics and methodological parameters of the included studies are summarised in online supplemental appendix 2 (online supplemental table 1). Overall, the analysis comprised 16 RCTs and 20 observational studies. The main reasons for patient's exclusion were major congenital abnormalities and need of intubation for resuscitation. The less or minimally invasive methods included the administration of surfactant via thin catheter (28 studies), laryngeal mask (5 studies), nebulisation (2 studies) and pharyngeal instillation (1 study). Premedication was used in seven studies and consisted of atropine alone or combined with fentanyl or ketamine. Thin catheter administration was performed with the aid of Magill forceps in 14 studies. Surfactant administration without endotracheal intubation was compared with the InSurE method in 32 studies and to conservative treatment without surfactant in 5 studies. The main patients' characteristics are summarised in table 1. The sample of neonates had a median gestational age of 29.6 weeks (IQR: 28.1–31) and birth weight of 1289 g (IQR: 1040.8–1622.5). Moreover, 77% of neonates were delivered by caesarean section, while antenatal corticosteroids were administered in 76.5% of cases. The majority of studies (47.2%) recruited patients from European countries, while 11 studies (30.6%) included patients from Asian regions, 4 (11.1%) from North America, 3 (8.3%) from Australia and 1 (2.8%) from Brazil. The direct comparisons among all interventions are depicted in network plots (figure 1 and online supplemental figure 2; online supplemental appendix 3).

Quality assessment

The outcomes of risk of bias evaluation are provided in online supplemental appendix 4 (online supplemental table 2, online supplemental figure 3). Specifically, the ROBINS-I tool indicated low risk of bias in 11 observational studies, moderate in 8 and high in 1 study. The main reasons for downgrading were concerns about potential confounding or selection bias, while risk of bias due to missing data and reporting of outcomes was unclear since the majority of studies provided inadequate information about missing parameters or had excluded them. In addition, few studies mentioned a board-approved protocol and none had a published one. On the contrary, the assessment of RCTs raised concerns of personnel blinding, as the majority of studies did not perform masking of interventions from care-providers. The overall risk of bias was judged to be low in the domains of randomisation, allocation concealment and reporting of outcomes.

Data analysis

The relative efficacy of interventions is illustrated in figure 2. Network meta-analysis was conducted in the outcomes of mortality (7 RCTs, 15 observational studies, 12 155 neonates), MV (14 RCTs, 13 observational studies, 5961 neonates), BPD (6 RCTs, 10 observational studies, 10 993 neonates), IVH (6 RCTs, 13 observational studies, 5364 neonates), pneumothorax (12 RCTs, 11 observational studies, 6043 neonates) and need of repeat surfactant dose (7 RCTs, 12 observational studies, 2953 neonates) while the outcomes of NEC (3 RCTs, 14 observational studies, 11 496 neonates), PDA (4 RCTs, 12 observational studies, 9024 neonates) and PVL (9 observational studies, 10 176 neonates) included only direct comparisons.

Thin catheter administration versus InSurE

For patients treated with InSurE, the median risk of mortality, MV and BPD was 7.8%, 42.1% and 10%, respectively. Compared

with InSurE, administration of surfactant via thin catheter was associated with significantly lower mortality (OR: 0.64, 95% CI: 0.54 to 0.76, moderate quality of evidence), need of mechanical ventilation (OR: 0.43, 95% CI: 0.29 to 0.63, moderate quality of evidence), incidence of BPD (OR: 0.57, 95% CI: 0.44 to 0.73, moderate quality of evidence), NEC (OR: 0.67, 95% CI: 0.41 to 0.93, low quality of evidence) and PVL (OR: 0.66, 95% CI: 0.53 to 0.82, moderate quality of evidence). As it is evident in table 2, the 95% PIs were significant in the outcomes of mortality, BPD, NEC and PVL, indicating that significant beneficial outcomes can be expected by the use of thin catheter administration by future studies in the field. Consequently, the administration of surfactant via thin catheters ranked as a better treatment than InSurE regarding the primary outcomes of mortality (p : 0.54 vs 0.15), need of mechanical ventilation (p : 0.84 vs 0.40) and BPD (p : 0.80 vs 0.31).

Alternative minimally invasive techniques

Thin catheter administration decreased the need of mechanical ventilation compared with no surfactant administration (OR: 0.21, 95% CI: 0.05 to 0.97, low quality of evidence) and led to lower incidence of pneumothorax when compared both with pharyngeal instillation (OR: 0.33, 95% CI: 0.13 to 0.94, moderate quality of evidence) and with no surfactant administration (OR: 0.28, 95% CI: 0.12 to 0.65, moderate quality of evidence).

No significant associations were estimated for administration for surfactant via laryngeal mask or nebulisation. Pharyngeal instillation of surfactant reduced mortality rates compared with no surfactant administration (OR: 0.55, 95% CI: 0.32 to 0.96, low quality of evidence) but did not affect the incidence of the remaining outcomes. Evidence concerning the endpoints of PDA and repeat surfactant dose was sparse, indicating no significant influence of surfactant administration.

