SURFACTANT INSTILLATION IN SPONTANEOUSLY BREATHING PRETERM INFANTS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Vincent Rigo, Caroline Lefebvre, Isabelle Broux

Neonatology division
CHU de Liège (University of Liège), CHR Citadelle,
Liège, Belgium
✉ vincent.rigo@chu.ulg.ac.be

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ABSTRACT

Less invasive surfactant therapies (LIST) use surfactant instillation through a thin tracheal catheter in spontaneously breathing infants. This review and meta-analysis investigates respiratory outcomes for preterm infants with respiratory distress syndrome treated with LIST rather than administration of surfactant through an endotracheal tube. Randomized controlled trials (RCT) full texts provided outcome data for bronchopulmonary dysplasia (BPD), death or BPD, early CPAP failure, invasive ventilation requirements, and usual neonatal morbidities. Relative risks (RR) from pooled data, with subgroup analyses, were obtained from a Mantel-Haenszel analysis using a random effect model. Six RCTs evaluated LIST: 4 versus InSurE, and 1 each versus delayed or immediate intubation for surfactant. LIST resulted in decreased risks of BPD (RR= 0.71 [0.52-0.99]; NNT=21), death or BPD (RR= 0.74 [0.58-0.94]; NNT=15), and early CPAP failure or invasive ventilation requirements (RR= 0.67[0.53-0.84]; NNT=8) and RR=0.69 [0.53-0.88]; NNT=6). Compared to InSurE, LIST decreased the risks of BPD or death (RR=0.63 [0.44-0.92]; NNT=11) and of early CPAP failure (RR= 0.71 [0.53-0.96]; NNT=11). Common neonatal morbidities were not different.
Conclusions: Respiratory management with LIST decreases the risks of BPD and BPD or death, and the need for invasive ventilation. This strategy appears safe, but long term follow-up is lacking.

Abbreviations

AMV	Avoidance of Mechanical Ventilation Study
BPD	Bronchopulmonary dysplasia (here: moderate to severe)
cPVL	Cystic periventricular leucomalacia
InSurE	Intubation-surfactant-extubation
IVH	Intraventricular haemorrhage
LISA	Less invasive surfactant administration
LIST	Less invasive surfactant therapy
MV	Mechanical ventilation
MIST	Minimally invasive surfactant therapy
nCPAP	Nasal continuous positive airway pressure
NEC	Necrotizing enterocolitis
NNT/H	Number needed to treat / to harm
NINSAP	Nonintubated Surfactant Application Study
PDA	Patent ductus arteriosus
RCT	Randomized controlled trial
ROP	Retinopathy of prematurity
RR	Relative risk

INTRODUCTION

Nowadays, the primary strategy to manage respiratory distress syndrome in preterm infants relies on the application of non invasive support, primarily nasal continuous positive airway pressure (nCPAP). Compared to intubation and ventilation, primary nCPAP decreases the combined risk of bronchopulmonary dysplasia (BPD) or death [27,29]. However, the failure rate of the nCPAP approach remains high, with 65% of very preterm infants requiring secondary mechanical ventilation (MV), and 50% surfactant therapy [27].

Different strategies aim to reduce the need of secondary ventilation. The InSurE (intubation-surfactant-extubation) technique still requires brief ventilation through an endotracheal tube. This approach is a beneficial alternative to intubation for surfactant followed by MV [28]. However, a recent meta-analysis of studies comparing this technique to secondary ventilation was unable to prove statistically significant improvements in respiratory outcomes, even if risks of BPD or death, of BPD and of airleak tended to decrease [14].

A more recent alternative consists in the insertion of a small diameter catheter in the trachea to instil surfactant while the infant breathes spontaneously on nCPAP. Different variants of this “less invasive surfactant therapy (LIST)” have been suggested [17,4,16], mostly differing in the type of catheter and the modality to guide it through the vocal cords. Data from animal studies show that while a substantial amount of surfactant does not reach the alveolar level, its efficacy is still improved compared to a surfactant and ventilation approach [2,21]. However, while the control animals in those studies were ventilated for relatively short times (a few hours), this lasted longer than what would be considered adequate for an InSurE modality.

