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.

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.

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 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 H_2O and requires Fio_2 >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).

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 age[6] 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' package[20]). 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 test[26] 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 the 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 ($0<w\leq1$). 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 tool[30] 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 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 *et al*[68]	Spain	Thin catheter	44	68	30.6	36	1516	10	68	91	11.6	–	–
		InSurE	31	71	30.7		1576	9	67	71	14.8	–	–
Attridge *et al*[67]	USA	Laryngeal mask	13	62	32	35	2001	8	77	54	–	–	–
		No surfactant	13	54	33		2130	9	38	46	–	–	–
Bao *et al*[66]	China	Thin catheter	47	60	29.1	32	1034	8.7	74	89	–	–	–
		InSurE	43	60	29.3		1087	8.8	77	93	–	–	–
Barbosa *et al*[65]	Brazil	Laryngeal mask	26	69	31	35	1515	9	69	54	–	–	–
		InSurE	22	41	31		1495	9	77	77	–	–	–
Berggren *et al*[64]	Sweden	Nebulised	16	38	31	33	1620	9	94	81	–	–	–
		No surfactant	16	31	31	34	1603	9	81	85	–	–	–
Berneau *et al*[62]	France	Thin catheter	127	54	28.1	29.1	1045	7	68	94	–	17	–
		InSurE	127	54	28.1		1040	7	67	94	–	17	–
Bertini *et al*[61]	Italy	Thin catheter	10	30	30.2	33	1399	8.4	90	100	–	–	–
		InSurE	10	40	30.9		1659	9	80	90	–	–	–
Buyuktiryaki *et al*[60]	Turkey	Thin catheter	205	50	28.1	29	1041	8	84	75	–	24	39
		InSurE	178	47	28		1029	8	83	74	–	19	31
Canals Candela *et al*[59]	Spain	Thin catheter	19	–	30	34	1484	8	–	–	–	–	–
		InSurE	28	–	32		1690	9	–	–	–	–	–
Dargaville *et al*[58]	Australia	Thin catheter	291	58	31	32	1550	8	54	77	–	–	–
		No surfactant	162	58	31		1540	9	50	63	–	–	–
Göpel *et al*[57]	Germany	Thin catheter	1103	53	28	32	985	–	–	92	–	–	–
		InSurE	1103	53	28		1020	–	–	91	–	–	–
Halim *et al*[56]	Pakistan	Thin catheter	50	56	33	34	1300	–	52	76	–	–	–
		InSurE	50	62	33		1400	–	48	60	–	–	–
Hanke *et al*[55]	Germany	Thin catheter	22	32	28.1	32	1140	–	95.6	68	–	23	50
		InSurE	6	67	29.6		1202	–	100	83	–	17	50
Härtel *et al*[54]	Germany	Thin catheter	2624	54	26.8	28	885	8	91	93	–	29	40
		InSurE	3695	55	26.2		814	7	87	88	–	29	43
Márquez Isidro *et al*[53]	Spain	Thin catheter	30	40	28.4	32	1058	–	–	73	11.4	13	–
		InSurE	30	60	29.1		1232	–	–	70	11	17	–
Jena *et al*[51]	India	Thin catheter	175	52	31	34	1630	9	60	61	1	–	–
		InSurE	175	44	31		1683	9	69	63	1	–	–
Kanmaz *et al*[14]	Turkey	Thin catheter	100	60	28	32	1093	7	75	73	–	–	32
		InSurE	100	52	28.3		1121	7	83	81	–	–	21
Klebermass-Schrehof *et al*[50]	Austria	Thin catheter	224	50	25.3	27	768	8	84	95	–	–	61
		InSurE	182	49	25.4		804	8	61	88	–	–	43
Krajewski *et al*[49]	Poland	Thin catheter	26	39	29.5	–	1304	7	–	81	–	–	–
		InSurE	60	45	29		1250	7	–	53	–	–	–
Kribs *et al*[12]	Germany	Thin catheter	107	59	25.3	26	711	8	88	82	–	–	–
		InSurE	104	50	25.2		674	8	92	76	–	–	–

Continued

Table 1 Continued

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

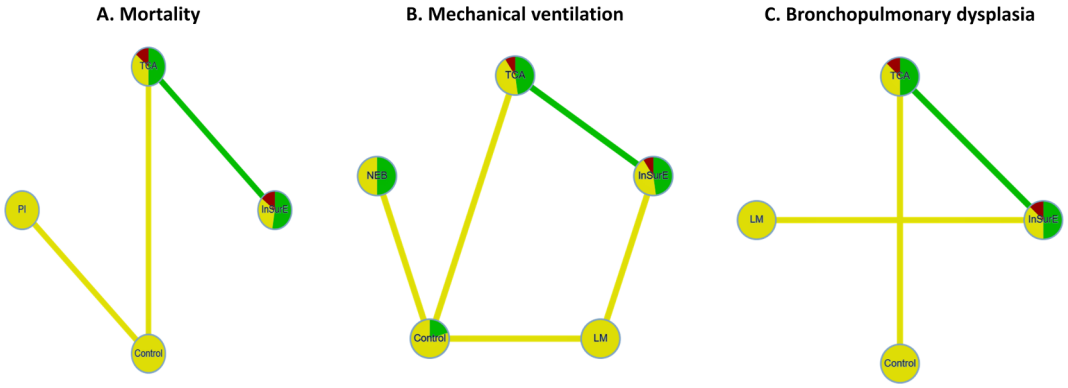

Figure 1 Network plots of the primary outcomes. The colours of circles are proportional to the risk of bias in studies including the treatment. Control refers to no surfactant administration. InSurE, intubation, surfactant administration, extubation; LM, laryngeal mask; NEB, nebulised; PI, pharyngeal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

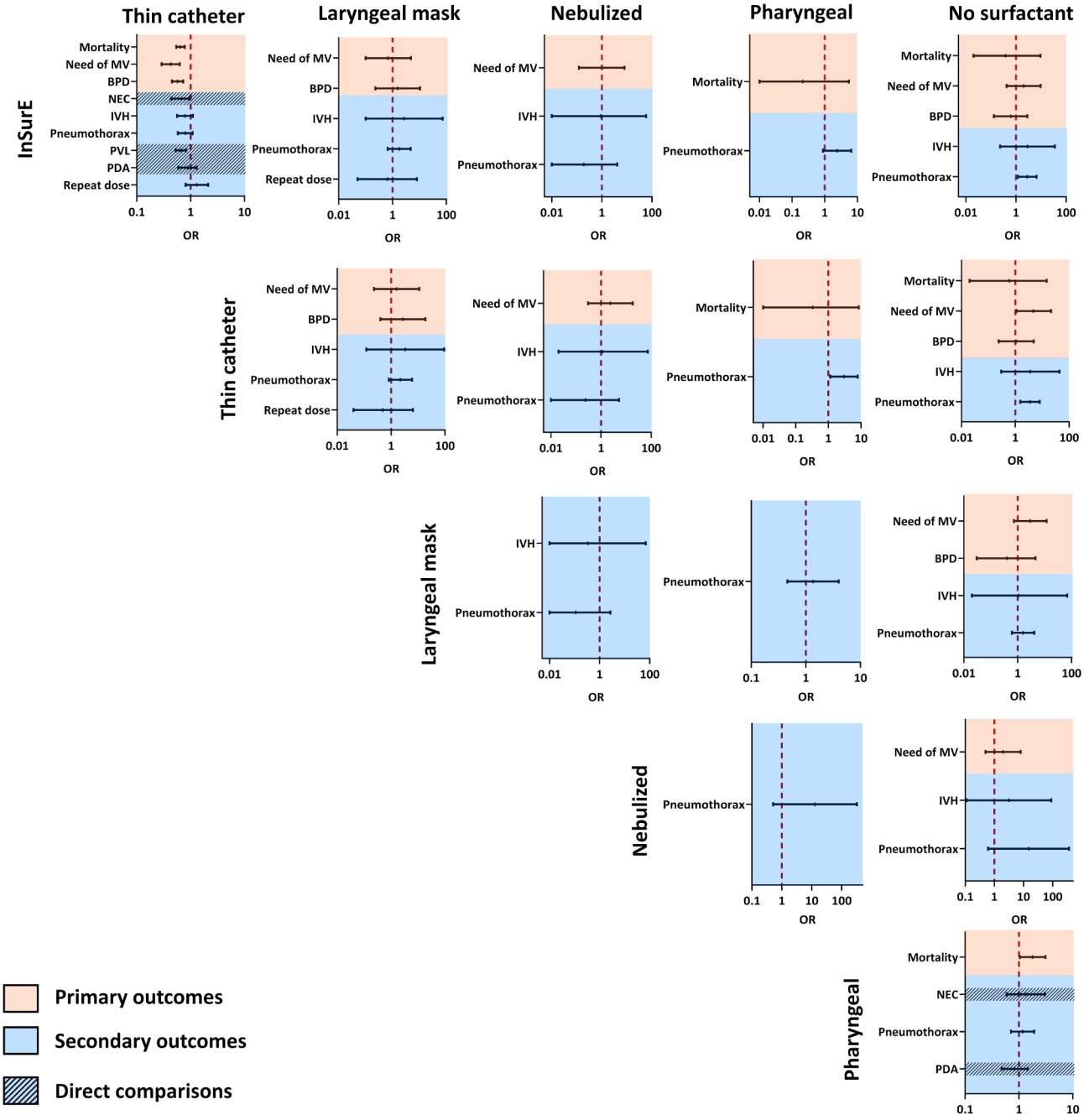

Figure 2 League table comparing the relative effects of interventions. ORs<1 favour the intervention of the row over the intervention of the column. BPD, bronchopulmonary dysplasia; InSurE, intubation, surfactant administration, extubation; IVH, intraventricular haemorrhage; MV, mechanical ventilation; 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	OR	–	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 25
	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 8.85	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 promising[69] 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. Firs, 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

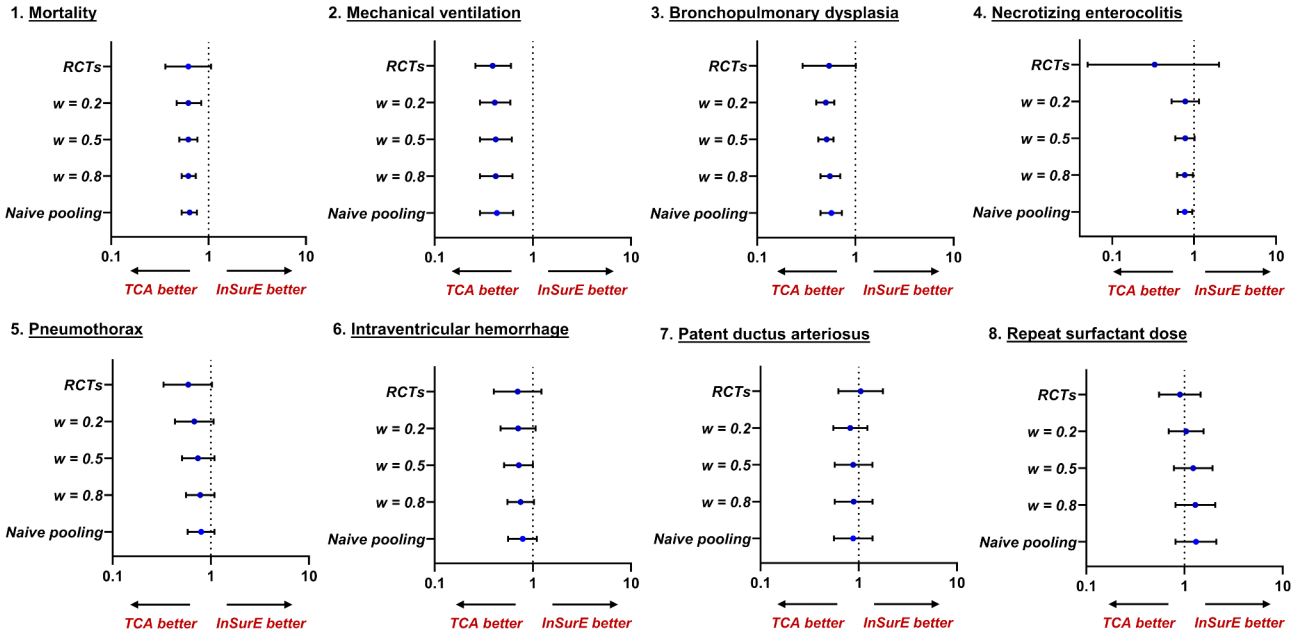

Figure 3 Outcomes of the design-adjusted analysis. increasing values of the parameter *w* give increasing weight to non-randomised evidence. InSurE, intubation, surfactant administration, extubation; RCT, randomised controlled trial; TCA, thin catheter administration.

