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Surfactant lavage for neonatal meconium aspiration syndrome—An updated meta-analysis

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Abstract

Background: Surfactant lavage seems to have a good application prospect both in experimental models and patients with meconium aspiration syndrome (MAS). Data regarding the effect of surfactant lavage on pulmonary complications of MAS are conflicting. In view of these uncertainties, an updated meta-analysis including the latest literatures is performed.

Methods: A search was conducted by two investigators involved in this research in PubMed, Embase, and Cochrane databases for studies in English and other languages, in Wanfang, VIP, and Cnki databases for Chinese studies (all last launched on December 18, 2018). Ultimately, we identified 11 original studies, including the surfactant lavage group (n = 189) and the control group (n = 204). Odds ratio and weighted mean difference were calculated using a random effects or fixed effects model, depending on the data type and heterogeneity of the included studies.

Results: The comparison of effectiveness on MAS: (1) With respect to oxygen index at 48 hours stage and 72 hours stage, data showed significant difference between surfactant lavage/control groups (we/ighted mean difference [WMD] = –3.37, 95% confidence interval [CI], –5.68 ~ –1.06; p = 0.004 and 95% CI, –5.03 ~ –2.37; p < 0.00001). (2) With respect to days on mechanical ventilation, the analysis showed that there was significant difference between surfactant lavage group and control group (WMD = –1.12, 95% CI, –1.40 ~ –0.84; p < 0.00001). (3) Regarding the need for extracorporeal membrane oxygenation, days of oxygen therapy, and hospital stay, no significant differences were found. The comparison of possible complications of MAS: (1) Regarding pneumothorax, the analysis showed there was significant difference between surfactant lavage and control groups (odds ratio [OR] = 0.46, 95% CI, 0.24 ~ 0.85; p = 0.01). (2) With respect to mortality, persist pulmonary hypertension and pulmonary hemorrhage, the results showed no difference between the two groups.

Conclusion: With respect to oxygen index and days on mechanical ventilation, surfactant lavage is significantly effective compared with control group, though didn't eventually shorten days of oxygen therapy and hospital stay. In addition, our meta-analysis showed that surfactant lavage does not increase the risk of complications.

Keywords: Meconium aspiration; Meta-analysis; Surfactant lavage

1. INTRODUCTION

Meconium aspiration syndrome (MAS) is a complex pulmonary disease in term infants and may result in considerable respiratory morbidity. This disease has classically been defined as severe respiratory distress with specified chest radiographic manifestation in infants born through meconium-stained amniotic fluid.[1,2] In emerging developing countries, MAS is still a serious problem.[3,4] For example, in China, though there haven't been detailed data from large sample and multicenter study, the incidence of MAS reported by different single centers has reached 0.2%–1.3%.[5,6] Therapy for this disease mainly depends on effective respiratory support. However, the use of innovative therapies such as inhaled nitric oxide (iNO) and high frequency ventilation (HFV) seems doesn't shorten the duration of ventilation or oxygen therapy.

In routine clinical practice, the deficiency of surfactant or surfactant dysfunction contributes to final respiratory failure in a broad group of disorders, just including MAS. In fact, meconium inhibits the surface tension-lowering properties of surfactant.[7,8] So, instillation of meconium into airways of term animals could lead to acute mechanical obstruction and worsening pulmonary mechanics and gas exchange.[8,9] In animals with experimentally induced meconium aspiration, treatment with large doses of animal-derived surfactant extract improves lung compliance and ventilation.[10] Consequently, in theory, surfactant lavage seems to have a good application prospect both in experimental models and patients with MAS. Data regarding the effect of surfactant lavage on pulmonary complications of MAS are still conflicting. Some recent studies have shown that surfactant lavage improves lung function and decreases morbidity in neonates with MAS.[11,12] In addition to that, previous meta-analysis of the data from these trials supports in reducing the use of extracorporeal membrane oxygenation (ECMO), but not a reduced incidence of pulmonary complications.[13]

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So, in view of the contradiction and uncertainty, an updated meta-analysis including the latest literature in different languages is performed to evaluate the potential effect of surfactant lavage on MAS.