Heterogeneity assessment

The results of 95% PI calculation are presented in table 2. Overall, the impact of interstudy heterogeneity was low, affecting mainly the outcome of mechanical ventilation regarding the comparisons of thin catheter administration with the InSurE and no surfactant administration. Meta-regression analysis indicated that the outcomes were not significantly influenced by study design (RCT or observational), sample size, type of surfactant and use of forceps during administration via thin catheter (online supplemental appendix 5, online supplemental table 3). In addition, analysis of neonates with gestational age <28 weeks indicated that thin catheter administration resulted in significantly lower mortality than the InSurE method (OR: 0.56, 95% CI: 0.46 to 0.67) (online supplemental appendix 6), online supplemental figure 4).

Observational studies

The separate analysis of observational studies indicated that, compared with InSurE, administration of surfactant via thin catheter was associated with significantly lower mortality (OR: 0.64, 95% CI: 0.53 to 0.76), need of mechanical ventilation (OR: 0.46, 95% CI: 0.24 to 0.88) and incidence of BPD (OR: 0.54, 95% CI: 0.43 to 0.68). Regarding secondary outcomes, the use of thin catheters was significantly associated with lower rates of NEC (OR: 0.77, 95% CI: 0.62 to 0.96) and PVL (OR: 0.65, 95% CI: 0.52 to 0.81) compared with InSurE. In addition, thin catheter administration was linked to significantly lower incidence of pneumothorax when compared both with

Table 1 Baseline patients' characteristics

Reference	Country	Intervention	Patients' no	Male gender (%)	GA (weeks)*	Max GA (weeks)	Birth weight (g)*	Apgar score (5 min)*	Caesarean section (%)	Antenatal steroids (%)	Time from birth to surfactant (h)*	Chorioamnionitis (%)	PROM (%)
Aguar <i>et al</i> ⁶³	Spain	Thin catheter InSurE	44 31	68 71	30.6 30.7	36	1516 1576	10 9	68 67	91 71	11.6 14.8	— —	— —
Attridge <i>et al</i> ⁶⁷	USA	Laryngeal mask No surfactant	13 13	62 54	32 33	35	2001 2130	8 9	77 38	54 46	— —	— —	— —
Bao <i>et al</i> ⁶⁶	China	Thin catheter InSurE	47 43	60 60	29.1 29.3	32	1034 1087	8.7 8.8	74 77	89 93	— —	— —	— —
Barbosa <i>et al</i> ⁶⁵	Brazil	Laryngeal mask InSurE	26 22	69 41	31 31	35	1515 1495	9 9	69 77	54 77	— —	— —	— —
Berggren <i>et al</i> ⁶⁴	Sweden	Nebulised No surfactant	16 16	38 31	31 31	33 34	1620 1603	9 9	94 81	81 85	— —	— —	— —
Bemeau <i>et al</i> ⁶²	France	Thin catheter InSurE	127 127	54 54	28.1 28.1	29.1	1045 1040	7 7	68 67	94 94	— —	17 17	— —
Bertini <i>et al</i> ⁶¹	Italy	Thin catheter InSurE	10 10	30 40	30.2 30.9	33	1399 1659	8.4 9	90 80	100 90	— —	— —	— —
Buyuktinyaki <i>et al</i> ⁶⁰	Turkey	Thin catheter InSurE	205 178	50 47	28.1 28	29	1041 1029	8 8	84 83	75 74	— —	24 19	39 31
Canals Candela <i>et al</i> ⁶⁹	Spain	Thin catheter InSurE	19 28	— —	30 32	34	1484 1690	8 9	— —	— —	— —	— —	— —
Dargaville <i>et al</i> ⁶⁸	Australia	Thin catheter No surfactant	291 162	58 58	31 31	32	1550 1540	8 9	54 50	77 63	— —	— —	— —
Göpel <i>et al</i> ⁶⁷	Germany	Thin catheter InSurE	1103 1103	53 53	28 28	32	985 1020	— —	— —	92 91	— —	— —	— —
Halim <i>et al</i> ⁶⁶	Pakistan	Thin catheter InSurE	50 50	56 62	33 33	34	1300 1400	— —	52 48	76 60	— —	— —	— —
Hanke <i>et al</i> ⁶⁵	Germany	Thin catheter InSurE	22 6	32 67	28.1 29.6	32	1140 1202	— —	95.6 100	68 83	— —	23 17	50 50
Härtel <i>et al</i> ⁶⁴	Germany	Thin catheter InSurE	2624 3695	54 55	26.8 26.2	28	885 814	8 7	91 87	93 88	— —	29 29	40 43
Márquez Isidro <i>et al</i> ⁶³	Spain	Thin catheter InSurE	30 30	40 60	28.4 29.1	32	1058 1232	— —	— —	73 70	11.4 11	13 17	— —
Jena <i>et al</i> ⁶¹	India	Thin catheter InSurE	175 175	52 44	31 31	34	1630 1683	9 9	60 69	61 63	1 1	— —	— —
Kanmaz <i>et al</i> ⁶⁴	Turkey	Thin catheter InSurE	100 100	60 52	28 28.3	32	1093 1121	7 7	75 83	73 81	— —	— —	32 21
Klebermass-Schnehof <i>et al</i> ⁶⁰	Austria	Thin catheter InSurE	224 182	50 49	25.3 25.4	27	768 804	8 8	84 61	95 88	— —	— —	61 43
Krajewski <i>et al</i> ⁶⁹	Poland	Thin catheter InSurE	26 60	39 45	29.5 29	—	1304 1250	7 7	— —	81 53	— —	— —	— —
Kribs <i>et al</i> ⁶²	Germany	Thin catheter InSurE	107 104	59 50	25.3 25.2	26	711 674	8 8	88 92	82 76	— —	— —	— —