	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 trial[83]
- 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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Supplementary Appendix

Contents

Appendix 1: Search strategy

MEDLINE: 802 articles

Scopus: 226 articles

Web of Science: 398 articles

Clinicaltrials.gov: 121 articles

CENTRAL: 47 articles

Additional sources (Google Scholar/snowball method): 6 articles

Total: 1,600 articles

Duplicates: 418 articles

Screened: 1,182 articles

Retrieved in full-text: 43 studies

Excluded with reasons: 7 studies

Included in the qualitative and quantitative synthesis: 36 studies

Intervention:

-Thin catheter administration: 28 studies

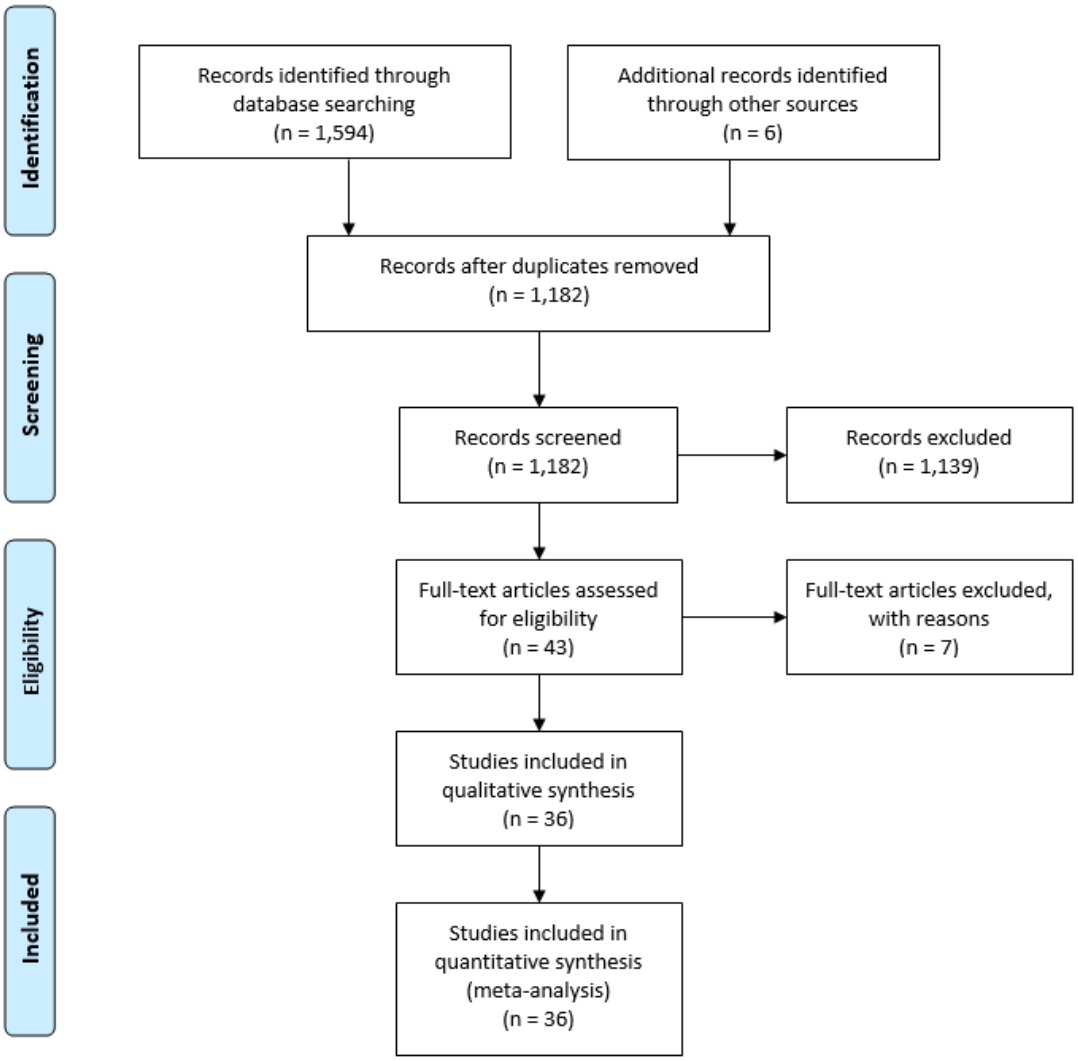
-Laryngeal mask: 5 studies

-Nebulization: 2 studies

-InSurE: 32 studies

-Pharyngeal instillation: 1 study

-No surfactant: 5 studies



Suppl. Figure 1. Search plot diagram

Appendix 2: Study characteristics

Year; Author	Study design	Inclusion criteria	Exclusion criteria	Method of SURE	Use of forceps	Pre-medication	Surfactant dose	Use of nCPAP	Comparator	Outcomes of interest
2019; Minocchieri	RCT	•Gestational age: 29-34 weeks •RDS diagnosis	•Major congenital abnormalities •Cardiopulmonary failure •History of intubation or surfactant •Pneumothorax at enrollment	Nebulization	NA	No	Curosurf®, 200 mg/kg	Yes	InSurE	•MV within 72h •BPD •Pneumothorax •IVH grade III/IV
2019; Legge	RC	•Birth weight >500 g •Gestational age >24 weeks •RDS diagnosis	•Major congenital abnormalities	Thin catheter	NR	NR	NR	Yes	InSurE	•Mortality •Pneumothorax • IVH grade >II •NEC •hs-PDA
2019; Jena	RCT	•Gestational age ≤34 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 6F nasogastric tube or 16G Angiocath	No	No	Neosurf®, 5 ml/kg	Yes	InSurE	•Mortality •MV within 72h •BPD •Pneumothorax •IVH grade ≥II •NEC stage ≥2 •hs-PDA
2019; Isidro	RC	•Gestational age <32 weeks •RDS diagnosis	•Need of intubation for resuscitation	Thin catheter	NR	NR	Survanta®, 100 mg/kg	Yes	InSurE	•Mortality •MV within 72h •NEC •hs-PDA •Repeat dose
2019; Hanke	PC	•Gestational age: 26-32 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter	Yes	No	Curosurf®, 100 mg/kg	Yes	InSurE	•Repeat dose
2019; Halim	RCT	•Gestational age ≤34 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 6F nasogastric tube	No	No	Survanta®, 100 mg/kg	Yes	InSurE	•Mortality •MV •Pneumothorax •hs-PDA
2019; Buyuktiryaki	RC	•Gestational age: 25-29 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 5F nasogastric tube	No	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV within 72h •BPD at 36w Pneumothorax •IVH grade >II •NEC stage ≥2 •PVL •hs-PDA •Repeat dose
2019; Berneau	RC	•Gestational age <30 weeks	•Major congenital abnormalities	Thin catheter/ 4F suction catheter	Yes	Atropine/ Ketamine	200 mg/kg	Yes	InSurE	•Mortality •MV within 72h •BPD at 36w •Pneumothorax •PVL •Repeat dose
2018; Seo	RC	•Gestational age >30 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 4-5F nasogastric tube	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•MV •BPD at 36w •Pneumothorax

										•IVH grade ≥II •NEC stage ≥2 •hs-PDA •Repeat dose
2018; Ramos-Navarro	PC	•Gestational age <32 weeks •RDS diagnosis	•No surfactant administration	Thin catheter/ 5F nasogastric tube	No	No	Survanta®, 200 mg/kg	Yes	InSurE	•Repeat dose
2018; Langhammer	Cross-sectional	•Birth weight <1500 g	•No surfactant administration	Thin catheter/ nasogastric tube	Yes	No	Curosurf® or Survanta®	Yes	InSurE	•MV •BPD at 36w •Pneumothorax •IVH grade >II •PVL •NEC stage ≥2 •hs-PDA
2018; Hartel	PC	•Birth weight <1500 g •Gestational age: 22-29 weeks	•Major congenital abnormalities	Thin catheter/ 5F nasogastric tube	NR	No	Curosurf®, 100 mg/kg	Yes	InSurE	•Mortality •BPD at 36w •IVH grade ≥II •NEC stage≥2 •PVL •hs-PDA
2018; Dargaville	RC	•Gestational age: 29-32 weeks •RDS diagnosis	•Major congenital abnormalities •PPROM ≥14 days	Thin catheter	NR	NR	Curosurf®,100 - 200 mg/kg	Yes	No surfactant	•Mortality •MV •BPD at 36w •Pneumothorax •IVH grade >II
2017; Tomar	PC	•Gestational age: 24-34 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 5F nasogastric tube	No	No	Survanta®, 100 mg/kg	Yes	InSurE	•Mortality •BPD at 36w •Pneumothorax •IVH •NEC stage ≥2 •PDA •Repeat dose
2017; Templin	PC	•Gestational age: 24-26 weeks •RDS diagnosis	•Major congenital abnormalities	Thin catheter/ 5F suction catheter	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV •BPD at 36w •Pneumothorax •IVH grade >II •NEC stage ≥2 •PVL •hs-PDA •Repeat dose
2017; Roberts	RCT	•Gestational age: 28-36 weeks •Birth weight >1250 g •RDS diagnosis	•Major congenital abnormalities •5-minute Apgar score <5 •History of intubation or surfactant	Laryngeal mask	NA	Atropine, sucrose	Curosurf®, 200 mg/kg	Yes	No surfactant	•Mortality •MV •Pneumothorax •IVH grade >II •PVL •Repeat dose
2017; Olivier	RCT	•Gestational age: 32-37 weeks •RDS diagnosis	•Major congenital abnormalities •History of intubation •Pneumothorax at enrollment	Thin catheter/ 5F nasogastric tube	Yes	Atropine/ Fentanyl	Survanta®, 100 mg/kg	Yes	InSurE	•MV •Pneumothorax •Repeat dose