Different LIST strategies have already been subjected to evaluation in randomized controlled trials (RCT), with beneficial effects. Mechanical ventilation requirements and durations were improved in those studies (Avoidance of mechanical ventilation-AMV, Take Care and Nonintubated surfactant application-NINSAP [9,16,18]). Lower rates of moderate to severe BPD were reported by the Take Care investigators [16], and the risk of oxygen dependency at 28 days was decreased in the AMV trial [9]. The NINSAP Study [18], assessing the most extremely premature infants, born below 27 weeks of gestation, described reductions in pneumothoraces and severe intraventricular haemorrhages (IVH) as well as improvement in survival without severe adverse event.

Recent meta-analyses included studies using LIST for preterm infants. Fischer et al [8] investigated the use of LIST (two studies), InSurE or nCPAP to avoid MV and demonstrated a reduction in the outcome of BPD or death. A network meta-analysis of non-invasive ventilation strategies compared 7 interventions including LIST (4 trials), InSurE, nCPAP and MV

[15]. They found that LIST, compared to invasive ventilation, was associated with reductions in death or BPD, BPD, and in severe IVH. Rates of death or BPD and of airleaks were decreased in indirect comparisons of LIST and nCPAP. Outcomes for LIST and InSurE were similar. Using a Surface under the cumulative ranking curve analysis, they estimated that LIST had the highest probability of being the best intervention to reduce death or BPD, BPD and airleaks.

With positive short and median term outcomes, the LIST strategy seems potentially beneficial. This study aims to assess this question: in preterm infants with respiratory distress syndrome, does a LIST strategy defined as above, compared to administration of surfactant through an endotracheal tube, improve respiratory outcomes (defined as death and/or BPD at 36 weeks) without increasing common neonatal morbidities.

METHODS

SEARCH STRATEGY AND STUDY SELECTION

Two investigators (VR, CL) independently searched PubMed, EMBASE and the Cochrane Central Register of Controlled trials for studies published between 2005 and June 2016, using the Mesh keywords “Pulmonary surfactant” and “Respiratory distress syndrome, newborn” and the filters “Clinical studies OR Clinical trial OR Randomized control trial”. Abstracts from relevant titles were reviewed for selection of articles. A search for studies citing one of 5 articles that we considered important in the field (3 early descriptions [31,17,4] and the first 2 RCTs [9,16]) was undertaken with Google Scholar. Additional publications were sought from review references and investigator archives. Evaluation of references was restricted to articles in English, French, Dutch, German, Portuguese, Spanish or Italian.

Studies included for analysis were RCTs comparing any form of surfactant instillation through a thin catheter in spontaneously breathing infants with other strategies (InSurE or intubation-surfactant-MV, either immediate or delayed). The primary outcome of this review was death and/or BPD at 36 weeks. Secondary outcomes were initial nCPAP failure defined as requirement for mechanical ventilation within 3 days of life, any MV requirement, pneumothorax, need for additional surfactant, patent ductus arteriosus (PDA), PDA requiring surgical ligation, severe retinopathy of prematurity (ROP), severe (Papille grade III or IV) intraventricular haemorrhage (IVH), any IVH reported, cystic periventricular leucomalacia (cPVL), necrotizing enterocolitis (NEC) and a composite outcome of death or severe morbidities. Data on durations of invasive and total respiratory support, oxygen therapy and length of stay were retrieved. Additional secondary outcomes included procedural complications, namely failed first attempt, desaturation, cough and surfactant reflux.

DATA RECORDING

Two investigators (VR, IB) independently recorded data on an electronic data collection form. Discrepancies were resolved by discussion with a third investigator (CL).

STATISTICAL ANALYSIS

For dichotomous outcomes, raw data provided the basis for individual study relative risk estimates, with 95% confidence intervals. Heterogeneity between studies was explored with an I^2 statistic. To acquire pooled relative risks (RR) estimates (presented as RR (95% confidence interval)), we used a Mantel-Haenszel statistical analysis with a random effect model, calculated with RevMan version 5.2 (Cochrane Collaboration 2014). Subgroup analyses were also performed according to the various control groups. Numbers needed to treat (NNT) or to harm (NNH) were computed for statistically significant effects.