2. METHODS

2.1. Study selection

Guidelines from the CONSORT (CONsolidated Standards Of Reporting Trials) group and the CONSORT statement were followed for this systematic review and meta-analysis.[14,15] To screen eligible studies published since each database was established, a search was conducted by two investigators involved in this research in PubMed, Embase, and Cochrane databases for studies in English and other languages, in Wanfang, VIP, and Cnki databases for Chinese studies (databases were last launched on December 18, 2018). The following search terms were employed: "meconium aspiration syndrome," "MAS," "surfactant lavage," and "surfactant." The inclusion criteria of this meta-analysis were as follows: (1) controlled test involving MAS with surfactant lavage treatment; (2) except surfactant lavage, treatment group and control group received the similar respiratory management, including oxygen inhalation, mechanical venation, etc.; and (3) human clinical studies. Hence, non-controlled studies, case reports, reviews, meta-analyses, animal experiments, and studies without sufficient clinically relevant data were excluded. Any discrepancies were independently resolved by a third investigator involved in this research.

2.2. Data abstraction

The CONSORT statement contains 22 items including participants, intervention, objectives, outcomes, randomization, blinding, statistical method, participant description, recruitment, baseline data, and others. The quality of all included studies was assessed by the CONSORT items and Jadad score. Finally, from the full-text and corresponding supplement information, the following eligibility items were collected and shown in tables for each study: author, year of publication, participants, gestation, mean timing of lavage, lavage volume, type of lavage, application of surfactant, respiratory strategy, use of ECMO, use of iNO, exclusion, primary outcomes, randomization, blinding, Jadad score, and CONSORT items. Subsequently, the outcomes were divided into two parts. First was the comparison of effectiveness of surfactant lavage treatment on MAS (including oxygen index, need for ECMO, days on mechanical ventilation, days of oxygen therapy, and hospital stay). Second, with respect to the possible complications of MAS, death, neonatal persist pulmonary hypertension (PPHN), pulmonary hemorrhage, and pneumothorax were compared between surfactant lavage and control groups.

2.3. Statistical analysis

For each outcome, either odds ratio (OR) or weighted mean difference (WMD) with the 95% confidence interval (95% CI) was calculated, depending on the data type. Both a fixed effects model and a random effects model were considered. For each meta-analysis, the χ^2-based Q statistic test (Cochran's