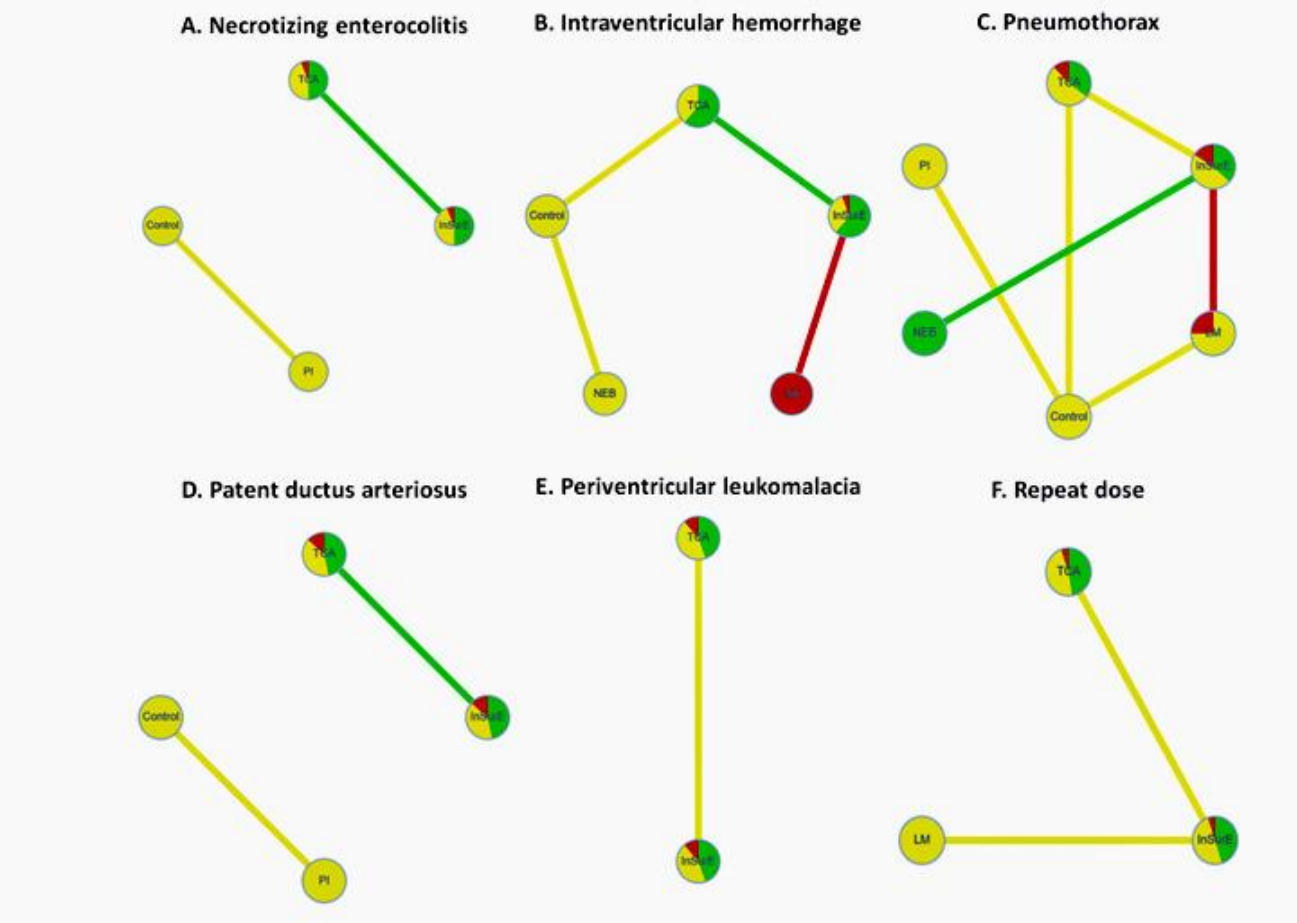
2017; Bertini	PC	•Gestational age ≤33 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 5F nasogastric tube	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV •BPD •IVH grade >II
2017; Barbosa	RCT	•Birth weight >1000 g •Gestational age: 28-35 weeks •RDS diagnosis	•Major congenital abnormalities •History of intubation •5-minute Apgar score <3 •History of chorioamnionitis •Fever/rupture of membranes >18 h	Laryngeal mask	NR	No	Curosurf®, 200 mg/kg	Yes	InSurE	•MV within 72h •Pneumothorax •IVH •Repeat dose
2016; Li	RC	•Gestational age: 27-32 weeks •RDS diagnosis	•Major congenital abnormalities •Perinatal asphyxia	Thin catheter/ 4F nasogastric tube	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •BPD •IVH •NEC •PVL
2016; Canals Candela	RC	•Gestational age <34 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ Angiocath	No	No	Curosurf®, 200 mg/kg	Yes	InSurE	•MV within 72h
2015; Teig	RC	•Gestational age <29 weeks •RDS diagnosis	•Major congenital abnormalities	Thin catheter/ 4F suction catheter	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV •hs-PDA •Repeat dose
2015; Pinheiro	RCT	•Gestational age: 29-37 weeks •RDS diagnosis	•Major congenital abnormalities •5-minute Apgar score ≤3 •History of intubation or surfactant •Birth weight <1000 g •Severe RDS	Laryngeal mask	NA	Atropine	Infasurf®, 3 ml/kg	Yes	InSurE	•Mortality •BPD at 36w •Pneumothorax
2015; Mohammadizadeh	RCT	•Birth weight: 1000-1800 g •Gestational age ≤34 weeks •RDS diagnosis	•Major congenital abnormalities •5-minute Apgar score ≤4 •History of chorioamnionitis •Need of intubation for resuscitation	Thin catheter/ 4F nasogastric tube	No	Atropine	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV within 72h •IVH •Repeat dose
2015; Kribs	RCT	•Gestational age: 23-26 weeks •RDS diagnosis	•Major congenital abnormalities •Cardiopulmonary failure	Thin catheter/ 4F nasogastric tube	Yes	No	Curosurf®, 100 mg/kg	Yes	InSurE	•Mortality •MV •BPD at 36w •Pneumothorax •IVH grade >II •NEC stage >2 •PVL •hs-PDA
2015; Göpel	PC	•Birth weight <1500 g •Gestational age <32 weeks	•Need of intubation for resuscitation	Thin catheter/ nasogastric tube	Yes	No	Curosurf®, 100 mg/kg	Yes	InSurE	•Mortality •MV •BPD at 36w •Pneumothorax •IVH grade >II •PVL •NEC stage >2
2015; Bao	RCT	•Gestational age: 28-32 weeks •RDS diagnosis	•Major congenital abnormalities •History of intubation	Thin catheter/ 16G Angiocath	No	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV within 72h •BPD at 36w •Pneumothorax •Repeat dose

2014; Krajewski	RC	•Gestational age <36 weeks •RDS diagnosis	•Need of intubation for resuscitation	Thin catheter/ 4F nasogastric tube	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV •BPD •IVH grade ≥II •NEC •PDA
2014; Aguar	PC	•Gestational age: 24-35 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 6F nasogastric tube	Yes	Atropine	Curosurf®, 100 mg/kg	Yes	InSurE	•Mortality •MV •BPD •IVH grade >II •NEC •PDA •Repeat dose
2013; Sadeghnia	RCT	•RDS diagnosis	•Major congenital abnormalities •Perinatal asphyxia	Laryngeal mask	NA	No	Survanta®, 100 mg/kg	Yes	InSurE	•MV •Pneumothorax •Repeat dose
2013; Mirnia	RCT	•Gestational age: 27-32 weeks •RDS diagnosis	•Major congenital abnormalities •5-minute Apgar score <6	Thin catheter/ 5F nasogastric tube	No	Atropine	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV •BPD at 36w •Pneumothorax •IVH grade ≥II •NEC stage ≥2 •PDA •Repeat dose
2013; Klebermass-Schrehof	RC	•Gestational age: 23-27 weeks •RDS diagnosis	•Need of intubation for resuscitation	Thin catheter/ 4F nasogastric tube	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV •Pneumothorax •IVH grade >II •NEC stage ≥2 •PVL •hs-PDA •Repeat dose
2013; Kanmaz	RCT	•Gestational age ≤34 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 5F nasogastric tube	No	No	Curosurf®, 100 mg/kg	Yes	InSurE	•MV •BPD at 36w •Pneumothorax •Repeat dose
2013; Attridge	RCT	•RDS diagnosis •Birth weight >1200 g	•Major congenital abnormalities •History of intubation or surfactant •Pneumothorax at enrollment	Laryngeal mask	N/A	No	Infasurf®, 3 ml/kg	Yes	No surfactant	•MV •Pneumothorax
2000; Berggren	RCT	•Gestational age <36 weeks •RDS diagnosis	•Major congenital abnormalities •a/A p_aO_2 <15	Nebulization	NA	No	480 mg	Yes	No surfactant	•MV •IVH
1987; Ten Centre Study Group	RCT	•Gestational age: 25-29 weeks •RDS diagnosis	•Major congenital abnormalities	Pharyngeal instillation	NA	No	100 mg	No	No surfactant	•Mortality •Pneumothorax •NEC •PDA

Suppl. Table 1. Methodological characteristics of the included studies. *nCPAP: nasal continuous positive airway pressure; NEC: necrotizing enterocolitis; PVL: periventricular leukomalacia; BPD: bronchopulmonary dysplasia; hs-PDA: hemodynamically significant patent ductus arteriosus; InSurE:*

intubation, surfactant administration and extubation; IVH: intraventricular hemorrhage; MV: mechanical ventilation; NA: not applicable; NR: not reported; PC: prospective cohort; PROM: premature rupture of membranes; RC: retrospective cohort; RCT: randomized controlled trial; RDS: respiratory distress syndrome; SURE: surfactant administration without extubation;

Appendix 3: Network plots

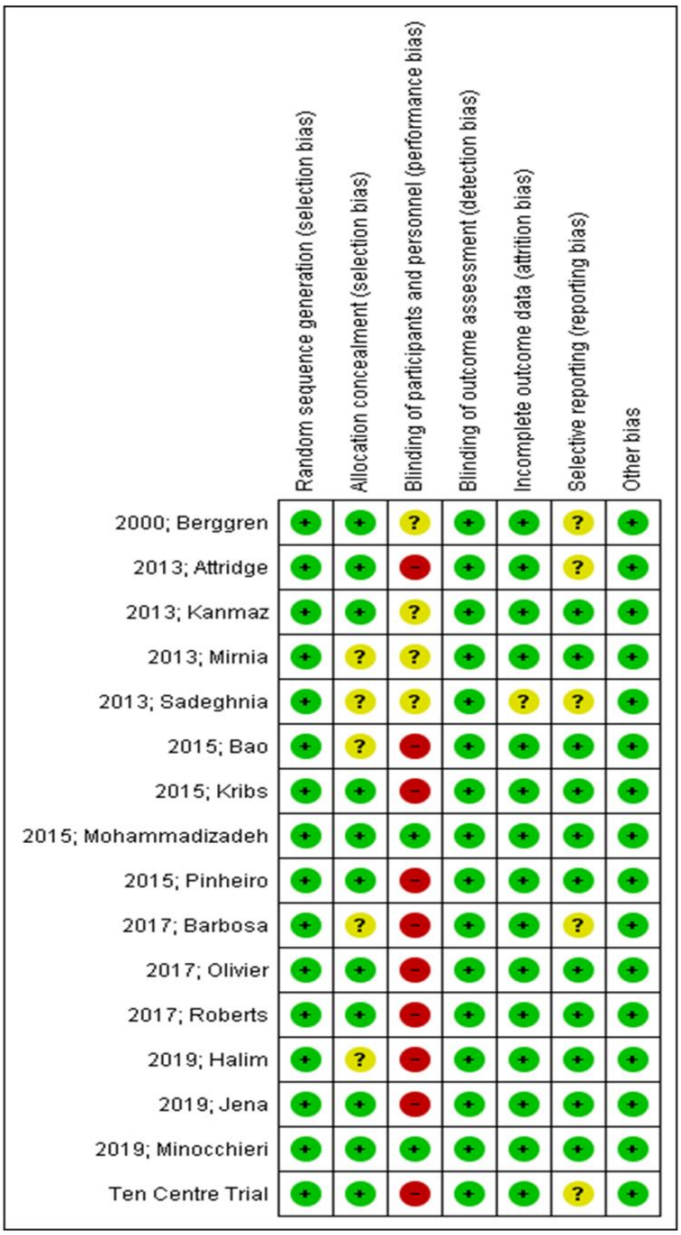


Suppl. Figure 2. Network plots of the secondary outcomes.