RESULTS

STUDIES SELECTION, DESCRIPTION, AND ASSESSMENT

The selection process for study inclusion is described in Figure-Online Resource 1. This process led to the selection of 6 RCTs [9,16,19,20,1,18]. Another publication [11] was not retained as it described single centre data derived from a multi-centre trial described in another reference [19]. Individual studies are summarized in Table 1. They compare various LIST modalities with different control strategies: four studies used InSurE [16,20,1,19], one nCPAP maintenance with a delayed intubation-surfactant approach [9], and one immediate intubation for surfactant [18]. In one study, the inclusion criteria were not driven by the respiratory status [9], with some infants not requiring any surfactant. The studies mostly investigated the management of very preterm infants, with the AMV [9] and NINSAP [18] studies focusing on extremely and the most extremely preterm infants, respectively. Additionally, Kanmaz et al reported BPD and MV requirements for infants of less than 29 0/7 weeks of gestation [16]. Most studies [9,16,20,1] considered the initial respiratory management as their main outcome. NINSAP [18] assessed survival without moderate to severe BPD, while Mirnia et al. [19] aimed to compare complications between LISA (Less invasive surfactant administration) and InSurE procedures.

	Göpel 2011 AMV [9]		Kanmaz 2013 [16]		Mirnia 2013 [19]		Mohammadizadeh 2015 [20]		Bao 2015 [1]		Kribs 2015 NINSAP[18]	
Method used	LISA		Take Care		TEC		LISA		MIST		LISA	
Catheter	NG+ Magill		NG		NG		NG+ Magill		16 G Angiocath		NG+ Maggil	
Controls	CPAP, delayed intubation		InSurE		InSurE		InSurE		InSurE		Intubation	
Randomized infants (n)	220		200		136		38		90		211	
Gestational ages (weeks)	26-28		<32		27-32		<35 (BW 1000-1800g)		28-32		23-26	
Stratification (GA in weeks)	/		/		/		/		(For inclusion)		23-24/ 25-26	
Randomisation time	<12h		<2h		/		<1h30		<2h		<2h	
Respiratory condition on inclusion	/		RDS: nCPAP, FiO_2>40%		RDS: nCPAP, FiO_2>30%		RDS: nCPAP, FiO_2>30%		RDS: nCPAP, FiO_2>30-35%		RDS: FiO2>30% or Silverman score ≥5	
Main outcome	MV (or respiratory failure) on day 2-3		MV by day 3		Complications		MV by day 3		MV by day 3		Death or BPD at 36 weeks	
Surfactant type and dose	Poractant-α (80% of treated patients), Ber-/Bov-actant (18%,2%) 100 mg/kg		Poractant-α 100 mg/kg		Poractant-α 200 mg/kg		Poractant-α 200 mg/kg		Poractant-α 200 mg/kg		Poractant-α ≥100 mg/kg	
Participants (n) (LIST/ Controls)	108 /	112	100 /	100	66 /	70	19 /	19	47 /	43	107 /	104
Birth weight (g) (LIST/ Controls)	975±244 /	938±205	1093±270 /	1121 ± 270	1339 ± 406/	1304 ± 331	1289 ±219 /	1428 ± 272	1034± 221 /	1087 ± 198	711 ± 195 /	674 ± 165
GA (weeks) (LIST/ Controls)	27.6 ±0.8 /	27.5 ±0.8	28.0 ± 2 /	28.3 ± 2	29.6 ±1.7/	29.6 ± 1.7	30 ±2 /	31 ± 2	29.1 ± 1.5/	29.3 ± 1.6	25.3 ± 1.1 /	25.2 ± 0.9

The risk of bias for individual studies is reviewed in Table-Online Resource 2. No study attempted to blind the procedure [5]. In the Mohammadizadeh et al. study [20], the exclusion criteria might have led to a selective report of outcome favouring the InSurE controls: infants were excluded if not extubated within a few minutes. Mirnia et al.[19] and Bao et al.[1] did not described their strategy to conceal treatment allocation. Some equivocal data and some discrepancies between the multicentre [19] and single-centre [11] reports of Mirnia et al. led to consider the risk of selective report bias unclear.

RESULTS FOR SPECIFIC OUTCOMES

FIG 1 summarises results for each dichotomous outcome. Forest plots and detailed data for each specific result are presented in Figure- Online Resource 3. Variations in the presentation of continuous outcomes data (mean and standard deviation, median and interquartile range, mean and standard error of the mean) prevented further analysis of length of stay, duration of respiratory support and oxygen therapy.