Continued

Table 1 Continued

Langhammer <i>et al</i> ⁴⁸	Germany	Thin catheter InSurE	148	51	28	32	1030	8	90	92	—	—	—
Legge <i>et al</i> ⁴⁷	Australia	Thin catheter InSurE	148	51	28	—	1031	8	94	92	—	—	—
			170	56	29.6	—	1468	7	—	60	—	—	26
			160	54	29.5	—	1447	8	—	61	—	—	17
Li <i>et al</i> ⁴⁶	China	Thin catheter InSurE	22	59	29.5	32	1089	8	36	73	—	—	—
			22	50	29.3	—	1145	8	32	77	—	—	—
Minocchieri <i>et al</i> ⁴⁹	Australia	Nebulised InSurE	32	69	31.4	34	1562	8	81	97	—	—	—
			32	81	31.4	—	1645	8	72	91	—	—	—
Mimia <i>et al</i> ⁴⁵	Iran	Thin catheter InSurE	66	50	29.6	32	1339	8	73	67	—	—	30
			70	60	29.6	—	1304	7	70	63	—	—	27
Mohammadizadeh <i>et al</i> ⁴⁴	Iran	Thin catheter InSurE	19	53	30	34	1289	—	100	84	—	—	—
			19	58	31	—	1428	—	90	90	—	—	—
Olivier <i>et al</i> ⁴³	Canada	Thin catheter InSurE	23	42	34	36	2157	9	75	67	—	—	—
			21	71	33	—	2277	7	86	52	—	—	—
Pinheiro <i>et al</i> ⁴²	USA	Laryngeal mask InSurE	30	70	32	36	2118	—	60	50	—	—	—
			30	57	34	—	1945	—	73	53	—	—	—
Ramos-Navarro <i>et al</i> ⁷⁵	Spain	Thin catheter InSurE	280	—	26	32	1000	—	—	66	—	—	—
			232	—	27	—	1100	—	—	59	—	—	—
Roberts <i>et al</i> ⁷⁴	USA	Laryngeal mask No surfactant	50	60	32	36	1968	—	—	72	—	—	—
			53	66	32	—	1995	—	—	64	—	—	—
Sadeghnia <i>et al</i> ⁷³	Iran	Laryngeal mask InSurE	35	54	—	36	2352	9	86	51	—	—	74
			35	43	—	—	2374	8	77	66	—	—	71
Seo <i>et al</i> ⁷²	South Korea	Thin catheter InSurE	16	50	33.9	36	2272	9	81	44	4.9	13	6
			45	58	34.6	—	2331	9	80	31	7.7	4	11
Teig <i>et al</i> ⁷¹	Germany	Thin catheter InSurE	53	53	26.1	28	905	7	96	83	0.3	—	—
			44	64	26.2	—	901	7	86	84	0.3	—	—
Templin <i>et al</i> ⁷⁰	France	Thin catheter InSurE	21	44	30.4	26	775	7	52	100	0.4	44	42
			36	48	30.3	—	781	7	48	93	0.4	45	48
Ten Centre Study Group ⁵²	United Kingdom	Pharyngeal No surfactant	159	51	27.6	29	1093	—	58	—	—	—	23
			149	54	27.6	—	1070	—	62	—	—	—	19
Tomar <i>et al</i> ⁶³	India	Thin catheter InSurE	64	47	30.3	34	1085	8	64	73	0.9	—	—
			68	51	30.6	—	1120	7	66	65	0.8	—	—

*Median values.
GA, gestational age; InSurE, intubation, surfactant administration and extubation; PROM, premature rupture of membranes.

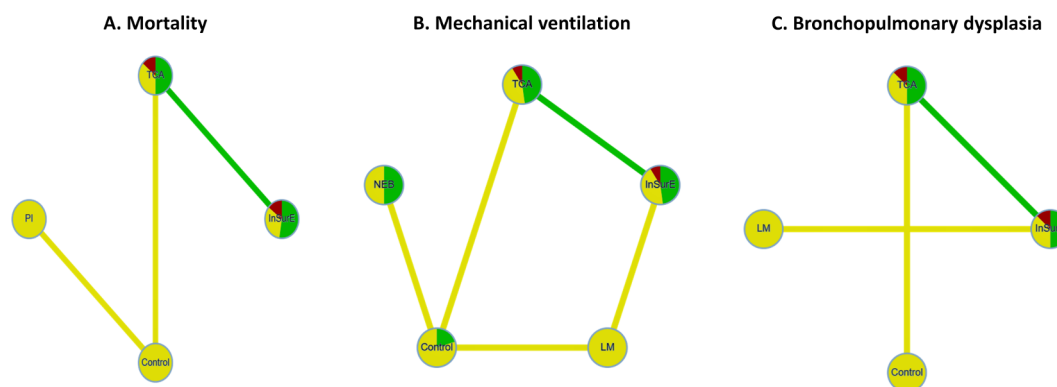


Figure 1 Network plots of the primary outcomes. The colours of circles are proportional to the risk of bias in studies including the treatment. Control refers to no surfactant administration. InSurE, intubation, surfactant administration, extubation; LM, laryngeal mask; NEB, nebulised; PI, pharyngeal instillation; TCA, thin catheter administration.

pharyngeal instillation (OR: 0.34, 95% CI: 0.13 to 0.90) and with no surfactant administration (OR: 0.29, 95% CI: 0.13 to 0.67). No significant differences were estimated between thin catheter administration and InSurE regarding IVH (OR: 0.84, 95% CI: 0.54 to 1.29), PDA (OR: 0.86, 95% CI: 0.50 to 1.49) and repeat surfactant dose (OR: 1.65, 95% CI: 0.77 to 3.53).

