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Surfactant Lavage Therapy for Meconium Aspiration Syndrome: A Systematic Review and Meta-Analysis

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Key Words
Meconium · Meconium aspiration syndrome · Surfactant · Pulmonary surfactant · Bronchoalveolar lavage · Neonate

Abstract
Background: Lung lavage with diluted surfactant has emerged as an innovative treatment for meconium aspiration syndrome (MAS). However, the treatment effect has not yet been fully established. ***Objective:*** To investigate the effects of surfactant lavage therapy for MAS by a systematic meta-analysis. ***Methods:*** Relevant studies were identified by database searches in MEDLINE (from 1950), EMBASE (from 1980), and CENTRAL, up to June 2010, and by additional hand searches. Meta-analyses were separately conducted for randomized controlled trials (RCTs) and non-randomized controlled studies (NRSs). Risk of bias was assessed and clinical as well as statistical heterogeneities were also investigated in explaining the potential bias. ***Results:*** Two RCTs (87 patients) and eight NRSs (178 patients) were identified. From the results of the meta-analysis of RCTs, surfactant lavage significantly decreased death or the need for extracorporeal membrane oxygenation (RR 0.34, 95% CI 0.11, 0.99). An interventional benefit was indicated for other outcomes, although it was not statistically significant based only on the two RCTs. Results from the analysis of outcomes from NRSs are consistent with those from RCTs and demonstrated a beneficial effect, which could be considered as supporting evidence. ***Conclusions:*** Lung lavage with diluted surfactant appeared to improve the clinical outcome in infants with MAS. Given that less than 100 infants were included in the two RCTs, the findings of this study may still be regarded as insufficient evidence. Further research will be needed to confirm the benefit as well as to refine the lavage technique.

Background

Meconium aspiration syndrome (MAS) is an important cause of respiratory distress in neonates, sometimes leading to respiratory failure and even death [1, 2]. Therapy for MAS is mainly supportive, but use of innovative treatments such as high-frequency ventilation or inhaled nitric oxide has increased and seems to be of benefit to patients who are refractory to conventional mechanical

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ventilation [2, 3]. However, these therapies are not routinely available.

The pathophysiology of MAS is characterized by airway obstruction, chemical pneumonitis by aspirated meconium, and pulmonary hypertension induced by in utero hypoxia [4, 5]. Meconium damages the alveolar epithelium and inhibits pulmonary surfactant function; this inhibitory action is concentration-dependent [6, 7]. Based on these rationales, surfactant therapy is thought to have a direct influence on the pathophysiology of MAS.

Treatment options with surfactant for MAS include bolus surfactant administration and lung lavage with diluted surfactant. Bolus surfactant therapy has been found to improve oxygenation [8, 9]. A recent systematic review based on four randomized controlled trials (RCTs) for bolus surfactant therapy in MAS suggested that surfactant therapy decreases progressive respiratory failure requiring extracorporeal membrane oxygenation (ECMO), though the effect on mortality or pulmonary morbidity was not shown [10].

Lung lavage with diluted surfactant has been proposed as an alternative method of surfactant use for MAS, which could, theoretically, alter the natural course of MAS by enhancing the removal of meconium from the airways and augment surfactant function [11]. Several investigators have reported that diluted surfactant lavage improved oxygenation in infants with MAS and surfactant lavage was done safely in most of the studies [12–16]. A review of surfactant therapy in MAS suggested a reduction in ventilator days and a lower incidence of pneumothorax for surfactant lavage therapy; however, clinical outcomes of interest other than those were not comprehensively evaluated [17].

In this study, we conducted a meta-analysis by systematically reviewing the most up-to-date available evidence in the current literature to assess the effectiveness of surfactant lavage therapy for infants with MAS.

Methods

Study Inclusion, Data Extraction, and Bias Assessment

We evaluated RCTs and non-randomized controlled studies (NRSs) meeting the following inclusion criteria: (1) the patients were infants with MAS, and (2) lung lavage with diluted surfactant was compared to a non-surfactant control. Case reports, letters, commentaries and narrative reviews were excluded.