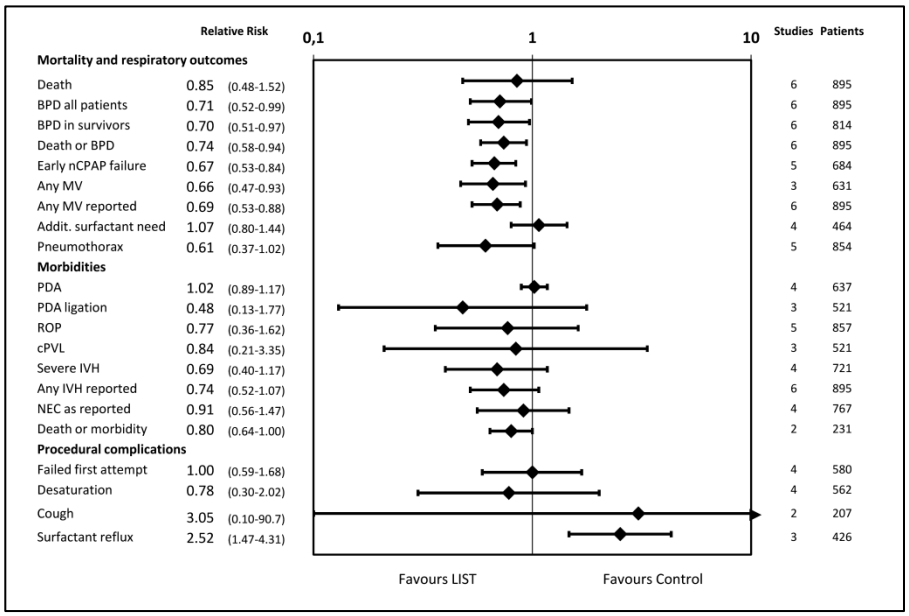

Figure 1: ***Risk ratios for each specific dichotomous outcome:*** **Studies, patients: number of studies and patients included for each outcome. BPD: Bronchopulmonary dysplasia; MV: Mechanical ventilation; PDA: patent ductus arteriosus; ROP: retinopathy of prematurity; cPVL: cystic periventricular leucomalacia; IVH intraventricular hemorrhage; NEC: necrotising enterocolitis. See text for definitions and Online Resource 3 for details.**

Respiratory outcomes are improved (FIG 2, Table 2). The risk of BPD (in all patients, in survivors, or as a combined outcome with death) is significantly reduced, with NNTs of 21, 19, and 15 respectively. Studies all tend in the same direction, with low heterogeneity. The subgroup analysis of studies comparing LIST and InSurE strategies find a reduction in the combined outcome of death or BPD (NNT= 11). The risk of early nCPAP failure is reduced compared to both InSurE and delayed intubation strategies, globally (NNT=8) and in subgroup analyses (vs InSurE: NNT=11; vs nCPAP: NNT= 6). The need for invasive ventilation at any time is reduced whether or not the NINSAP study (where the control arm required intubation for surfactant and MV) is included, with NNTs of 5 and 6. Additionally, occurrence of pneumothoraces tended to be reduced: RR= 0.61(0.37-1.02).

In infants born below 29 0/7 weeks (Figure- Online Resource 4), the rate of BPD in all infants is significantly reduced: RR= 0.61(0.39-0.96); NNT=12. No change is seen in early nCPAP failure (RR= 0.80 (0.47-1.34)), but MV requirements during NICU stay decreases: RR= 0.65 (0.45-0.95); NNT=4.

Commonly reported morbidities are not different, neither in global or subgroup analyses. In the smallest infants, pooled data from the AMV and NINSAP trials give a trend toward reduction in a composite outcome of death or major complications (severe IVH,