Randomised controlled trials

Pooling of RCTs demonstrated that thin catheter administration of surfactant led to significantly lower incidence of mechanical ventilation (OR: 0.39, 95% CI: 0.26 to 0.60) and a trend towards lower rates of mortality and BPD, although statistical significance was not reached (OR: 0.62, 95% CI: 0.36 to 1.06 and OR: 0.54, 95% CI: 0.29 to 1.01, respectively). No significant differences were noted for the remaining outcomes (online supplemental appendix 7, online supplemental table 4).

Design-adjusted analysis

Figure 3 depicts the comparison of thin catheter administration with InSurE regarding all outcomes informed by both RCTs and various levels of confidence placed on observational studies. It is evident that the outcomes of non-randomised studies corroborated those of RCTs and increased precision, leading to significant association in the outcomes of mortality and BPD. Concerning NEC, increasing values of w resulted in a significant result favouring thin catheter administration (OR: 0.62, 95% CI: 0.77 to 0.97, at $w=0.8$). No significant associations were noted for the remaining outcomes, irrespective of the confidence placed on non-randomised studies.

Transitivity assessment

No significant differences were noted concerning the distribution of potential confounding factors (gender, gestational age, birth weight, 5 min Apgar score, caesarean section, antenatal steroids, chorioamnionitis, PROM and time from birth to surfactant administration); hence, the transitivity assumption was not compromised (online supplemental appendix 8, online supplemental figures 5-13). Consistency was assessed in the networks of MV and pneumothorax due to the presence of closed loops. Specifically, no evidence of global inconsistency was observed by the design-by-treatment interaction test in the outcomes of both MV ($\chi^2=0.041$, $p=0.839$) and pneumothorax ($\chi^2=0.001$, $p=0.978$), while the SIDE-splitting test revealed no significant disagreement between direct and indirect comparisons, posing thus no challenge to the consistency assumption

(online supplemental appendix 9, online supplemental table 5). For the remaining outcomes, no closed loops were present and thus consistency could not be evaluated. Inspection of funnel plots did not reveal evidence of publication bias in the majority of outcomes, with the exception of IVH concerning the comparisons of surfactant administration via laryngeal mask or nebulisation (online supplemental appendix 10, online supplemental figures 14-16). However, it should be acknowledged that the extreme observed values may be also attributed to potential unmeasured confounding and network inconsistency.

Credibility of evidence

The results of CINeMA evaluation for the primary outcomes are depicted in figure 4. No concerns were raised in the domains of indirectness and reporting bias. Downgrading occurred mainly due to imprecision, as the estimated CIs were wide and extended towards the range of equivalence, as well as due to incoherence since the networks of mortality and BPD did not contain closed loops. Heterogeneity was low for most outcomes, except for the comparisons of thin catheter administration in the endpoint of MV, where disagreement of CIs and PIs was noted. Similarly, evaluation of secondary outcomes revealed low to moderate credibility of evidence, mainly due to concerns about imprecision and incoherence (online supplemental appendix 11, online supplemental table 6).

DISCUSSION

The administration of exogenous surfactant without endotracheal intubation is becoming widespread and different techniques are now available for neonatologists and neonatal proceduralists.⁷⁶ The results of the present network meta-analysis show that, among all methods for surfactant administration without endotracheal intubation, surfactant delivery via thin catheters shows the highest effectiveness in comparison with InSurE in terms of decrease of mortality, need of MV and BPD (figure 2). Furthermore, our results showed that thin catheter administration led to lower incidence of PVL and NEC, which confute the alarming findings reported by Härtel *et al*⁵⁴ regarding an increased risk of focal intestinal perforation in a subset of infants born at 23–24 weeks' GA receiving LISA. Moreover, thin catheter administration decreased the incidence of pneumothorax when compared both with pharyngeal instillation and with no surfactant administration, possibly as a consequence of a more even ventilation of the lungs. Indeed, in the past