Three electronic databases, MEDLINE (from 1950), EMBASE (from 1980), and CENTRAL (Cochrane Central Register of Controlled Trials) were searched up to June 2010. We also screened abstracts published from 2000 to June 2010 in *Pediatric Research* or from meetings of Pediatric Academic Societies. Search strategies were constructed using the terms 'meconium', 'meconium aspiration syndrome', 'surfactant', and 'lavage'. Some local databases and bibliographies of relevant articles were also searched. No language restrictions were applied.

A standardized form was used for data extraction and the following outcomes were abstracted: mortality, need for ECMO, air leaks (pneumothorax, pulmonary interstitial emphysema, pneumomediastinum, and pneumopericardium), pneumothorax, duration of mechanical ventilation, duration of supplemental oxygen, and duration of hospital stay. The composite outcome of death or need for ECMO was considered the primary outcome.

The quality of eligible RCTs was assessed using Cochrane Collaboration's tool for assessing the risk of bias for RCTs [18]. For the NRSs, the methodological quality was assessed regarding the selection of the intervention group, the comparison with contemporary groups, the baseline comparability of groups, and the blinding of the investigators and outcome assessments [19]. The decision on eligibility, data extraction and the risk of bias assessment was done by at least two reviewers independently and any differences in assessment were resolved by discussions between the authors.

Statistical Analysis

A meta-analysis was done with the relative risk calculated for dichotomous outcomes. We primarily used a fixed-effects model with weighting of each individual study parameter according to the reciprocal of its variance since there was no statistical heterogeneity present. The random-effects model was additionally used to check how the results might differ with a change in the model assumption. The test for heterogeneity was done based on χ^2 statistics and the statistical heterogeneity was evaluated at a 10% significance level. I^2 values were also calculated to assess the appropriateness of combining study results. Continuous outcomes were descriptively presented in a table without statistical pooling due to the skewness of the data. All analyses were separately conducted according to the study design (RCT vs. NRS) for each outcome. An additional subgroup analysis was also done to identify the effect of intervention on mortality according to ECMO availability. Publication bias was assessed by funnel plot asymmetry and Egger's test [20]. All analyses were done using the Stata Statistical Package Version 11 (Stata Corp., College Station, Tex., USA).

Results

Study Description

Out of 474 articles identified by the initial search strategies, ten studies were included in the analyses: two RCTs [13, 21] and eight NRSs [12, 14–16, 22–25] (Appendix 1). The characteristics of the studies included are presented in table 1. One study performed saline lavage for some of the patients in the control group [22]. In all the other studies, respiratory management for the control group did not differ from that for the intervention group except for the performance of surfactant lavage. Surfactant bolus therapy was given when necessary, irrespective of the