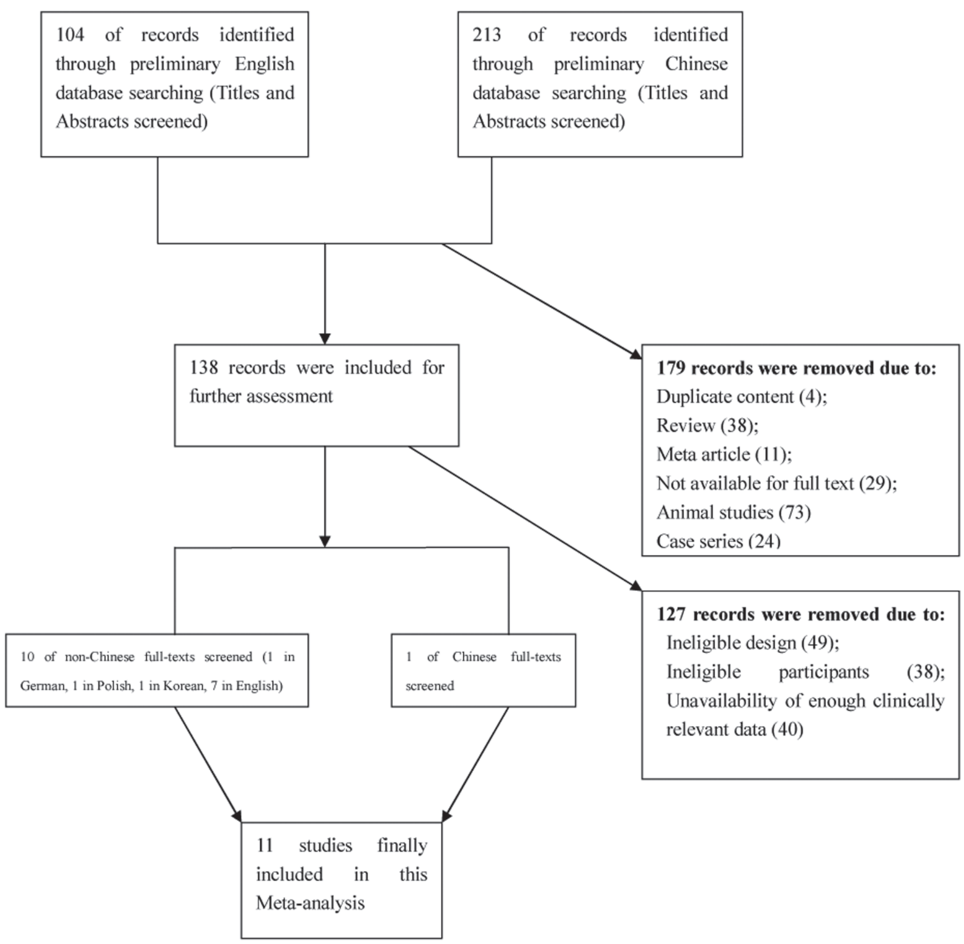

Fig. 1 Flow diagram of selection of studies for inclusion in the meta-analysis.

Table 1

Demographic characteristics of trials included in the meta-analysis

Study	Experiment/control (Gestational age)	Mean timing of lavage (hours)	Lavage volume	Type of lavage	Application of surfactant	Respiratory strategy	Use of ECMO	Use of iNO	Main exclusion criteria	Primary outcomes
Lam et al.[18]	6/6 (39.3 ± 0.2 vs. 40.8 ± 0.4 weeks)	3 (2–6)	15 mL/kg	NR	Survanta (bovine) (5 mg/mL)	Conventional or high-frequency mechanical ventilation	No	NR	NR	Fio_2; MAP; OI; a/APO_2; days on O_2 and ventilation; death; complications
Kowalska et al.[19]	11/11 (>35weeks)	<6	15 mL/kg	Saline + surfactant	Survanta (bovine) (5 mg/mL)	Conventional or high-frequency mechanical ventilation	NR	NR	Not clear	OI; Fio_2; Pao_2; days on IMV; death
Schlösser et al.[20]	11/7 (38–42 weeks)	NR	20 mL	Diluted surfactant	Survanta (bovine) (5 mg/mL)	Conventional or high-frequency mechanical ventilation	Yes	Yes	NR	OI; use of high frequency ventilation or ECMO; days on O_2 and ventilation; death
Wiswell et al.[21]	15/7 (39.9 ± 1.2 vs. 39.4 ± 1.9 weeks)	14–15	16 mL/kg, for three times	Diluted surfactant	Surfaxin (synthetic) (2.5–10 mg/mL)	Conventional frequency mechanical ventilation	Yes	Yes	Congenital anomaly; air leak; PH; hydrops fetalis; severe IVH	OI; use of ECMO; days on O_2 and ventilation; death
Chang et al.[22]	12/10 (39.3 ± 0.6 vs. 39.7 ± 1.6 weeks)	4.2 (2–7) or 5.2 (2–9)	6–7 or 12–14 mL/kg	Diluted surfactant	Survanta (bovine) (5 or 10 mg/mL)	Conventional or high-frequency mechanical ventilation	NR	Yes	CHD; congenital anomaly; diaphragmatic hernia	OI; use of iNO; days on O_2 and ventilation; complications; death
Salvia-Roiges et al.[23]	7/6 (39–41weeks)	6	15 mL/kg	Saline + surfactant	Survanta (bovine) (3 mg/mL)	Conventional mechanical ventilation	NR	Yes	IVH; infection; congenital anomaly	OI; days on O_2, iNO and ventilation; death
Dargaville et al.[24]	8/34 (37–42 weeks)	23 (8-83)	15 mL/kg, for two times	Saline + surfactant	Survanta (bovine) (5 mg/mL)	High-frequency mechanical ventilation	Yes	Yes	NR	OI; Use of iNO or ECMO; Days on O2 and ventilation; Complications; Death
Lee et al.[25]	7/8 (37–42 weeks)	10.35±6.35	20 mL/kg	Saline + surfactant	Newfactan (bovine) (5.3 mg/mL)	Conventional or high-frequency mechanical ventilation	NR	NR	Not clear	MAP; VI; OI; days on O2 and ventilation; complications; death
Dargaville et al.[26]	30/35 (38–41weeks)	14.0 ± 5.9	15 mL/kg, for two times	Saline + surfactant	Survanta (bovine) (5 mg/mL)	Conventional or high-frequency mechanical ventilation + CPAP	Yes	Yes	Structural cardiac diseases; cardio-respiratory instability	OI; use of iNO or ECMO; days on O_2 and ventilation; complications; death
Gu[27]	51/51 (40.37 ± 1.10 vs. 40.33 ± 1.05 weeks)	NR	3–5 mL/once, for three times	Saline + surfactant	Curosurf (porcine) (12 mg/mL)	Conventional or high-frequency mechanical ventilation	No	NR	NR	a/APO_2; OI; complications
Bandiya et al.[28]	31/29 (38–39 weeks)	<2	20 mL/kg	Saline + surfactant	Survanta (bovine) (5 mg/mL)	Ventilation + CPAP	NR	NR	Congenital anomaly; CHD; PH; peneumothorax; Hydrops fetalis	Days on O_2 and ventilation; complications; death