The colors 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: nebulized; PI: pharyngeal instillation; TCA: thin catheter administration

Appendix 4: Risk of bias evaluation



Suppl. Figure 3. Quality assessment of randomized controlled trials.

Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool								
Year; Author	***Bias due to confounding***	***Bias in selection of participants into the study***	***Bias in classification of interventions***	***Bias due to deviations from intended interventions***	***Bias due to missing data***	***Bias in measurement of outcomes***	***Bias in selection of the reported result***	***Overall bias***
2019; Legge	**Moderate**	**Low**	**Low**	**NI**	**Low**	**Low**	**Low**	**Moderate**
2019; Isidro	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**	**Low**	**Low**
2019; Hanke	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**	**NI**	**Moderate**
2019; Buyuktiryaki	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**	**Low**	**Low**
2019; Berneau	**Low**	**Low**	**Low**	**Moderate**	**Low**	**Low**	**Low**	**Moderate**
2018; Seo	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**
2018; Ramos-Navarro	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**	**NI**	**Moderate**
2018; Langhammer	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
2018; Hartel	**High**	**Low**	**Low**	**Low**	**Low**	**Low**	**NI**	**High**
2018; Dargaville	**Moderate**	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**	**Moderate**
2017; Tomar	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**	**Low**	**Low**
2017; Templin	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
2017; Bertini	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**
2016; Li	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**
2016; Canals Candela	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**	**Low**	**Low**
2015; Teig	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Moderate**
2015; Göpel	**Low**	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**	**Moderate**
2014; Krajewski	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
2014; Aguar	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
2013; Klebermass-Schrehof	**Moderate**	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**	**Moderate**

Suppl. Table 2. Quality assessment of observational studies.
NI: no information

Appendix 5: Meta-regression analysis

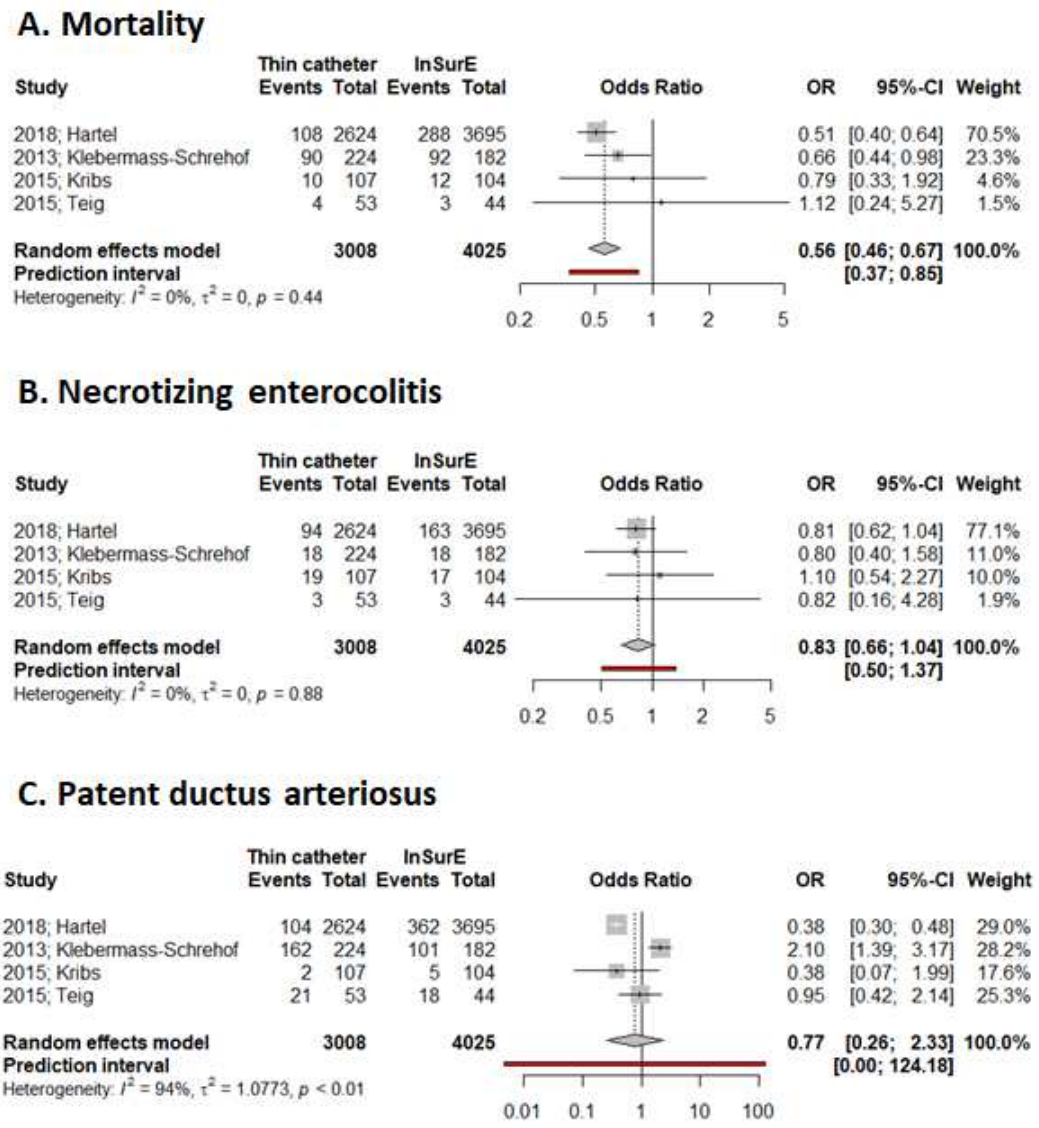
Comparison	RCT	Sample size	Type of surfactant	Premedication	Use of forceps
Mortality	-0.196 (-0.859 to 0.366)	0.459 (-0.288 to 1.200)	-0.094 (-0.805 to 0.615)	-0.275 (-1.018 to 0.327)	0.088 (-0.536 to 0.823)
Need of MV	-0.339 (-1.594 to 0.817)	0.484 (-0.674 to 1.713)	-0.747 (-2.451 to 0.983)	0.404 (-0.901 to 1.637)	-0.523 (-1.741 to 0.789)
BPD	-0.145 (-0.907 to 0.604)	0.673 (-0.112 to 1.464)	-0.525 (-2.975 to 1.303)	0.778 (-0.081 to 1.628)	0.443 (-0.360 to 1.268)
NEC	-0.313 (-1.434 to 0.459)	0.086 (-0.822 to 1.130)	0.097 (-0.689 to 1.122)	-0.835 (-2.487 to 0.320)	0.873 (-0.096 to 1.963)
IVH	-0.099 (-0.927 to 0.732)	0.772 (-0.143 to 1.669)	-0.344 (-1.327 to 0.457)	0.322 (-0.545 to 1.213)	-0.124 (-0.850 to 0.719)
Pneumothorax	-0.374 (-1.123 to 0.380)	0.353 (-0.537 to 1.287)	-0.604 (-1.764 to 0.527)	0.217 (-0.732 to 1.177)	0.418 (-0.407 to 1.258)
PVL	0.153 (-0.721 to 0.974)	-0.170 (-1.792 to 1.259)	0.011 (-14.825 to 15.767)	0.780 (-0.326 to 2.054)	0.039 (-1.012 to 1.128)
PDA	0.098 (-0.697 - 0.876)	0.178 (-0.579 to 0.923)	0.202 (-0.563 to 1.010)	0.100 (-0.646 to 0.849)	-0.092 (-0.806 to 0.554)
Repeat dose	-0.587 (-1.690 to 0.589)	0.186 (-1.021 to 1.397)	-0.158 (-1.270 to 0.980)	0.104 (-1.099 to 1.347)	-0.109 (-1.427 to 1.143)

Suppl. Table 3. Outcomes of the meta-regression analysis.

Data expressed as β coefficient (95% confidence intervals). InSurE was set to be the reference treatment. No significant associations were noted.

PVL: periventricular leukomalacia; IVH: intraventricular hemorrhage; MV: mechanical ventilation; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; RCT: randomized controlled trials