Table 1. Characteristics of the studies included

Study (first author)	Study design	Study population (treatment year, number of subjects)	Baseline OI (i/c)	Mean timing of lavage (h after birth)	Total lavage volume	Aliquot volume	Lavage fluid concentration	ECMO availability	Use of HFV (i, c)	Use of iNO (i, c)
Wiswell 2002 [13]	RCT	(i) n = 15 (c) n = 7	average 12	14–15	48 ml/kg	8 ml/kg	Lucinactant 2.5–10 mg/ml	yes	yes	yes
Dargaville 2011 [21]	RCT	(i) n = 30 (c) n = 35	average 25	14	30 ml/kg	15 ml/kg	Beractant 5 mg/ml	available in some centers	yes	yes
Dargaville 2007 [16]	NRS	(i) 1999–2002, n = 8 (c) 1997–2003, n = 34 concurrent control	40/34	29.5 (median 23)	9–30 ml/kg	3–15 ml/kg	Beractant 5 mg/ml	yes	yes (100%)	yes (88%, 71%)
Chang 2003 [14]	NRS	(i) 2000–2002, n = 12 (c) 2000–2002, n = 10 concurrent control	32.5/31.4	4.2 or 5.2	6–7 ml/kg or 12–14 ml/kg	2 ml	Beractant 10 mg/ml or 5 mg/ml	not reported	yes (100%)	yes (42%, 90%)
Schlösser 2002 [22]	NRS	(i) 1987–1998, n = 11 (c) 1987–1998, n = 7 concurrent control	22/15.8	not reported	20 ml	5 ml	Beractant 5 mg/ml	yes	yes (18%, 14%)	yes (55%, 71%)
Kawano 1999 [25]	NRS	(i) 1992–1997, n = 17 (c) 1987–1992, n = 17 historical control	not reported	6.3	approx. 7–10 ml/kg	approx. 2–3 ml/kg	Lavage fluid not specified 6 mg/ml	yes	yes	(i) yes (since 1993) (c) no
Lee 2008 [23]	NRS	(i) 2006–2007, n = 7 (c) 2005–2006, n = 8 historical control	16.9/15.3	10.35	20 ml/kg	2.5 ml/kg	Beractant 5.3 mg/ml	not reported	not reported	not reported
Lam 1999 [12]	NRS	(i) 1996–1997, n = 6 (c) 1994–1995, n = 6 historical control	18.4/20.9	3	15 ml/kg	2 ml	Beractant 5 mg/ml	no	not reported	not reported
Salvia-Roiges 2004 [15]	NRS	(i) 1997–2000, n = 7 (c) 1996–1997, n = 6 historical control	31.0/27.2	median 6	15 ml/kg	3.75 ml/kg	Beractant 5 mg/ml	not reported	no	yes
Kowalska 2002 [24]	NRS	(i) 1998–2000, n = 11 (c) 1995–1997, n = 11 historical control	19.0/22.4	<6	15 ml/kg	not reported	Beractant 5 mg/ml	not reported	not reported	not reported

i = Intervention group; c = control group; OI = oxygen index; ECMO = extracorporeal membrane oxygenation; HFV = high-frequency ventilation; iNO = inhaled nitric oxide; RCT = randomized controlled study; NRS = non-randomized study.

treatment group, in both the RCTs and two NRSs [16, 25]. The studies included were observed to be clinically heterogeneous in the severity of the disease, method of surfactant lavage, initial intervention time, and combined treatment modalities.

Risk of Bias Assessment

Of the two RCTs, the patient allocation procedure was adequate in one study [21]. In the other study, the allocation procedure was unclear and it was also thought that performance bias may have existed because the number of patients receiving rescue therapy was more than the number of patients with treatment failures, though rescue therapies were not allowed unless patients met treatment failure [13]. The study was conducted without a formal sample size calculation but based on an estimate for assessing the safety and potential of efficacy in a rather exploratory fashion.

For the three NRSs with concurrent control [14, 16, 22], the choice of combined treatments, such as high-frequency ventilation or inhaled nitric oxide, could have been biased by the knowledge of the allocation of intervention. With five NRSs having historical control [12, 15, 23–25], advances in respiratory support in neonate intensive care are thought to be components able to cause bias. For baseline comparability, Kowalska et al. [24] reported that the proportion of infants with an Apgar score of 0–3 points in the first minute after delivery in the con-

Table 2. Risk of bias assessment of the studies included

Study design/ID	How allocation occurred	Comparability between groups	Blinding of intervention	Free of other bias
RCT				
Wiswell, 2002	no description for process of randomization and allocation concealment	yes	no	no
Dargaville, 2011	adequate process of randomization and allocation concealment	yes	no	yes
NRS				
Dargaville, 2007	concurrent controls by clinician's decision	no	no	unclear
Chang, 2003	concurrent controls upon parent's consent	yes	no	unclear
Schlösser, 2002	concurrent controls; no description of method of allocation	no	no	unclear
Kawano, 1999	historical controls	yes	no	unclear
Lee, 2008	historical controls	yes	no	unclear
Lam, 1999	historical controls	yes	no	unclear
Salvia-Roiges, 2004	historical controls	yes	no	unclear
Kowalska, 2002	historical controls	no	no	unclear