a/APO_2 = alveoli/artery O_2; CHD = congenital heart disease; ECMO = extracorporeal membrane oxygenation; IMV = intermittent mandatory ventilation; iNO = inhaled nitric oxide; IVH = intraventricular hemorrhage; MAP = mean airway pressure; OI = oxygenation index; VI = ventilation index.

Table 2

Report quality of trials included in the meta-analysis

Study	Title and abstract	Participant flow	Baseline data	Randomization	Blinding	Follow-up	CONSORT items (22)	Jadad score (5)
Lam et al.[18]	Yes	No	Yes	Yes	No	No	18	4
Kowalska et al.[19]	Yes	No	Yes	No	No	No	16	3
Schlösser et al.[20]	Yes	No	Yes	Yes	No	No	16	3
Wiswell et al.[21]	Yes	No	Yes	No	No	Yes	18	4
Chang et al.[22]	Yes	No	Yes	No	No	No	17	4
Salvia-Roiges et al.[23]	Yes	No	Yes	No	No	No	17	4
Dargaville et al.[24]	Yes	No	Yes	No	No	No	17	4
Lee et al.[25]	Yes	No	Yes	No	No	No	16	3
Dargaville et al.[26]	Yes	Yes	Yes	Yes (with description of allocation concealment)	Not	Yes	21	5
Gu[27]	Yes	No	Yes	No	No	No	16	3
Bandiya et al.[28]	Yes	Yes	Yes	Yes (with description of allocation concealment)	Yes	No	21	5

Q statistic)[16] was applied to test for heterogeneity, and the I^2 statistic was also used to quantify the proportion of the total variation attributable to heterogeneity.[17] For p values < 0.05 or $I^2 > 50$, the assumption of homogeneity was assumed to be invalid, and the random-effects model was used; for p value ≥ 0.05 and $I^2 \leq 50$, data were assessed using the fixed-effects model. Publication bias was investigated by funnel plot, and an asymmetric plot suggested possible publication bias. Statistical analyses were performed using Review Manager 4.2 (Cochrane Collaboration, Nordic Cochrane Centre). A two-tailed p value of <0.05 was deemed statistically significant.

3. RESULTS

3.1. Demographic characteristics of the studies

After searching the above databases, 138 potentially relevant studies were obtained. Details of the searching process are shown in Fig. 1. A search of other aforementioned databases did not identify any additional eligible studies. Ultimately, we identified 11 original studies (7 in English, 1 in German, 1 in Polish, 1 in Korean, and 1 in Chinese),[18–28] including the surfactant lavage group (n = 189) and the control group (n = 204) (Table 1). This meta-analysis included 4 randomized controlled studies and 7 nonrandomized controlled ones. The quality of all studies included into this meta-analysis was assessed by Jadad score and CONSORT items (Table 2).