Appendix 6: Gestational age <28 weeks



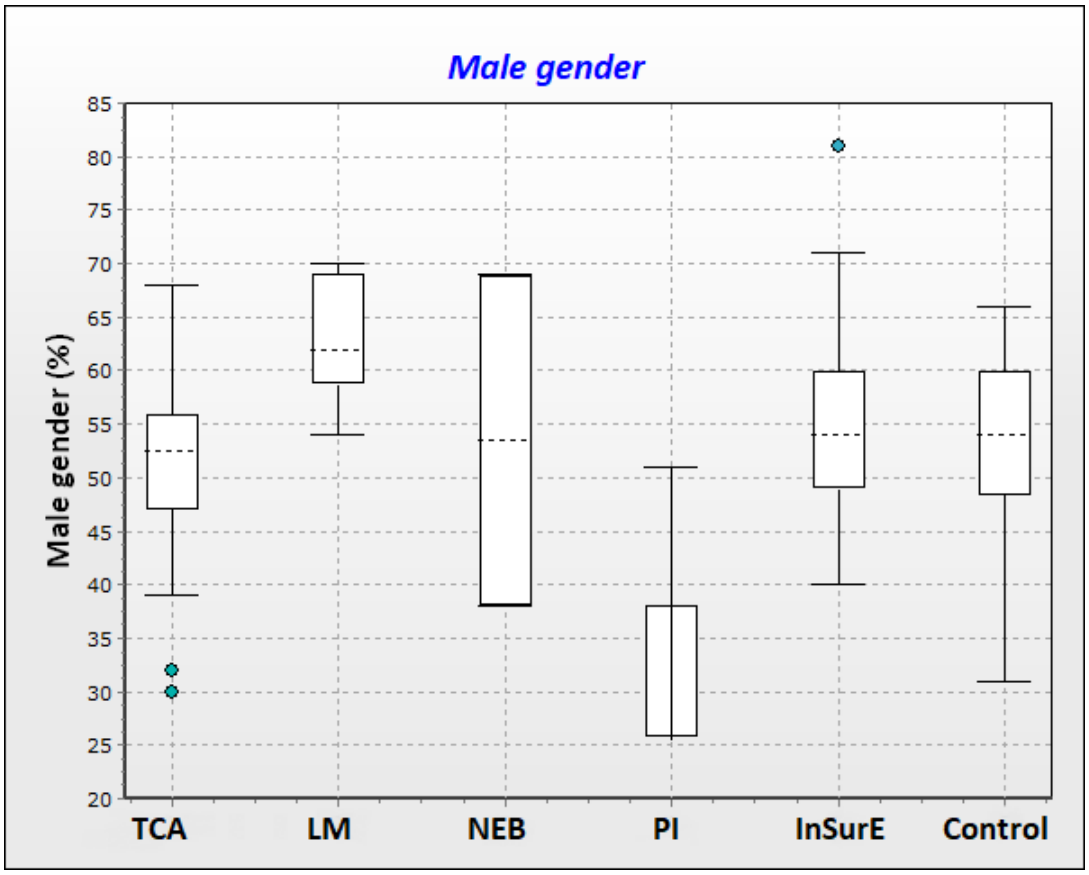
Suppl. Figure 4. Outcomes of sensitivity analysis examining neonates with gestational age <28 weeks. Analysis was based on direct evidence.

Appendix 7: Randomized vs. non-randomized evidence

Outcome	Randomized controlled trials	Observational studies
Mortality	0.62 (0.36-1.06)	0.64 (0.53-0.76) *
Mechanical ventilation	0.39 (0.26-0.60) *	0.46 (0.24-0.88) *
Bronchopulmonary dysplasia	0.54 (0.29-1.01)	0.54 (0.43-0.68) *
Necrotizing enterocolitis	0.33 (0.05-2.02)	0.77 (0.62-0.96) *
Periventricular leukomalacia	N/A	0.65 (0.52-0.81) *
Pneumothorax	0.59 (0.33-1.03)	0.91 (0.63-1.33)
Intraventricular hemorrhage	0.70 (0.40-1.23)	0.84 (0.54-1.29)
Patent ductus arteriosus	1.05 (0.62-1.77)	0.86 (0.50-1.49)
Repeat surfactant dose	0.90 (0.55-1.46)	1.65 (0.77-3.53)

Suppl. Table 4. Outcomes of randomized controlled trials and observational studies regarding the comparison of thin catheter administration and InSurE.
*Data expressed as odds ratio (95% confidence intervals). *p-value <0.05; N/A: not applicable*

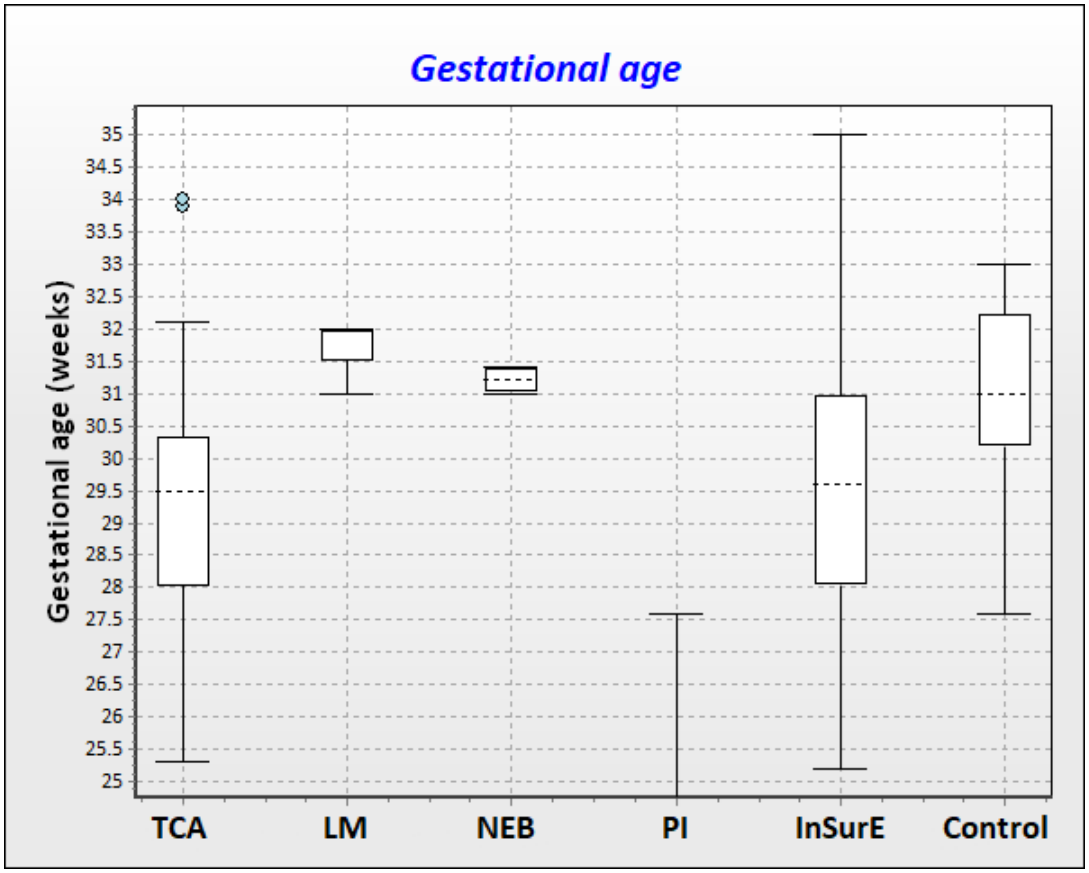
Appendix 8: Transitivity assessment



Suppl. Figure 5. Boxplot of gender distributions among different interventions.

No significant difference was noted (overall median: 54, χ^2: 7.16, *p-value*=0.21).

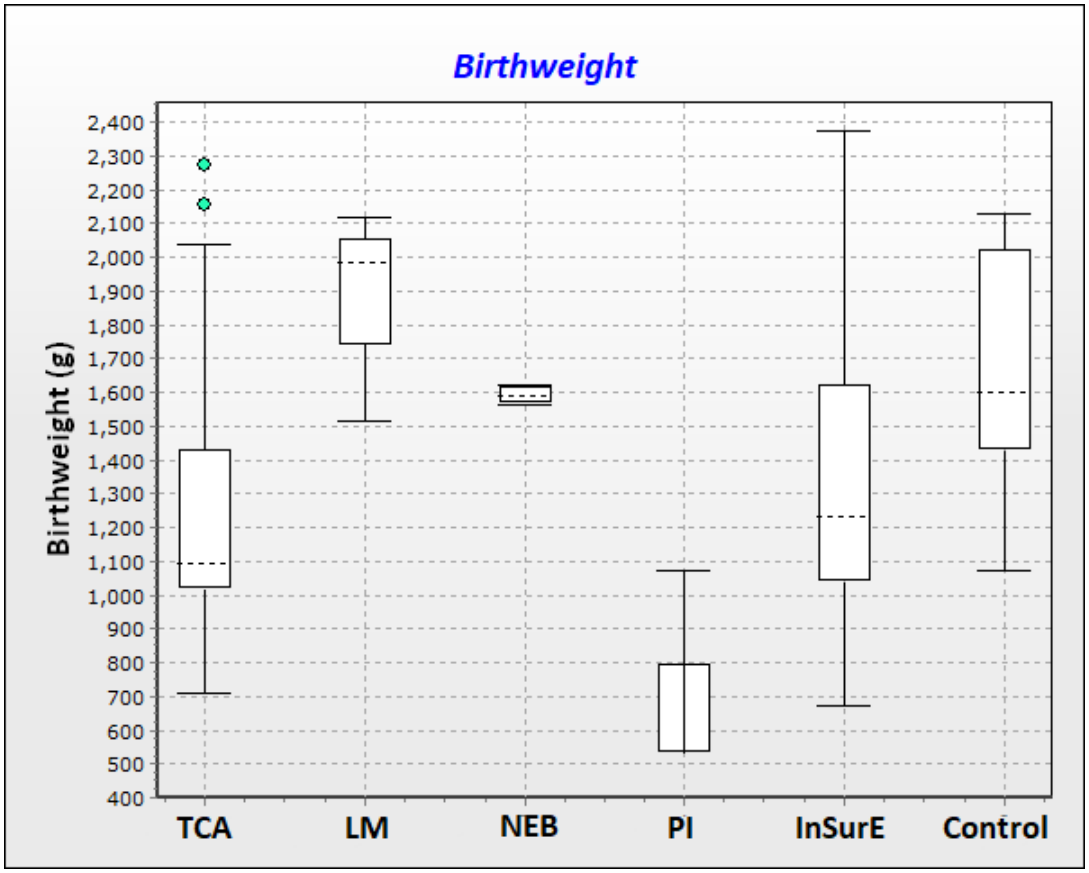
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation;



Suppl. Figure 6. Boxplot of gestational age distributions among different interventions.

No significant difference was noted (overall median: 29.6, χ^2: 10.38, *p-value*=0.07).

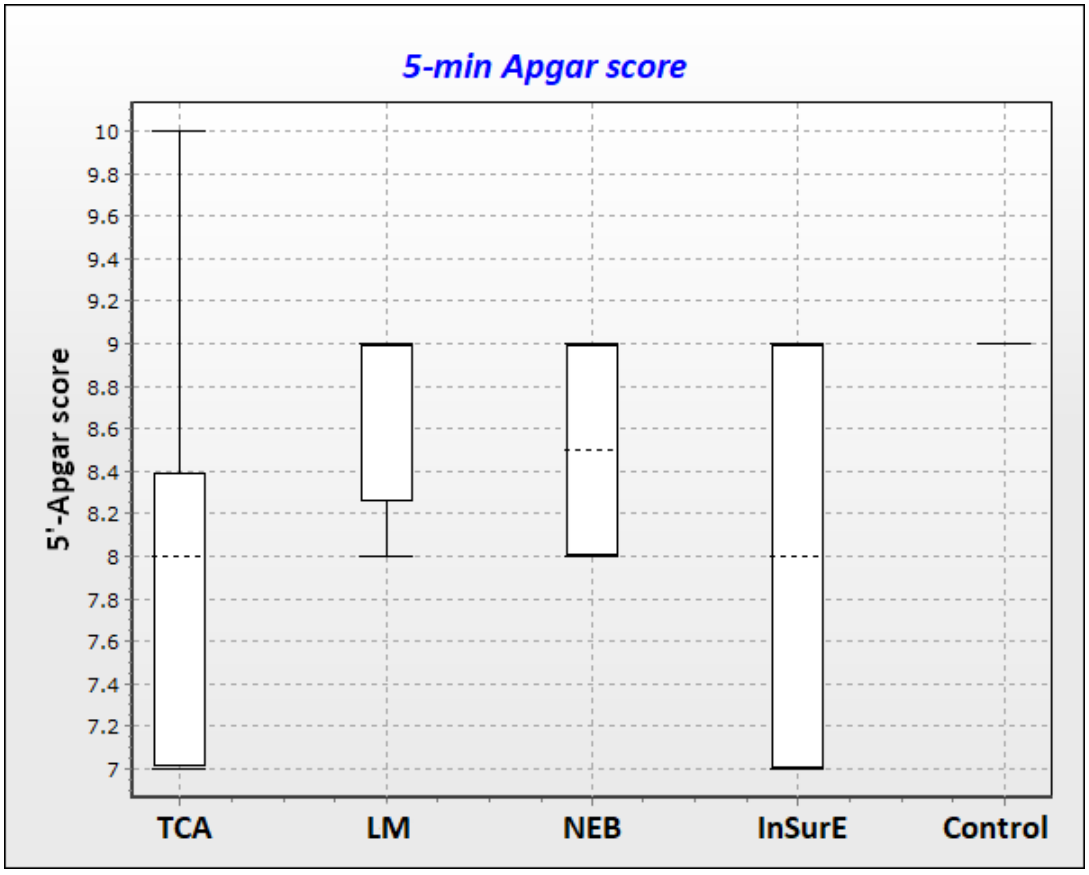
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation;



Suppl. Figure 7. Boxplot of birthweight distributions among different interventions.