Table 3. Summary of meta-analyses

Outcome	RCT					NRS				
	studies n	patients n (i/c)		RR (95% CI)	I^2 (p value)	studies n	patients n (i/c)		RR (95% CI)	I^2 (p value)
Death or need for ECMO	2	45/42	fixed random	**0.34 (0.11–0.99)** **0.34 (0.12–1.00)**	0% (0.794)	6	64/57	fixed random	**0.35 (0.13–0.94)** **0.33 (0.11–1.00)**	0% (0.698)
Mortality (overall)	1	30/35	fixed random	0.44 (0.13–1.50)	NA	6	55/74	fixed random	0.41 (0.13–1.26) 0.43 (0.13–1.48)	0% (0.820)
ECMO available	1	11/14	fixed random	1.27 (0.21–7.65)	NA	2	19/41	fixed random	1.64 (0.19–14.58) 1.61 (0.18–14.40)	0% (0.845)
ECMO unavailable	1	19/21	fixed random	0.18 (0.02–1.39)	NA	4	36/33	fixed random	**0.23 (0.05–1.01)** **0.24 (0.05–1.04)**	0% (0.988)
Need for ECMO	2	26/21	fixed random	0.27 (0.04–1.86) 0.30 (0.04–2.08)	0% (0.617)	3	36/55	fixed random	0.41 (0.11–1.48) 0.43 (0.10–1.86)	0% (0.371)
Air leak	–	–	–	–		6	56/82	fixed random	**0.52 (0.28–0.96)** 0.61 (0.33–1.14)	0% (0.698)
Pneumothorax	2	45/42	fixed random	0.39 (0.08–1.95) 0.42 (0.07–2.37)	0% (0.327)	5	58/51	fixed random	**0.45 (0.23–0.89)** 0.52 (0.23–1.20)	15.4% (0.316)

RCT = Randomized controlled trial; NRS = non-randomized controlled study; n = number; i = intervention group; c = control group; RR = risk ratio; CI = confidence interval; NA = not applicable.

Results of statistical significance or of marginally statistical significance at the 5% level are indicated in boldface.

Studies that reported the outcome but in which no event occurred in any of the treatment groups, and therefore are of no contribution to the analysis, were excluded from counts of the number of studies and patients.

trol group was greater than in the intervention group. In the studies by Schlösser et al. [22] and Dargaville et al. [16], the initial oxygen index of the intervention group was higher on average than that of the control group. In the other studies, the difference in the baseline characteristics between the groups was not considered a concern.

Investigators were not blinded in any of the RCTs or NRSs. Though all outcomes are considered objective measures, some outcomes, such as duration of mechanical ventilation or oxygen therapy, can also possibly be affected by the clinicians' blinding because those are determined under their direct control. Results of the assessments of both RCTs and NRSs are summarized in table 2.