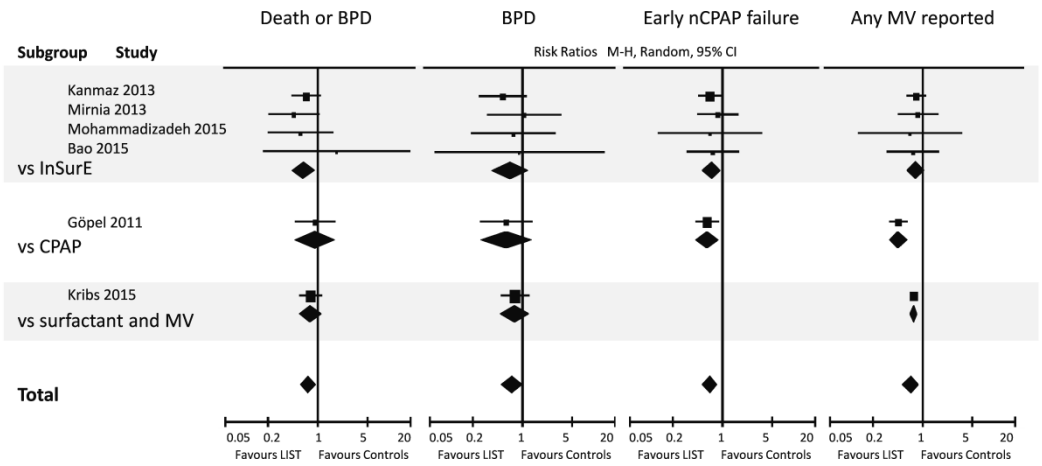

Figure 2 **Forest plots for respiratory outcomes.** See Table 2 caption.

	Death or BPD					BPD					Early CPAP failure					Any MV reported				
	Events/ Total					**Events/ Total**					**Events/ Total**					**Events/ Total**				
	LIST	**Controls**	***Wt %***	**RR**	**[95°% CI]**	**LIST**	**Controls**	***Wt%***	**RR**	**[95°% CI]**	**LIST**	**Controls**	***Wt %***	**RR**	**[95°% CI]**	**LIST**	**Controls**	***Wt %***	**RR**	**[95°% CI]**
vs InSurE																				
Kanmaz 2013	22/ 100	32/ 100	*27.1*	0.69	[0.43, 1.10]	9/ 100	17/ 100	*18.6*	0.53	[0.25, 1.13]	30/ 100	45/ 100	*44.1*	0.67	[0.46, 0.96]	40/ 100	49/ 100	*24.3*	0.82	[0.60, 1.12]
Mirnia 2013	7/ 66	16/ 70	*8.5*	0.47	[0.20, 1.06]	5/ 66	5/ 70	*7.4*	1.06	[0.32, 3.50]						13/ 66	16/ 70	*10.4*	0.86	[0.45, 1.65]
Mohamma-dizadeh 2015	4/ 19	7/ 19	*5.4*	0.57	[0.20, 1.63]	3/ 19	4/ 19	*5.8*	0.75	[0.19, 2.91]	2/ 19	3/ 19	*2.2*	0.67	[0.13, 3.55]	2/ 19	3/ 19	*2.3*	0.67	[0.13, 3.55]
Bao 2015	2/ 47	1/ 43	*1.1*	1.83	[0.17, 19.47]	1/ 47	1/ 43	*1.4*	0.91	[0.06, 14.18]	8/ 47	10/ 43	*8.7*	0.73	[0.32, 1.68]	8/ 47	10/ 43	*7.9*	0.73	[0.32, 1.68]
Subtotal	35/ 232	56/ 232	*40.9*	**0.63**	**[0.44, 0.92]**	18/ 232	27/ 232	*32.9*	**0.67**	**[0.38, 1.19]**	53/ 232	74/ 232	*60.5*	**0.71**	**[0.53, 0.96]**	63/ 232	78/ 232	*40.6*	**0.81**	**[0.62, 1.05]**
	Heterogeneity: Tau² = 0.00; Chi² = 1.48, df = 3 (P = 0.69); I² = 0%					Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 3 (P = 0.80); I² = 0%					Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 3 (P = 0.93); I² = 0%					Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 3 (P = 0.99); I² = 0%				
	Test for overall effect: Z = 2.38 (P = 0.02)					Test for overall effect: Z = 1.37 (P = 0.17))					Test for overall effect: Z = 2.26 (P = 0.02)					Test for overall effect: Z = 1.56 (P = 0.12)				
vs nCPAP																				
Göpel 2011	15/ 108	17/ 112	*14.3*	**0.92**	**[0.48, 1.74]**	8/ 108	14/ 112	*15.6*	**0.59**	**[0.26, 1.36]**	30/ 108	51/ 112	*45.1*	**0.61**	**[0.42, 0.88]**	36/ 108	82/ 112	*25.5*	**0.46**	**[0.34, 0.61]**
	Test for overall effect: Z = 0.27 (P = 0.79)					Test for overall effect: Z = 1.24 (P = 0.22)					Test for overall effect: Z = 2.65 (P = 0.008)					Test for overall effect: Z = 5.33 (P < 0.00001)				
vs MV and surfactant																				
Kribs 2015	35/ 107	43/ 104	*46.8*	**0.79**	**[0.55, 1.13]**	25/ 107	31/ 104	*52.3*	**0.78**	**[0.50, 1.23]**						80/ 107	103/ 104	*34.4*	**0.75**	**[0.68, 0.84]**
	Test for overall effect: Z = 1.29 (P = 0.20)					Test for overall effect: Z = 1.05 (P = 0.29)										Test for overall effect: Z = 4.93 (P < 0.00001)				
Total	85/ 447	116/ 448	*100*	**0.74**	**[0.58 , 0.94]**	51/ 447	72/ 448	*100*	**0.71**	**[0.51, 0.99]**	83/ 340	125/ 344	*100*	**0.67**	**[0.53, 0.84]**	179 / 447	263/ 448	*100*	**0.67**	**[0.51, 0.87]**
	Heterogeneity: Tau² = 0.00; Chi² = 2.69, df = 5 (P = 0.75); I² = 0%					Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 5 (P = 0.92); I² = 0%					Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 4 (P = 0.93); I² = 0%					Heterogeneity: Tau² = 0.05; Chi² = 12.68, df = 5 (P = 0.03); I² = 61%				
	Test for overall effect: Z = 2.50 (P = 0.01)					Test for overall effect: Z = 2.03 (P = 0.04)					Test for overall effect: Z = 3.43 (P = 0.0006)					Test for overall effect: Z = 2.95 (P = 0.003)				
	Test for subgroup differences: Chi² = 1.21, df = 2 (P = 0.55), I² = 0%					Test for subgroup differences: Chi² = 0.40, df = 2 (P = 0.82), I² = 0%					Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%					Test for subgroup differences: Chi² = 11.11, df = 2 (P = 0.004), I² = 82.0%				