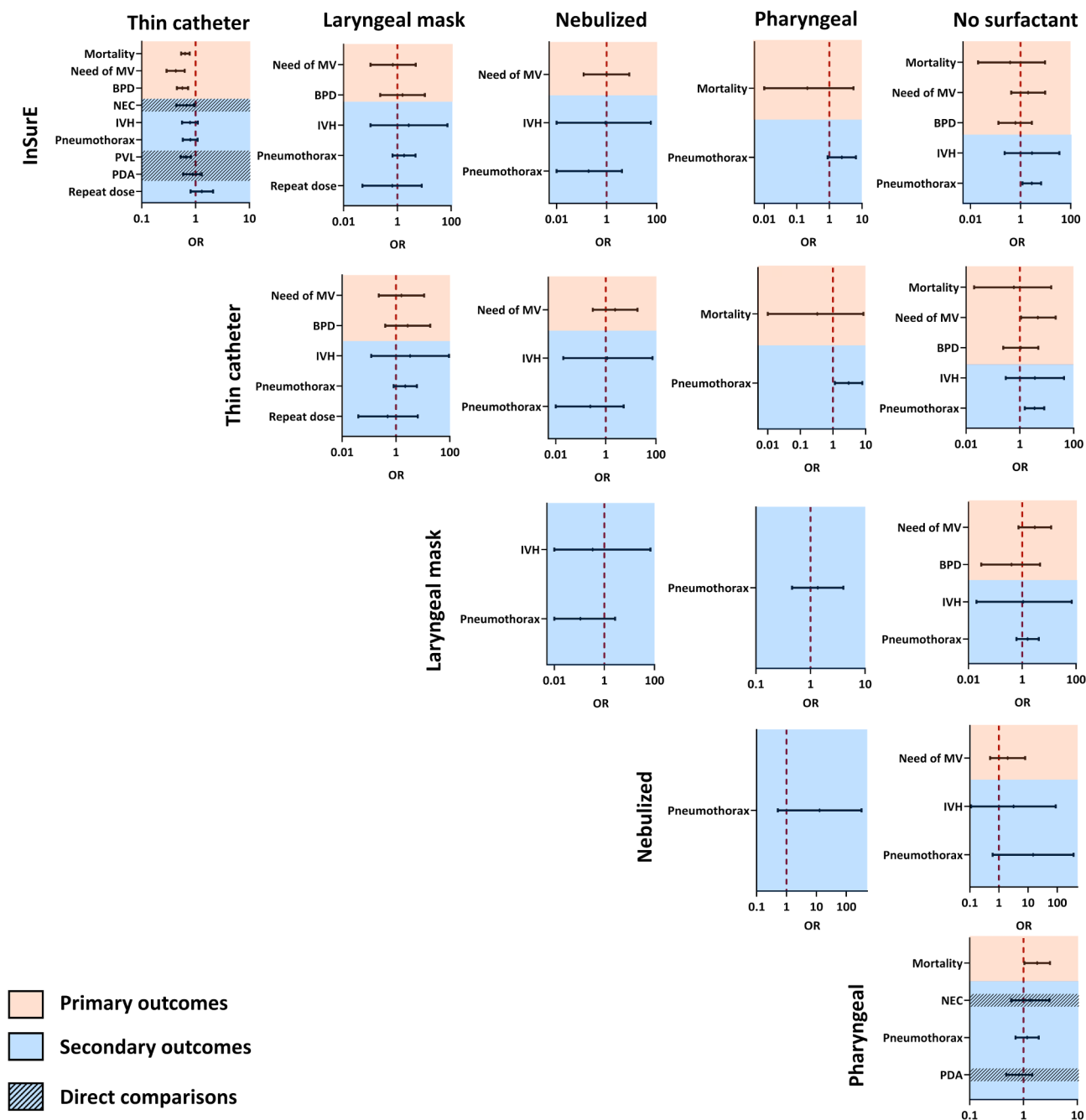


Figure 2 League table comparing the relative effects of interventions. ORs<1 favour the intervention of the row over the intervention of the column. BPD, bronchopulmonary dysplasia; InSurE, intubation, surfactant administration, extubation; IVH, intraventricular haemorrhage; MV, mechanical ventilation; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia.

years, a small-scale study implementing electrical impedance tomography in preterm neonates born at a mean gestational age of 29 weeks indicated that thin catheter administration was linked to a more uniform lung aeration than with intubation.⁷⁷ Our results also indicate that pharyngeal instillation of surfactant reduced mortality rates compared with no surfactant administration, although supporting evidence behind this finding is not robust and needs further investigation. Most notably, mortality was significantly decreased in the subgroup <28 weeks' GA treated with exogenous surfactant via thin catheter administration compared with InSurE (Appendix 6), showing that this technique may be successfully applied even in the most premature neonates.

The results of the present network meta-analysis confirm that exogenous surfactant administration via thin catheter is currently the most common alternative method applied worldwide, since only few studies have assessed laryngeal mask (five studies), nebulisation (two studies) and pharyngeal instillation (one study) so far. The shortage of studies regarding laryngeal mask is partly due to the lack of appropriate LMA sizes for the most premature babies, which still represent a challenge for the diffusion of this method of surfactant delivery in the population of infants that need it the most. As for pharyngeal instillation, the main drawback is the complexity of the procedure, which has to be performed before the neonate's first breath and requires the