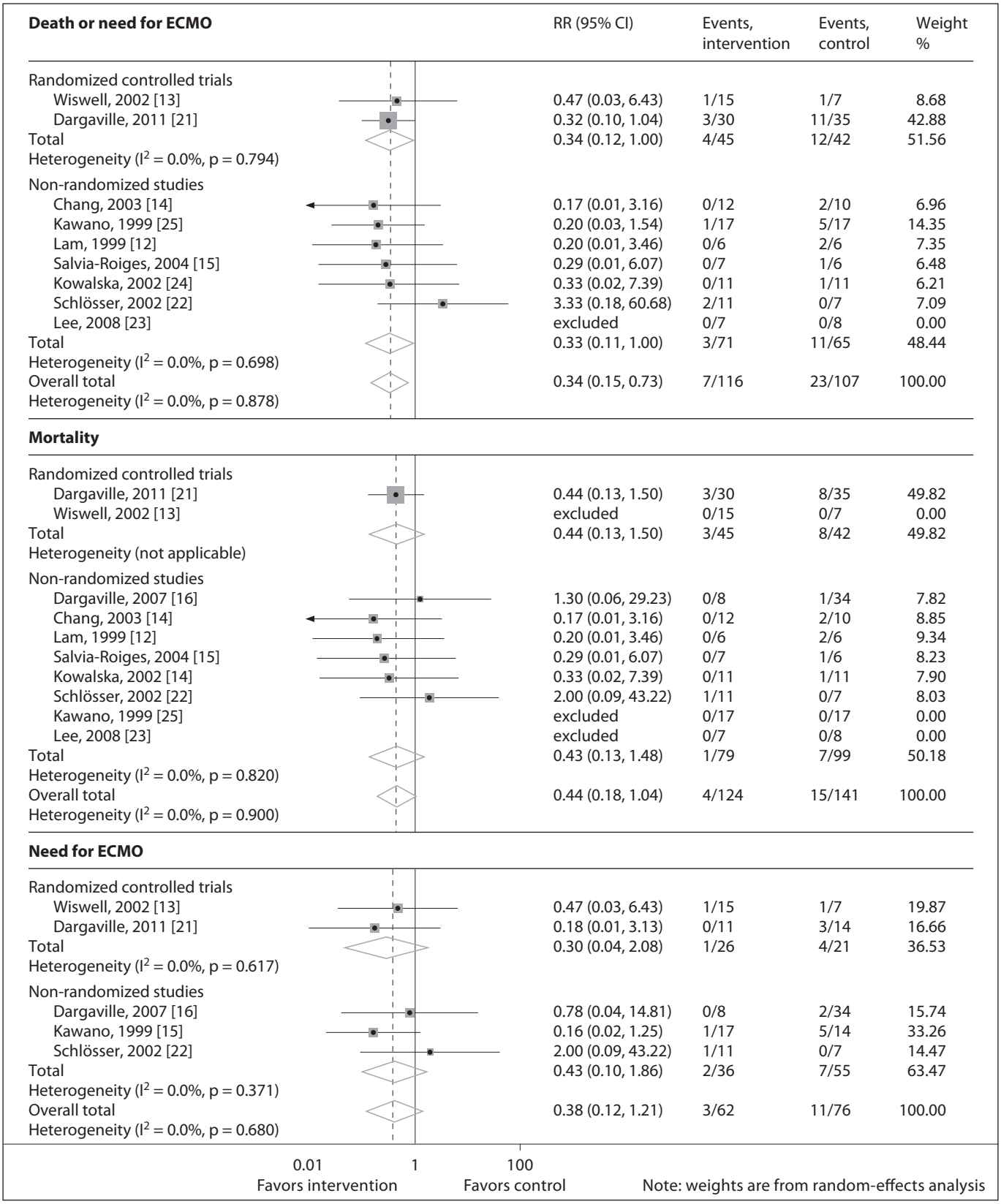

Fig. 1. Forest plot of main outcomes: death or need for ECMO, mortality, need for ECMO. CI = Confidence interval; RR = risk ratio.

Table 4. Results of continuous outcomes

Study design	Study (first author)	Number of patients (i/c)	Duration of mechanical ventilation		Duration of supplemental oxygen		Duration of hospital stay	
			intervention	control	intervention	control	intervention	control
RCT	Wiswell, 2002 [13]	7/15	4.6 (1.1–22.3)	7.6 (1.1–28)	13.5 ± 9.3	12.1 ± 10.7	12.7 ± 8.7	13.1 ± 10.3
	Dargaville, 2011 [21]	30/35	5.5 (3.4–12)	6.0 (4.3–10)	14 (6.7–21)	14 (11–18)	16 (9.7–23)	18 (10–24)
NRS	Dargaville, 2007 [16]	8/34	5.7 (–)	4.9 (–)	–	–	–	–
	Chang, 2003 [14]	12/10	10.0 ± 4.9	10.4 ± 7.8	13.2 ± 5.4	15.3 ± 12	17.6 ± 6.1	19.5 ± 9.7
	Schlösser, 2002 [22]	11/7	5.9 ± 7.3	7.3 ± 2.4	8.6 ± 7.0	7.3 ± 2.8	–	–
	Kawano, 1999 [25]	17/17	13.8 ± 11.6	17.6 ± 9.3	13.5 ± 5.9	25.4 ± 15.4	31.8 ± 15.1	45.6 ± 14.4
	Lee, 2008 [23]	7/8	1.7 ± 0.1	2.8 ± 0.4	2.2 ± 0.6	3.4 ± 0.3	9.0 ± 2.3	12.6 ± 4.1
	Lam, 1999 [12]	6/6	2.3 ± 2.1	5.4 ± 2.5	4.1 ± 0.5	20.1 ± 8.1	–	–
	Salvia-Roiges, 2004 [15]	7/6	7.0 (5–10)	7.0 (4–8)	8.0 (6–12)	10.0 (7–13)	22.0 (14–29)	19.0 (13–28)
	Kowalska, 2002 [24]	11/11	5.6 ± 4.1	5.9 ± 4.8	–	–	20.5 ± 8.8	22.4 ± 11.3