Table 2: Relative risks for respiratory outcomes.

Relative risks for Death or BPD (Bronchopulmonary dysplasia), Moderate to Severe BPD, Early nCPAP failure (mechanical ventilation by day 3) and any Mechanical ventilation (MV) reported (Mirnia 2013, Mohammadizadeh 2015 and Boa 2015 reported up to day 3, other studies during hospitalisation), by study, subgroups and total. RR: relative risk (Mantel- Haenszel, random effect); CI Confidence interval; Wt%: Study weight in %.

cPVL, NEC or intestinal perforation requiring surgery, PDA ligation and ROP, with [18] or without [9] BPD): RR= 0.80 (0.64, 1.00).

In the analysis of procedural events, the rate of first attempt success is similar between the different approaches. Significantly more extremely preterm infants experience desaturation with a LIST procedure compared to those intubated for surfactant (NNH= 3). This side effect is not different when compared to InSurE. Surfactant reflux is more often described with LIST procedures than with InSurE (NNH= 8).

While the diversity in the reporting of continuous outcome data did not allow their analysis, individual studies (Tables- Online Resource 5) described significant improvements in the durations of mechanical ventilation [9,18,16], of nCPAP therapy [16,11], of any (invasive and non-invasive) respiratory support [1] and oxygen therapy [20]. In most studies reporting statistically similar continuous outcomes, parameters were numerically shorter with LIST strategies.

DISCUSSION

This meta-analysis, including six RCTs addressing LIST strategies, highlights that this modality is associated with improved respiratory outcomes: it decreases early nCPAP failure and mechanical ventilation requirements. Rates of pneumothoraces tend to decrease with LIST. Most importantly, intermediate term respiratory morbidity is improved, with a decreased risk of BPD, either evaluated in all patients or in survivors, or when assessed as a combined outcome with death.