Table 2 Summary of findings and heterogeneity assessment

Comparison	Mortality	Need of MV	BPD	NEC	IVH	Pneumothorax	PVL	PDA	Repeat dose
Thin catheter vs									
Laryngeal mask	—	0.63	0.37	—	0.30	0.45	—	—	2.03
95% CI	—	0.09 to 4.37	0.05 to 2.53	—	0.01 to 8.33	0.17 to 1.22	—	—	0.15 to 2.5
95% PI	—	0.05–8.40	0.04–3.26	—	0.01–11.90	0.15–1.31	—	—	0.07–55.56
Nebulised									
OR	—	0.43	—	—	0.88	4.26	—	—	—
95% CI	—	0.05 to 3.33	—	—	0.01 to 55.56	0.19 to 90.91	—	—	—
95% PI	—	0.03–6.23	—	—	0.01–83.33	0.15–125	—	—	—
Pharyngeal									
OR	3.02	—	—	—	—	0.33	—	—	—
95% CI	0.12 to 76.92	—	—	—	—	0.13 to 0.87*	—	—	—
95% PI	0.09–100	—	—	—	—	0.12–0.94*	—	—	—
InSurE									
OR	0.64	0.43	0.57	0.77	0.79	0.80	0.66	0.88	1.32
95% CI	0.54 to 0.76*	0.29 to 0.63*	0.44 to 0.73*	0.63 to 0.95*	0.56 to 1.10	0.58 to 1.09	0.53 to 0.82*	0.56 to 1.39	0.81 to 2.13
95% PI	0.51–0.80*	0.08–2.22	0.33–0.99*	0.62–0.97*	0.36–1.72	0.57–1.11	0.51–0.86*	0.17–4.55	0.19–9.09
No surfactant									
OR	1.68	0.21	0.93	—	0.28	0.28	—	—	N/A
95% CI	0.07 to 41.67	0.05 to 0.97*	0.21 to 4.18	—	0.02 to 3.33	0.12 to 0.65*	—	—	N/A
95% PI	0.05–52.63	0.02–2.04	0.16–5.24	—	0.02–4.52	0.11–0.70*	—	—	N/A
Laryngeal mask vs									
Nebulised									
OR	—	0.68	—	—	2.96	9.43	—	—	—
95% CI	—	0.10 to 4.85	—	—	0.01 to 613.6	0.37 to 238.4	—	—	—
95% PI	—	0.05–9.31	—	—	0.01–1020.5	0.29–305.2	—	—	—
Pharyngeal									
OR	—	—	—	—	—	0.74	—	—	—
95% CI	—	—	—	—	—	0.25 to 2.17	—	—	—
95% PI	—	—	—	—	—	0.23–2.36	—	—	—
InSurE									
OR	—	0.68	1.56	—	2.63	1.75	—	—	0.65
95% CI	—	0.10 to 4.76	0.23 to 10.00	—	0.10 to 100	0.66 to 8.33	—	—	0.05 to 8.33
95% PI	—	0.05–9.10	0.18–14.29	—	0.07–100	0.61–5.00	—	—	0.02–16.67
No surfactant									
OR	—	0.34	2.53	—	0.93	0.63	—	—	N/A
95% CI	—	0.08 to 1.37	0.22 to 29.28	—	0.01 to 58.82	0.24 to 1.65	—	—	N/A
95% PI	—	0.04–2.98	0.16–39.24	—	0.01–90.9	0.22–1.77	—	—	N/A
Nebulised vs									
Pharyngeal									
OR	—	—	—	—	—	0.08	—	—	—
95% CI	—	—	—	—	—	0.01 to 1.98	—	—	—
95% PI	—	—	—	—	—	0.01–2.54	—	—	—
InSurE									
OR	—	1.00	—	—	0.89	0.19	—	—	—
95% CI	—	0.12 to 8.07	—	—	0.01 to 50	0.01 to 4.00	—	—	—
95% PI	—	0.07–15.19	—	—	0.01–100	0.01–5.26	—	—	—
No surfactant									
OR	—	0.50	—	—	0.31	0.07	—	—	N/A
95% CI	—	0.13 to 1.99	—	—	0.01 to 10.0	0.01 to 1.63	—	—	N/A
95% PI	—	0.06–4.35	—	—	0.01–12.66	0.01–2.08	—	—	N/A
Pharyngeal vs									
InSurE									
OR	0.21	—	—	—	—	2.38	—	—	—
95% CI	0.01 to 5.56	—	—	—	—	0.88 to 6.67	—	—	—
95% PI	0.01–6.67	—	—	—	—	0.82–7.14	—	—	—

Continued

Table 2 Continued

No surfactant	OR	0.55	-	-	0.74	-	0.86	-	1.2	N/A
	95% CI	0.32 to 0.96*	-	-	0.33 to 1.7	-	0.52 to 1.41	-	0.69 to 2.1	N/A
	95% PI	0.31–1.01	-	-	N/A	-	0.50–1.46	-	N/A	N/A
InSurE vs										
No surfactant	OR	0.60	2.00	0.62	-	2.86	2.78	-	-	N/A
	95% CI	0.02 to 14.29	0.42 to 10	0.13 to 2.86	-	0.23 to 33.33	1.19 to 6.67*	-	-	N/A
	95% PI	0.02–20	0.20–20	0.11–3.57	-	0.17–50	1.11–7.14*	-	-	N/A

BPD, bronchopulmonary dysplasia; InSurE, intubation, surfactant administration, extubation; IVH, intraventricular haemorrhage; MV, mechanical ventilation; N/A, not applicable; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia.

collaboration of the mother or the obstetrician to briefly interrupt the delivery as soon as the baby's head appears on the perineum or at the operative incision. Nebulisation has faced great difficulties at the very beginning of its history for the ineffectiveness of the first devices.⁷⁸ However, the latest results obtained applying new miniature vibrating membrane nebulisers are more promising⁶⁹ and certainly deserve some interest in consideration of the fact that this method ideally permits to avoid intubation, PPV and discomfort of the neonate. On the contrary, the diffusion of the specific nebulisers on a large scale is likely to hamper a wide application of this technique, especially in low-income regions.