No significant difference was noted (overall median: 1.29, χ^2: 10.37, *p-value*=0.07).

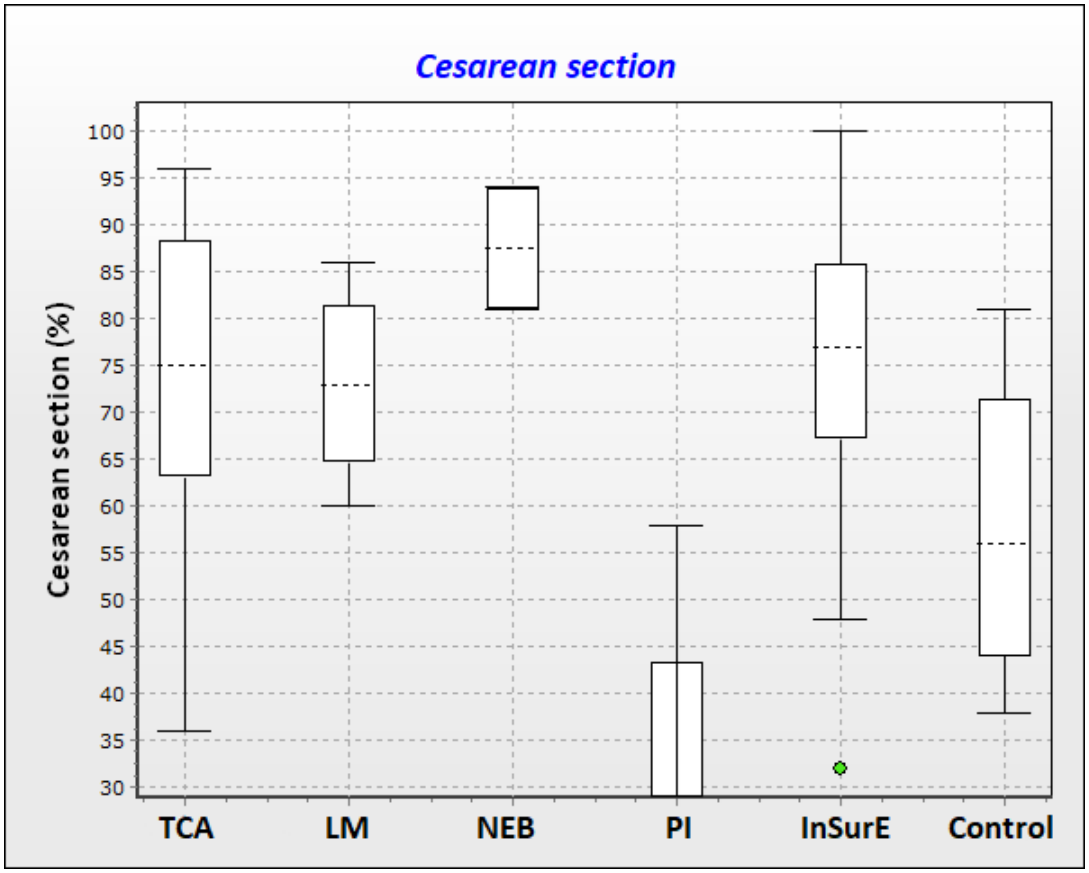
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation;



Suppl. Figure 8. Boxplot of 5-min Apgar score distributions among different interventions.

No significant difference was noted (overall median: 8, χ^2: 10.01, *p-value*=0.16).

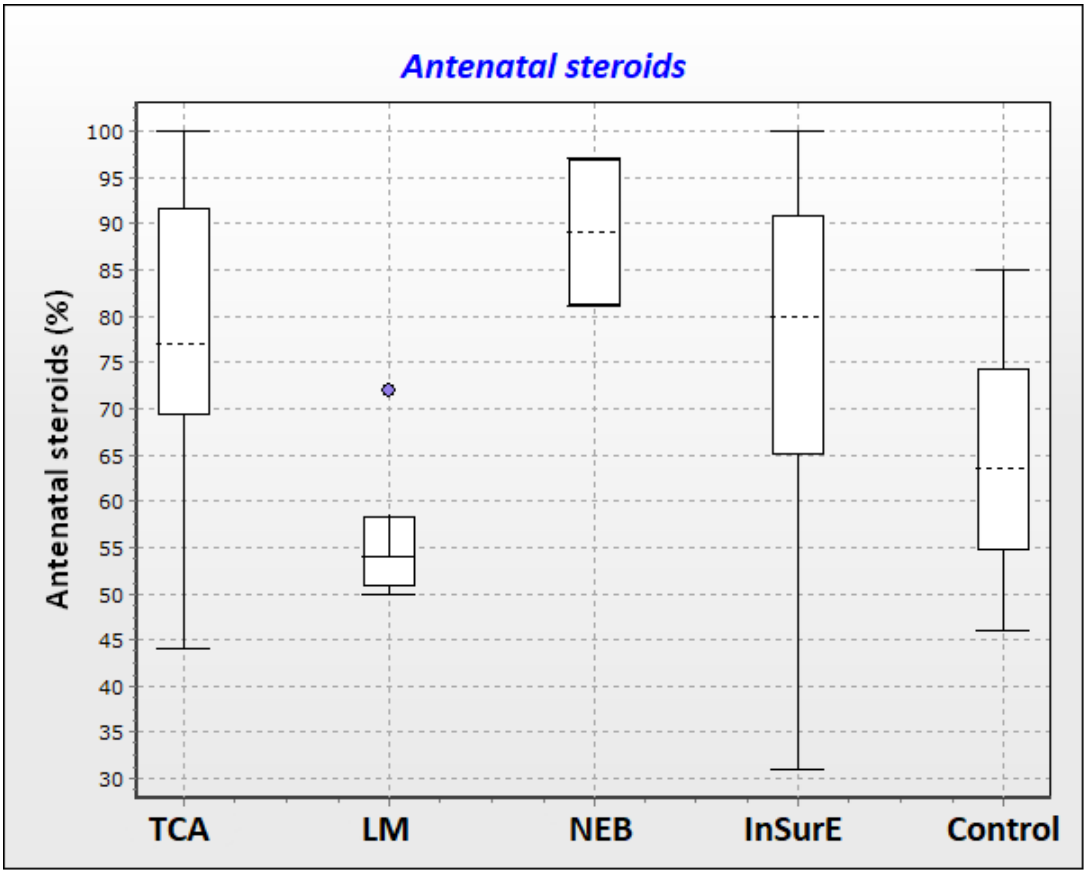
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation;



Suppl. Figure 9. Boxplot of cesarean section distributions among different interventions.

No significant difference was noted (overall median: 77, χ^2: 4.54, *p-value*=0.34).

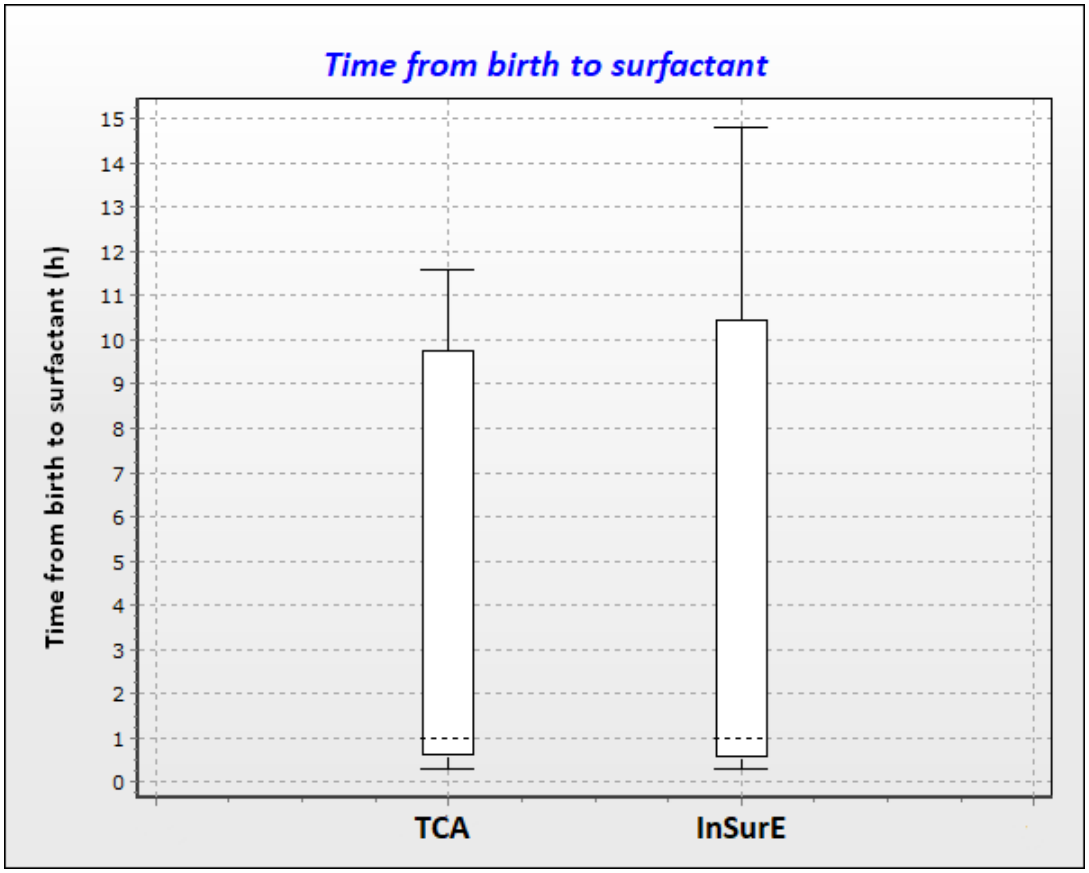
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation;



Suppl. Figure 10. Boxplot of antenatal steroid administration distributions among different interventions.