This improvement in rates of BPD and BPD or death may be important, with relative risks of 0.71 and 0.74, and NNTs of 21 and 15, respectively. However, the confidence intervals remain large, and the effect may be as low as a 1% - 6% RR reduction. Significantly, the reductions in BPD rate and MV requirements are also observed in infants born before 29 0/7 weeks, where moderate to long term respiratory morbidity remains a concern. We hypothesize that this improvement is associated with the decrease in invasive ventilation requirements, a major BPD risk factor, reported in the LIST group. Differences in intra-alveolar interactions between surfactant and lung tissues, as shown in a rabbit model, may also play a role [2].

LIST also reduces risk of the composite outcome of BPD or death when compared to InSurE, a finding not previously reported. Both strategies aim to avoid MV; however, infants treated by LIST do breathe spontaneously, while those receiving surfactant by InSurE are exposed to some insufflations. Additionally, a proportion of infants remain intubated after InSur(E) (up to 13.5% in those born below 29 weeks [26,7]). It has been recognised in animals that a few insufflations in the early perinatal period may trigger pulmonary inflammatory mechanisms, an important step in the pathology of BPD [32,12]. The increased risk of early nCPAP failure with InSurE may lead to similar events. The potential differences in risks of minor trauma to the laryngo-tracheal structures and mucosa [8] have not been evaluated.

Notably, the included studies did not restrict their results description to respiratory outcomes, but also reported common neonatal morbidities [13]. The absence of increased risk, and in the smallest patients even a trend toward a reduction in death or composite morbidity, are reassuring: management changes toward LIST should not be associated with a trade-off between respiratory outcomes and other intermediate term complications. This finding is reflected by the results of a large case-control study of very preterm infants from the German Neonatal Network [10], where cases and controls experienced similar neonatal morbidities. Follow-up of extremely preterm infants was reported after the implementation of the LISA strategy in Köln (Cologne), Germany, with an increase in survival without major impairment at 6 years [23]. Another German study reported long term outcomes after a similar change in practice and found improvements in the Physical Developmental Index as well as a trend toward better Mental Developmental Index at 3 years of age [30]. However, long term follow-up data from the randomized studies are still needed to conclude in long term security.

While this meta-analysis gives encouraging results, two large studies comparing MIST with nCPAP and delayed intubation are underway (OPTIMIST A and B trials [5]). Their investigators are planning to include above 1000 patients, more than the total number of infants included in this review. Conversely to the studies included in this meta-analysis, treatment allocation in the OPTIMIST trials will be blinded to caregivers, improving the validity of their results. Besides, other ongoing or planned studies are using InSurE as control group (MISurf, MISTCPAP, ECALMIST, and LISPAP studies; Clinicaltrial.gov, accessed on 01/08/2016).

Some limitations remain in our analysis. In all studies, the intervention consisted of surfactant instillation through a thin catheter in spontaneously breathing preterm infants. Conversely, the control groups were more heterogeneous, using various respiratory management strategies where surfactant was administered through an endotracheal tube with positive pressure insufflations. Those control groups do however reflect the current practice, aiming for the shortest MV duration. The random model effect used in our calculations is more appropriate to heterogeneous studies and, while considered to be more conservative, still leads to positive results. Additionally, the I^2 evaluations of heterogeneity between studies' results were found to be low in the assessments of BPD, BPD or death and early nCPAP failure. On a clinical ground, results similar to those of this review were described in the large case-control study of very preterm infants from the German Neonatal Network [10]. Nevertheless, we acknowledge that different approaches may also lead to different outcomes and we therefore presented the detailed data with subgroup analyses (Online Resource 3). Given this limitation, caution must be used when assessing RR and NNTs from combined outcomes.

The design of two studies potentially downsized the evaluation of LIST benefits. The AMV study [9] used different inclusion criteria than those originally specified for this review: patients were included on the basis of gestational age, irrespective of their respiratory status. It is unlikely that they differed in respiratory distress syndrome incidence as both groups were

adequately matched, notably regarding baseline respiratory status. A reduction in study group populations would have therefore resulted in more pronounced differences favouring the LIST modality. The same study also compared LISA with a delayed surfactant strategy rather than two different techniques with a same threshold for surfactant. In a supplementary file, the AMV investigators provided respiratory and death outcomes stratified by surfactant intervention. Analyses were repeated with the data for surfactant treated infants (thus, patients are different at baseline in this post-hoc analysis, with Control patients having higher oxygen requirements). This post-hoc analysis was then restricted to patients who effectively received LISA in the intervention group and controls who received surfactant. This likely increased bias further, as this additionally excludes patients receiving surfactant while intubated, who were possibly sicker, from the intervention group. For both approaches, results were similar to those of the meta-analysis (data not shown). In the Mohammadizadeh et al. study [20], the risk of selective outcome reporting related to the exclusion of infants remaining intubated after InSurE, if significant, would also likely have influenced results toward LIST appearing less beneficial.