i = Intervention group; c = control group; RCT = randomized controlled study; NRS = non-randomized study.
All variables expressed by mean ± SD or median (interquartile range).

Results of Meta-Analyses

Surfactant lavage significantly decreased death or the need for ECMO in both RCTs (RR 0.34, 95% CI 0.11, 0.99) and NRSs (RR 0.35, 95% CI 0.13, 0.94) (fig. 1; table 3). All studies except one by Schlösser et al. [22], in which more severe patients were involved in the treatment group at the baseline, consistently showed intervention-favorable results.

All studies reported on mortality, but one RCT [13] and two NRSs [23, 25] found that no actual event occurred. Mortality risk favored the intervention group in all studies in the analysis but two NRSs [16, 22] (fig. 1). In those two studies, the actual patients involved had a higher initial oxygen index in the intervention group at baseline. If adjusting for the baseline condition, the treatment difference could be shifted towards a more consistent direction of beneficial effect as with other studies' results.

The mortality was reported separately for ECMO-available centers and ECMO-unavailable centers in the RCT [21]. Out of six NRSs included in the analysis of mortality, three NRSs did not specifically mention the availability of ECMO during the study [14, 15, 24]; however, we determined from the circumstances that ECMO was not an available option for those studies. A subgroup analysis showed that the relative risk of mortality was fairly lower in the settings where ECMO was unavailable. The analyses of need for ECMO showed similar results of an interventional benefit both in the RCTs and the NRSs, although it was not statistically significant in either meta-analysis.

Only the NRSs reported on air leaks [12, 15, 16, 23–25], and the overall treatment effect was significant without a statistical heterogeneity. Both RCTs and five of the NRSs [14, 15, 22, 24, 25] reported on pneumothorax. The treatment difference did not reach a statistical significance in the RCTs. All the NRSs also suggested a reduced number of pneumothorax events in the intervention group and the combined effect was statistically significant. However, in those NRSs, whether the event occurred before or after the intervention was given was not clearly described.

No statistical heterogeneity was present in any of the meta-analyses. The spread of results in individual studies for the primary outcome and other outcomes is shown in figure 1. The combined result for each outcome using the random-effects model was also presented side by side with the result by the fixed-effects model in table 3. Both results were very similar in the two models on the whole, although there was a slight change from the statistical significance to the marginal borderline significance in the primary outcome, and the results on air leaks and pneumothorax from the NRSs lost statistical significance. Funnel plot assessment did not reveal an indication for publication bias (Appendix 2). The significant asymmetry was not observed by Egger's test (p = 0.686).

Treatment Effects on Continuous Outcomes

Studies that reported on duration of mechanical ventilation, duration of supplemental oxygen, and duration of hospital stay are summarized in table 4. Most of the studies, except for the two NRSs [15, 16, 24], showed a shorter duration for mechanical ventilation in the intervention group. In the two RCTs, no treatment effect on the duration of supplemental oxygen was observed, while in the NRSs significant heterogeneity was present. Some

NRSs [12, 25] showed more than a 10-day decrease in duration of supplemental oxygen in the intervention group compared to the control group, whereas the other studies showed similar results with around 2 days of difference between the groups. Despite the observed variability of the results, most of the studies both in the RCTs and NRSs showed a shorter length of stay in the intervention group except one NRS.