Such setbacks are counterbalanced by the procedural ease and feasibility of thin catheter techniques. Currently, there are no in vivo studies directly comparing various methods of catheter insertion or different types of catheter for surfactant administration. However, Rigo *et al*⁷⁹ recently conducted a simulation study based on video recordings of 20 neonatologists applying various instillation methods and catheter types intubation mannequin. Their results showed that tracheal catheterisation with a semirigid or stylet-guided catheter was successfully carried out at an equal time to ETT insertion, but was more rapid compared with a flexible tube, with and particularly without, the use of Magill forceps. Failure rates (7%–20%) were not different between methods, even though they resulted higher than for ETT insertion, for which no failed insertions were reported. Furthermore, regarding the subjective impressions of neonatologists, they indicated rigid or stylet-guided catheters as the simplest to use.⁸⁰

The present study has several methodological strengths. All the available evidences in the field were taken into account by systematically searching six literature databases. A network meta-analytic model was applied evaluating both direct and indirect comparisons. Heterogeneity was thoroughly assessed by conducting meta-regression analysis, while its impact was evaluated by the estimation of 95% PIs, indicating agreement with CIs in most comparisons. Specifically, meta-regression analysis demonstrated that the outcomes were not significantly affected by sample size, type of surfactant, use of premedication or forceps. The analysis of RCTs indicated significantly lower rates of MV for the thin catheter administration group, as well as a trend towards favourable outcomes concerning mortality and BPD, although the available evidence for these outcomes was limited to reach firm conclusions. The distributions of potential confounders were also compared across interventions, indicating no threats to the transitivity assumption. In addition, the credibility of evidence was judged by the CiNeMA approach, providing a realistic overview of the existing evidence in the field.

Nonetheless, we acknowledge some limitations to our study. First, confounders such as antenatal steroids, management in the delivery room, caffeine administration and timing, and different ventilation modalities have not been directly addressed in the present network meta-analysis. In addition, both randomised and non-randomised studies were pooled aiming to increase the available comparisons and achieve more precise results; however, the inclusion of non-balanced observational studies may increase the risk of confounding, threatening thus the transitivity assumption. The analysis was based on raw unadjusted data; however, the ROBINS-I evaluation indicated low to moderate risk of bias due to confounding in the majority of studies.

Second, the CiNeMA evaluation raised concerns of imprecision in the majority of outcomes, reflecting the wide estimated

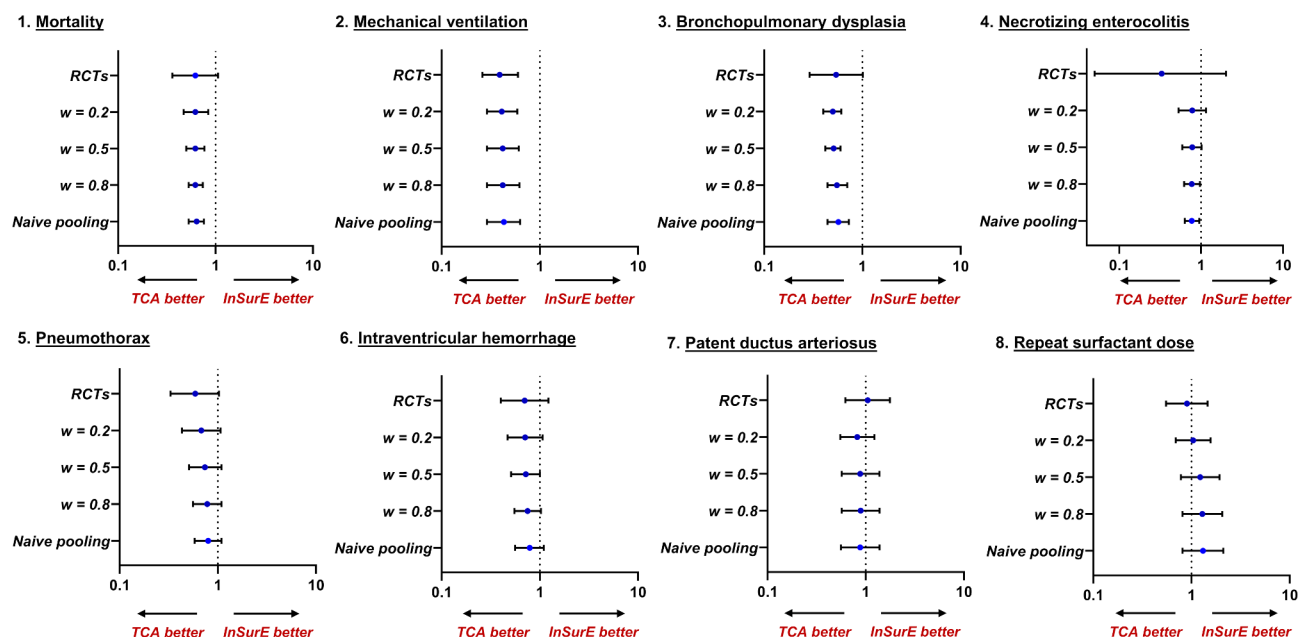


Figure 3 Outcomes of the design-adjusted analysis. increasing values of the parameter w give increasing weight to non-randomised evidence. InSurE, intubation, surfactant administration, extubation; RCT, randomised controlled trial; TCA, thin catheter administration.

	Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall quality
Mortality								
Mixed evidence	TCA vs. InSurE	Some concerns	Undetected	No concerns	No concerns	No concerns	Major concerns	Moderate
	TCA vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	Low
	PI vs. Control	Some concerns	Undetected	No concerns	No concerns	Some concerns	Major concerns	Low
Indirect evidence	InSurE vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	Low
	InSurE vs. PI	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	Low
	TCA vs. PI	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	Low
Need of mechanical ventilation								
Mixed evidence	TCA vs. InSurE	Some concerns	Undetected	No concerns	No concerns	Major concerns	No concerns	Moderate
	TCA vs. Control	Some concerns	Undetected	No concerns	No concerns	Major concerns	No concerns	Moderate
	InSurE vs. LM	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
	LM vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
	NEB vs. Control	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Indirect evidence	InSurE vs. NEB	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
	InSurE vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
	LM vs. NEB	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
	TCA vs. LM	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
	TCA vs. NEB	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Bronchopulmonary dysplasia								
Mixed evidence	TCA vs. InSurE	Some concerns	Undetected	No concerns	No concerns	No concerns	Major concerns	Moderate
	TCA vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	Low
	InSurE vs. LM	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	Low
Indirect evidence	InSurE vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	Low
	TCA vs. LM	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	Low
	LM vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	Low

Figure 4 Evaluation of the credibility of primary outcomes. InSurE, intubation, surfactant administration, extubation; LM, laryngeal mask; NEB, nebulised; PI, pharyngeal instillation; TCA, thin catheter administration.

95% CIs and PIs. This was true especially for the effects of alternative minimally invasive techniques and for secondary outcomes due to the limited number of the available studies resulting in ill-connected networks. Imprecision may complicate the interpretation of outcomes, limiting the ability to predict the treatment effects to be expected in clinical practice. However, it should be noted that low concerns of imprecision were assigned for the comparison of thin catheter administration and InSure regarding the primary outcomes of mortality, MV and BPD (figure 4).

Third, the lack of a stratification for GA may account for a bias in GA-related outcomes, such as mortality, BPD and IVH. A stratification for GA is desirable to make final findings more uniform, also in consideration of the fact that a recent practical guide has suggested different treatment thresholds according to GA.⁸¹ In a recent systematic review by Pandita *et al*, we found many similar benefits with surfactant delivery using thin catheters.⁸² The paucity of studies assessing LMA, nebulisation and pharyngeal instillation does not permit to draw final conclusions regarding the effectiveness of such methods that nowadays are still in the province of research. Moreover, the issue of sedation is not addressed in the present network meta-analysis, although it represents a relevant challenge to achieve the accomplishment of the procedure. Indeed, the use of premedication may enhance comfort of the neonate but, on the contrary, depress spontaneous breathing, which is crucial for the even dispersion of surfactant from the trachea to the lungs. Concerns may be different according to the gestational age, since coughing and reflux may be more problematic in near-term infants whereas the apnoea risk may be higher in immature neonates. Hence, gestational age should guide clinical choices regarding premedication or any means to provide comfort. Lastly, other open questions regard the effective transmission of CPAP to the lungs throughout the procedure and whether surfactant is actually evenly dispersed in the alveoli after the administration of exogenous surfactant without endotracheal intubation. Therefore, large RCTs answering all these questions are required before drawing final conclusions.

CONCLUSION

The delivery of exogenous surfactant by means of thin catheters has become a widespread reality in the last decades. Conversely, other alternative techniques (ie, LMA, nebulisation and pharyngeal instillation) lay still in the province of research and are not extensively employed in clinical practice. Despite the growing interest in the administration of surfactant without ETT, nowadays studies comparing thin catheter administration, LMA, nebulisation and pharyngeal instillation between them are still lacking. To the best of our knowledge, the present network meta-analysis provides a comprehensive review of current evidence and adds an indirect comparison between all these methods. Our results support the delivery of surfactant via thin catheters, since this technique has proven feasible and effective in reducing MV, BPD and mortality also in the most immature infants. Future RCTs comparing surfactant administration through thin catheter, nebulisation, laryngeal mask or pharyngeal instillation are needed to reach conclusions about whether thin catheter approach is really advantageous over the other techniques. Furthermore, evaluation of the risk to benefit ratio linking the administration of premedication prior to thin catheter surfactant delivery requires further investigation, including data on long-term neurodevelopmental outcomes.

Further open questions are:

- The clinical benefits of surfactant administration via thin catheter versus CPAP alone, which is being assessed in the OPTIMIST trial⁸³
- The reproducibility of results in infants supported with other means of NIV (eg, high-flow therapy, nasal high-frequency oscillatory ventilation);
- Methods for determining the correct position of the catheter in the trachea;
- The usefulness of video laryngoscopy during the procedure.

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