The techniques used for surfactant instillation differ between trials. Three studies described the tracheal introduction of an end-hole feeding catheter held with Maggil forceps [9,20,18]. This procedure corresponds to LISA as suggested by Kribs et al. [17] In the Take Care study, the feeding catheter was handled directly [16]. Mirnia et al. don't report use of Maggil forceps in their Thin Endotracheal Catheter method, which is therefore similar to Take Care [19]. Finally, Bao et al. used a 13 cm angiocath to catheterize the trachea [1]. While Dargaville et al. originally coined the name MIST for this technique [4], Bao et al. used the abbreviation LISA in their study. The purpose of the new acronym LIST in this report is to inclusively name all those methods. Surfactant administered with those different techniques will most likely have similar mechanisms of action. However, procedural effectiveness might differ according to the device used; this will require further study [25].

The different LIST trials used nearly exclusively the surfactant poractant-α (31 patients received bovine derived surfactant in the AMV trial [9]). The doses differed between studies, ranging from 100 mg/kg [9,16] or at least 100mg/kg [18] to 200 mg/kg [11,1,20]. For comparison, treatment of very preterm infants intubated for respiratory distress syndrome with 200 mg/kg of poractant-α rather than 100 mg/kg was associated with less need for additional doses and a decrease in mortality [24]. As an animal model showed better surfactant association with lung tissues with spontaneous breathing [2], assuming identical results with LIST strategies is not straightforward.

While coined "Less Invasive", the LIST strategies still require the insertion of a laryngoscope blade to expose the vocal cords. While this clearly is a noxious procedure, the use of analgesia or sedation remains controversial as it might decrease the respiratory drive. Its use wasn't allowed in the studies using InSurE as control [11,16,20,1]. Only in the AMV study were procedural medications optional. One small retrospective study found an improved comfort score during laryngoscopy and surfactant instillation when propofol analgesia was used, without adverse effects reported [6].

Other aspects of the procedure will require additional investigations. The modality of non-invasive respiratory support during and after the procedure is important, as using nasal intermittent positive-pressure ventilation rather than nCPAP decreased respiratory failures and moderate to severe BPD [22].

While LIST strategies are associated with reductions in invasive ventilation requirements, their failure rate remains elevated: 40% (in the NINSAPP study LISA arm, 75% of the extremely preterm infants required intubation during their stay). It will be important to characterize factors associated with the highest rates of failure [3] and to investigate if alternative managements offer better outcomes for selected high risk infants.

In conclusion, surfactant instillation through a thin catheter in spontaneously breathing preterm infants decreases the risks of BPD and of BPD or death and reduces invasive ventilation requirements. The only side effect reported is an increase in procedural desaturation in the most preterm infants (<27 weeks)[18]. When compared to InSurE, infants treated with LIST experience less composite outcome of BPD or death. While those results are promising, both the results of ongoing blinded large studies and long term follow-up data are awaited to strengthen the analysis. Studies comparing LIST and InSurE should also report results stratified by GA to allow evaluation of important outcomes, notably in extremely low gestational age infants.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest: VR has received speaker honoraria and sponsoring to attend a scientific meeting from Chiesi Belgium, a surfactant-producing company. The company was not involved in this study. CL and IB declare having no conflict of interest.

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Ethical approval: this article does not contain any study with human participants performed by any of the authors. All studies included in the meta-analysis were approved by ethical review boards and requested parental consent.

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ADDITIONAL FIGURES AND TABLES

Online Resoucre 1: Figure: Flow diagram for selection of eligible studies.

Online Resource 2: Table: Risk of bias assessment.

Online Resource 3: Figure: Forest plots for each dichotomous outcomes.

Online Resource 4: Figure: Forest plots for infants born below 29 weeks.

Online Resource 5: Table: Data for continous outcomes.