No significant difference was noted (overall median: 76.5, χ^2: 8.65, *p-value*=0.07).

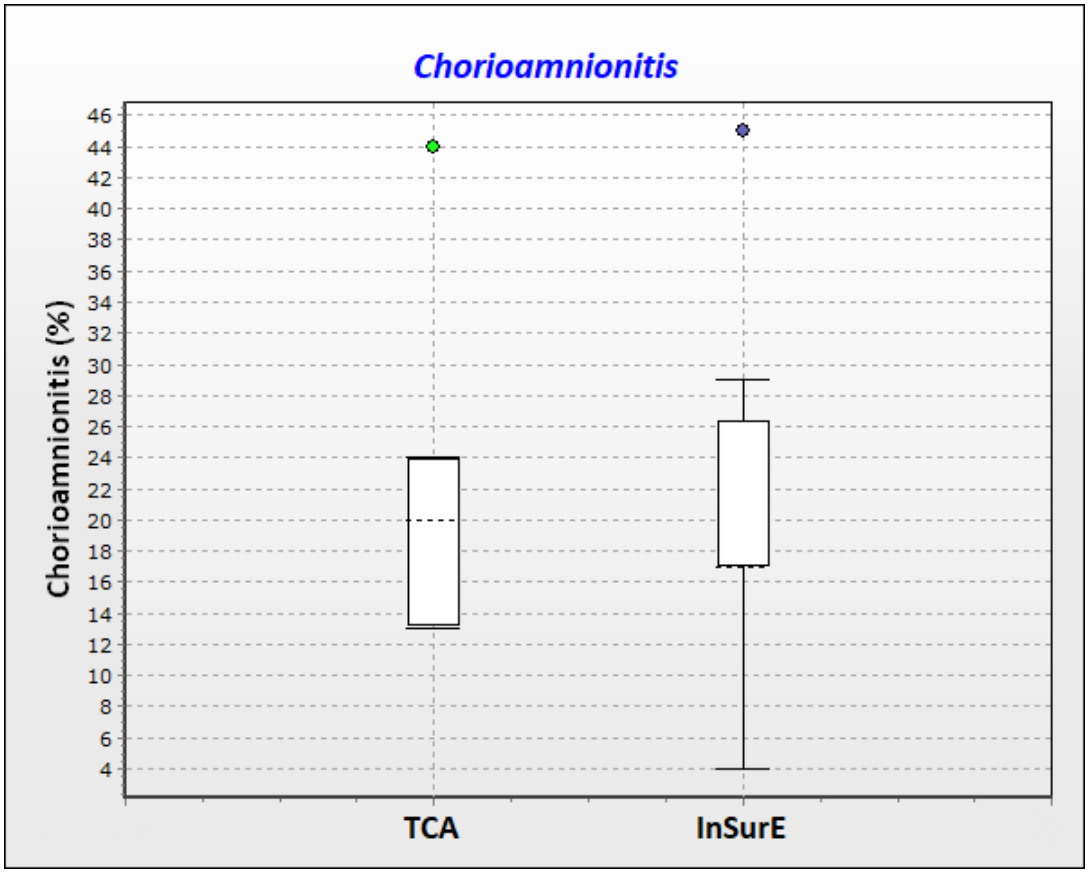
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation;



Suppl. Figure 11. Boxplot of time from birth to surfactant distributions among different interventions.

No significant difference was noted (overall median: 1, χ^2: 0.29, *p-value*=0.59).

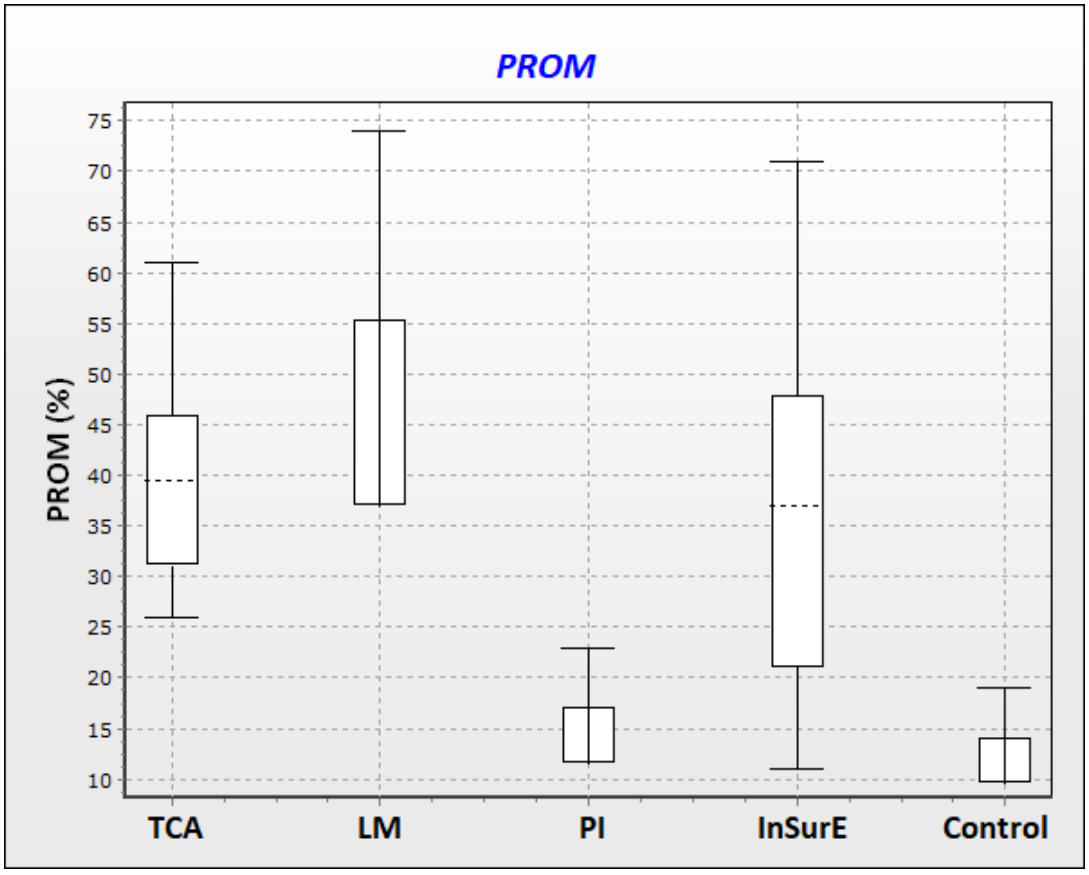
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration



Suppl. Figure 12. Boxplot of chorioamnionitis distributions among different interventions.

No significant difference was noted (overall median: 17, χ^2: 0.14, *p-value*=0.71).

InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration



Suppl. Figure 13. Boxplot of premature rupture of membrane distributions among different interventions.

No significant difference was noted (overall median: 17, χ^2: 0.14, *p-value*=0.71).

InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration; LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation; PROM: premature rupture of membranes

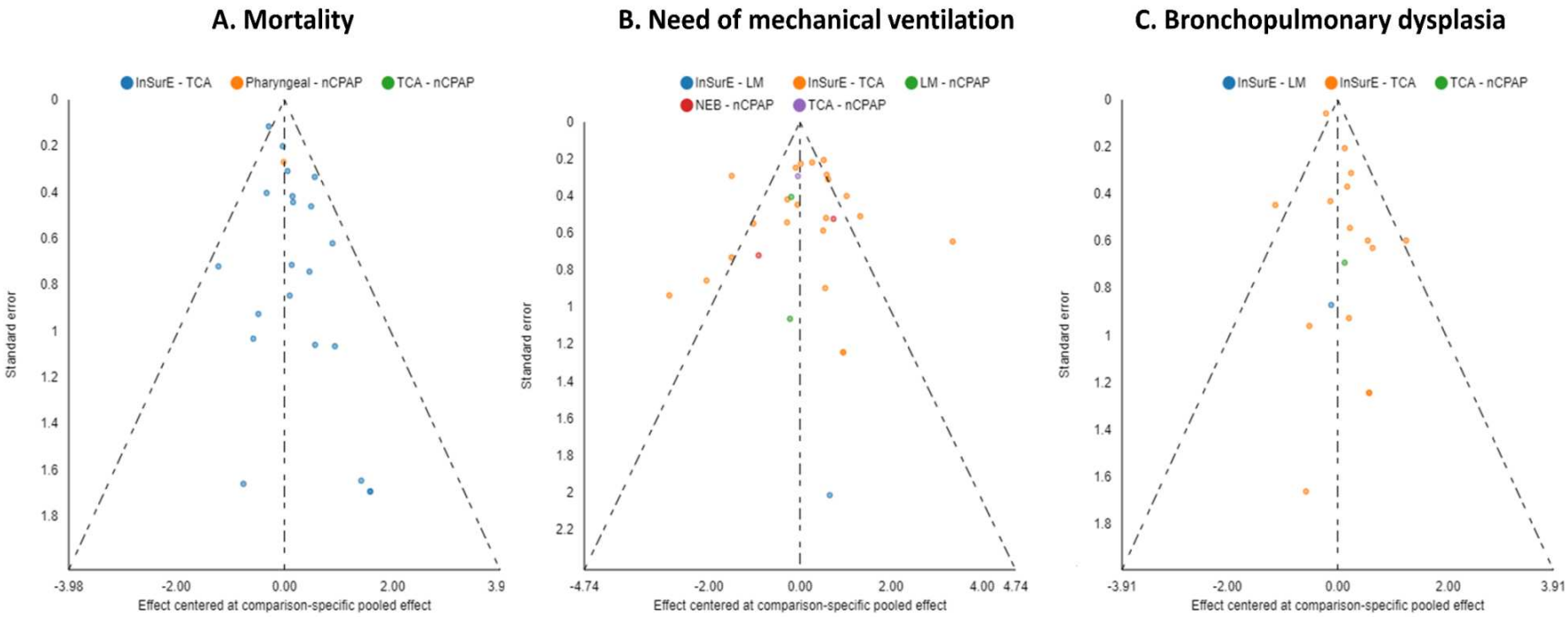
Appendix 9: Inconsistency assessment

Comparison	Direct odds ratio	Indirect odds ratio	Ratio of odds ratios	*p-value*
Need of mechanical ventilation				
InSurE vs. TCA	2.36 (1.59-3.51)	1.44 (0.01-167.7)	1.64 (0.014-194.2)	0.839
Control vs. TCA	4.44 (0.88-22.41)	7.28 (0.08-650.2)	0.61 (0.005-72.24)	0.839
InSurE vs. LM	1.00 (0.02-68.51)	1.64 (0.18-15.09)	0.61 (0.005-72.24)	0.839
Control vs. LM	3.09 (0.71-13.38)	1.88 (0.02-177.1)	1.64 (0.014-194.2)	0.839
Control VS. NEB	2.00 (0.50-7.99)	-	N/A	N/A
InSurE vs. NEB	-	1.00 (0.12-8.07)	N/A	N/A
Control vs. InSurE	-	2.00 (0.42-9.53)	N/A	N/A
LM vs. NEB	-	0.68 (0.10-4.85)	N/A	N/A
LM vs. TCA	-	1.60 (0.23-11.13)	N/A	N/A
NEB vs. TCA	-	2.35 (0.30-18.38)	N/A	N/A
Pneumothorax				
InSurE vs. TCA	1.25 (0.92-1.71)	1.29 (0.18-9.35)	0.97 (0.13-7.24)	0.978
Control vs. TCA	3.54 (1.38-9.06)	3.44 (0.59-20.28)	1.03 (0.14-7.65)	0.978
InSurE vs. LM	0.57 (0.16-2.04)	0.56 (0.12-2.63)	1.03 (0.14-7.65)	0.978
InSurE vs. NEB	5.32 (0.25-115.5)	-	N/A	N/A
Control vs. LM	1.57 (0.48-5.18)	1.61 (0.32-8.09)	0.97 (0.13-7.24)	0.978
Control vs. PI	1.17 (0.71-1.92)	-	N/A	N/A
LM vs. TCA	-	2.22 (0.82-5.99)	N/A	N/A
NEB vs. TCA	-	0.24 (0.01-5.19)	N/A	N/A
PI vs. TCA	-	3.01 (1.14-7.94)	N/A	N/A
Control vs. InSurE	-	2.81 (1.19-6.64)	N/A	N/A
InSurE vs. PI	-	0.42 (0.15-1.13)	N/A	N/A
LM vs. NEB	-	9.43 (0.37-238.4)	N/A	N/A
LM vs. PI	-	0.74 (0.25-2.17)	N/A	N/A
NEB vs. PI	-	0.08 (0.01-1.98)	N/A	N/A
Control vs. NEB	-	14.95 (0.61-364.75)	N/A	N/A