Discussion

Surfactant lavage showed a statistically significant beneficial effect on the primary outcome of death or need for ECMO in the meta-analysis of the two RCTs. A result of the subgroup analysis done to identify the effect of intervention on mortality according to ECMO availability suggested that a composite evaluation of mortality and the need for ECMO, rather than mortality only, should be considered, since the mortality can be underestimated where ECMO was available. Although other outcomes, including mortality and a need for ECMO, did not demonstrate a statistical significance based on those RCTs, a clear trend towards the beneficial effect in most of the outcomes was observed. Considering that there were only two randomized controlled studies available and that the number of patients included in those two RCTs combined was less than 100, this may be regarded as insufficient evidence, but yet indicative of a beneficial effect.

As there were not enough RCTs available in the current literature, we also investigated the results from nonrandomized comparative studies using a systematic approach to consider them as a supporting source of evidence. The strength of the evidence to support the effect of surfactant lavage would have to be considered only as supporting evidence by taking into account the fact that there was a higher risk of bias in the NRSs. Some NRSs used a historical control, which can cause the later group, the intervention group, favorable results, as survival of infants with MAS has improved over time [2]. On the other hand, the allocation methods in the NRSs with a concurrent control seemed to be prone to a selection bias. Nonetheless, comparing the results found from the RCTs, we have confirmed that the direction and the magnitude of the treatment effect were observed to be highly consistent, which suggested that the evidence from the selected NRSs could supplement the current lack of RCTs. In the NRSs, the results of the meta-analysis suggested that surfactant lavage had a significant effect on air leaks, pneumothorax, and death or the need for ECMO.

The timing of the lavage may contribute to the results as discussed in some studies [21, 26]. Early intervention is possibly more effective. Physiological changes started acutely within 1 h after the instillation of meconium and peak lung injury by meconium was observed between 12 and 24 h in animal models [5, 27]. The timing of the surfactant lavage in the studies that were included ranged on average from 3 to 30 h after birth and the postnatal age at the time of intervention in the RCTs tended to be late compared to that in the NRSs. The delay in administering the treatment in the RCTs may be due to the randomization procedure in that the time for confirmation of inclusion, acquisition of parent's consent, and randomization and allocation were all required which was also mentioned in one study [21].

Of the two RCTs, the subjects of one study had milder MAS than those of the other study (average baseline oxygen index of 12 vs. 25). Results from the study in milder patients showed a trend towards reduction in duration of mechanical ventilation by surfactant lavage, while none of the patients died in either treatment group. On the other hand, the other study that involved patients with more severe conditions did not suggest a notable difference in the duration of respiratory support, but the surfactant lavage appeared to affect mortality. This suggests that whether the patients have a greater benefit from the intervention could depend on the disease severity. Some further analyses stratified by the timing of the lavage or baseline severity of MAS would have been helpful to evaluate how these factors affect the effect of intervention. However, it was not possible to do such analyses in the current framework without having access to the individual patient data of each study.

Though many studies presented a positive effect for surfactant lavage, there are still some concerns about its safety, that is, whether infants with MAS can tolerate the procedure or not. A large volume of fluid instillation to a lung might be a burden on a newborn, especially in cases of severe MAS with pulmonary hypertension; lung lavage may exacerbate hypoxia and lead to mortality [28, 29]. In some NRSs, transient hypoxemia, bradycardia, or hypotension was reported, which usually recovered spontaneously and sometimes needed supportive management [12, 14–16, 23]. In one RCT, 1 patient with intractable pulmonary hypertension died 3 h after the lavage [21]. The other RCTs described 3 patients who failed to complete lavage therapy, though investigators explained that it might be partially related with another concomitant morbidity, not with lavage therapy. Patients in the RCTs received relatively large volumes of

lavage fluid compared to those of the NRSs, which could be one of the reasons for the more frequent and more serious events found in the RCTs. An observational study comparing a small (20 ml) and a large (40 ml) volume of diluted surfactant lavage for MAS reported fewer adverse events for the small lavage volume [30]. Using a large volume of lavage in severe MAS would require caution because its risk can outweigh the potential benefit.