Suppl. Table 5. Outcomes of the SIDE-splitting test, suggesting no inconsistency.

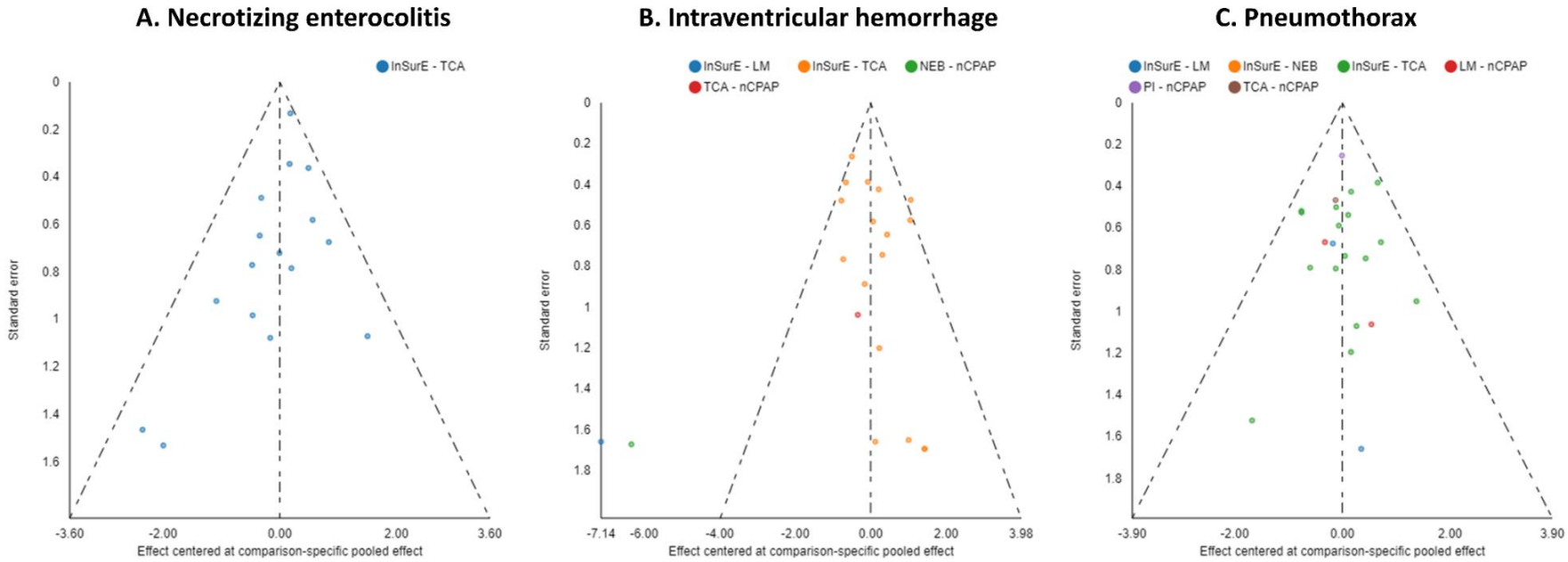
InSurE: intubation, surfactant administration, extubation; LM: laryngeal mask; N/A: not applicable; NEB: nebulized; PI: pharyngeal instillation; TCA: thin catheter administration;

Appendix 10: Publication bias assessment



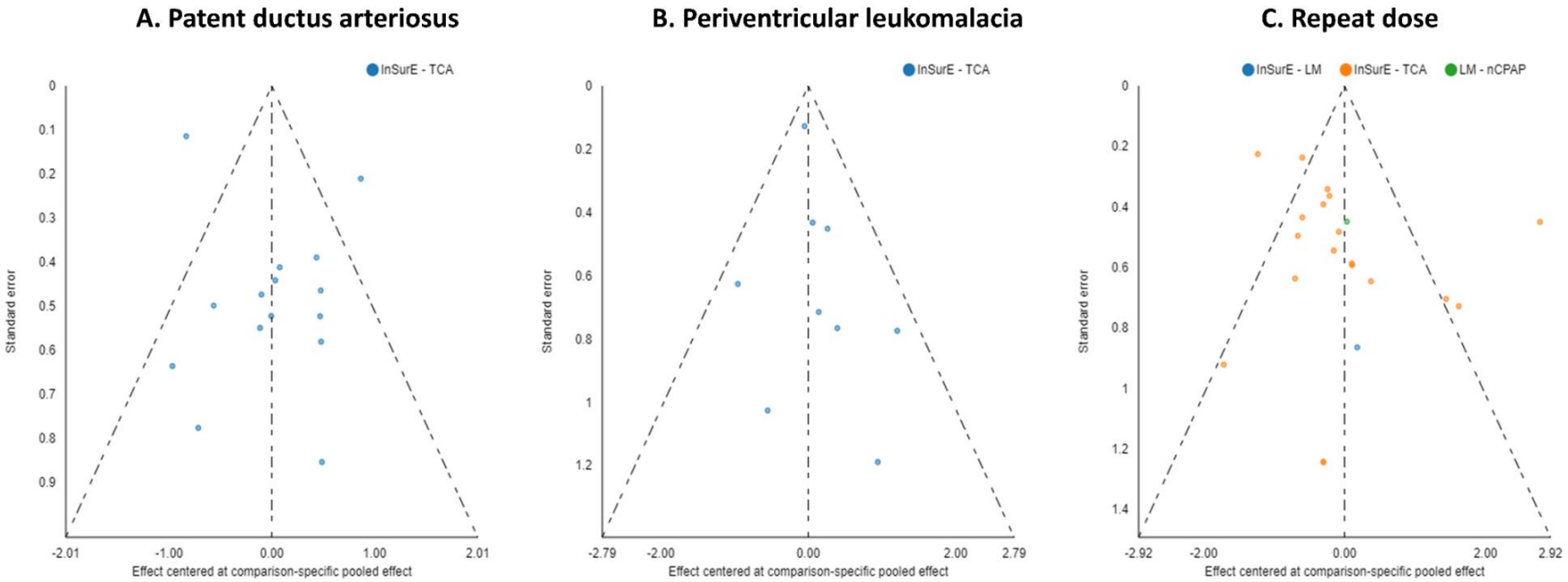
Suppl. Figure 14. Comparison-adjusted funnel plots of primary outcomes.

nCPAP: nasal continuous positive airway pressure; *InSurE: intubation, surfactant administration, extubation; LM: laryngeal mask; NEB: nebulized; TCA: thin catheter administration*



Suppl. Figure 15. Comparison-adjusted funnel plots of necrotizing enterocolitis (A), intraventricular hemorrhage (B) and pneumothorax (C).

nCPAP: nasal continuous positive airway pressure; *InSurE: intubation, surfactant administration, extubation; LM: laryngeal mask; NEB: nebulized; TCA: thin catheter administration*



Suppl. Figure 16. Comparison-adjusted funnel plots of patent ductus arteriosus (A), periventricular leukomalacia (B) and repeat dose of surfactant (C).

nCPAP: nasal continuous positive airway pressure; *InSurE: intubation, surfactant administration, extubation; LM: laryngeal mask; NEB: nebulized; TCA: thin catheter administration*

Appendix 11: Confidence In Network Meta-Analysis (CiNeMA)

	Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall quality
	Intraventricular hemorrhage							
Mixed evidence	TCA vs. InSurE	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	**Low**
	TCA vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	**Low**
	InSurE vs. LM	Major concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
	NEB vs. Control	Some concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
Indirect evidence	*TCA vs. LM*	Some concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
	TCA vs. NEB	Some concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
	InSurE vs. NEB	Some concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
	InSurE vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	**Low**
	LM vs. NEB	Some concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
	LM vs. Control	Some concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
	Pneumothorax							
Mixed evidence	TCA vs. InSurE	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	**Moderate**
	TCA vs. Control	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	**Moderate**
	InSurE vs. LM	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	InSurE vs. NEB	No 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**
	PI vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
Indirect evidence	TCA vs. LM	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	TCA vs. NEB	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	TCA vs. PI	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	**Moderate**
	InSurE vs. Control	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	**Moderate**
	InSurE vs. PI	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**
	LM vs. PI	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	NEB vs. PI	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	NEB vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	Repeat dose							
Mixed evidence	TCA vs. InSurE	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	TCA vs. LM	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	**Low**
	Necrotizing enterocolitis							
Direct evidence	TCA vs. InsurE	Some concerns	Undetected	No concerns	Some concerns	No concerns	Major concerns	**Low**
	PI vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	Patent ductus arteriosus							
	TCA vs. InsurE	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	**Low**
	PI vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	Periventricular leukomalacia							
	TCA vs. InsurE	Some concerns	Undetected	No concerns	No concerns	No concerns	Major concerns	**Moderate**

Suppl. Table 6. Credibility of evidence of secondary outcomes. Control refers to no surfactant administration.

InSurE: intubation, surfactant administration, extubation; LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation; TCA: thin catheter administration

Appendix 12: PRISMA checklist

Section/Topic	Item #	Checklist Item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**2**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	**3**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**4**
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	**4**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly*	**4-5**

		describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**5**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**5**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**5-6**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**6**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**6**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	**6**
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**7**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**6**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	**6-7**

Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	**7**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**6-7**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	**6-7**
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**8, Appendix 1**
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**Figure 1, Appendix 3**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**8**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**9, Appendix 2, Table 1**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	**10, Appendix 4**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**9**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger*	**9-10**

		networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	**10, Appendix 8-9**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	**10-11, Appendix 10**
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	**9-10, Appendix 5-7**
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	**14-15**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	**16**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**16-17**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	**17**