Further trials should be supplemented to refine the method of surfactant lavage. Trials that compare different combinations of volumes, concentrations, and methods of delivery would be appropriate. The efficacy of surfactant lavage compared to other approaches such as surfactant bolus or combined use of surfactant lavage with bolus remains to be determined. Long-term benefits such as reduction in neurological sequelae should be further assessed. Safety by disease severity should also be investigated.

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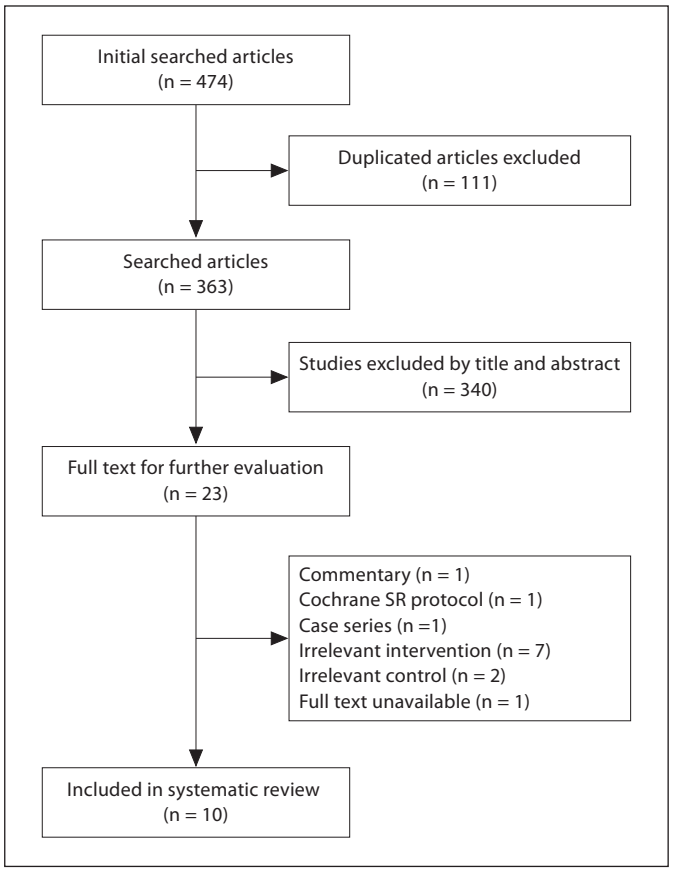
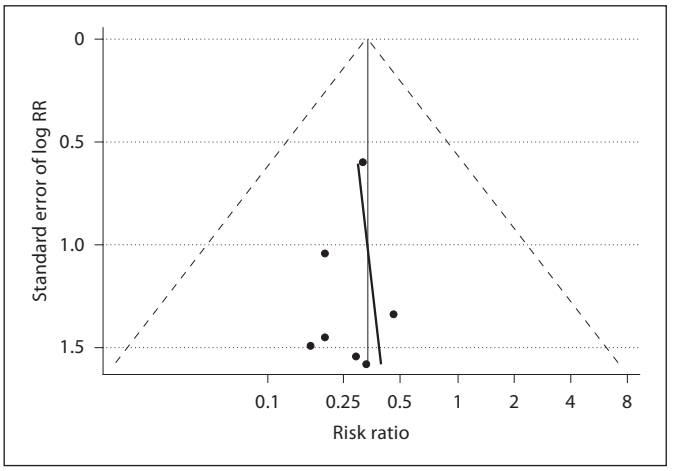
Appendix 1

Flow of systematic selection of literature.



Appendix 2

Funnel plot for evaluation of publication bias: the primary outcome of death or need for ECMO. The fitted line corresponds to the regression test for funnel plot asymmetry proposed by Egger et al. [20]. RR = Risk ratio; log RR = log of the risk ratio.



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