3.2. The comparison of effectiveness of surfactant lavage treatment on MAS

(1) With respect to oxygen index, data were reported by three trials at 24-hours stage (surfactant lavage group/control group = 57/49) (Fig. 2). There wasn't heterogeneity ($\chi^2 = 1.10$, $p = 0.58$; $I^2 = 0\%$). Data showed no significant difference between surfactant lavage/control groups (WMD = −3.81, 95% CI, −8.07 ~ 0.45; $p = 0.08$); Consider the effect of nonrandomization, we analyzed the oxygen index at 24-hours stage, which includes two randomized studies. Data also showed no significant difference between surfactant lavage/control groups (WMD = −3.87, 95% CI, −8.47 ~ 0.72; $p = 0.10$) (Fig. 3). With respect to oxygen index at 48-hours stage, data were reported by five trials (surfactant lavage group/control group = 80/70) (Fig. 2). There wasn't heterogeneity ($\chi^2 = 4.83$, $p = 0.31$; $I^2 = 17.2\%$). Meta-analysis showed significant difference between surfactant lavage/control groups (WMD = −3.37, 95% CI, −5.68 ~ −1.06; $p = 0.004$); We also analyzed the oxygen index at 48-hours stage, which includes two randomized studies. Data showed significant difference between surfactant lavage/control groups (WMD = −3.87, 95% CI, −7.04 ~ −0.70; $p = 0.02$) (Fig. 3). With respect to oxygen index at 72 hours, data were reported by four trials (surfactant lavage group/control group = 108/100) (Fig. 2). There wasn't heterogeneity ($\chi^2 = 1.33$, $p = 0.72$; $I^2 = 0\%$). Meta-analysis showed significant difference between surfactant lavage/control groups (WMD = −3.70, 95% CI, −5.03 ~ −2.37; $p < 0.00001$); We analyzed the oxygen index at 72-hours stage, which includes two randomized studies. Data showed significant difference between surfactant lavage/control groups (WMD = −2.59, 95% CI, −4.94 ~ −0.25; $p = 0.03$) (Fig. 3).

(2) With respect to days on mechanical ventilation, six studies were included into this meta-analysis (surfactant lavage group/control group = 62/49). There was no significant heterogeneity among the trials ($\chi^2 = 2.84$, $p = 0.72$; $I^2 = 0\%$). The analysis showed that there was significant difference between surfactant lavage group and control group (WMD = −1.12, 95% CI, −1.40 ~ −0.84; $p < 0.00001$); Consider the effect of nonrandomization, we analyzed the days on mechanical ventilation, which includes two randomized studies. Data also showed significant difference between surfactant lavage/control groups (WMD = −2.69, 95% CI, −4.97 ~ 0.41; $p = 0.02$) (Fig. 4).

(3) Regarding the need for ECMO, there were four eligible studies included (surfactant lavage group/control group = 64/83), and no significant heterogeneity was detected among these trials ($\chi^2 = 1.42$, $p = 0.70$; $I^2 = 0\%$). No significant difference was found in the comparison of two groups (OR = 0.49, 95% CI, 0.12 ~ 1.98; $p = 0.31$); Consider the effect of nonrandomization, we analyzed the need for ECMO which includes two randomized studies. Data also showed no significant difference between surfactant lavage/control groups (OR = 0.43, 95% CI, 0.07 ~ 2.71; $p = 0.37$) (Fig. 4).

(4) Regarding days of oxygen therapy, there were five eligible studies included (surfactant lavage group/control group = 51/38), and there was significant heterogeneity among the trials ($\chi^2 = 21.39$, $p = 0.0003$; $I^2 = 81.3\%$). Therefore, a random effects model was applied. No significant difference was found in the comparison of two groups (WMD = −3.22, 95% CI, −8.24 ~ 1.80; $p = 0.21$);

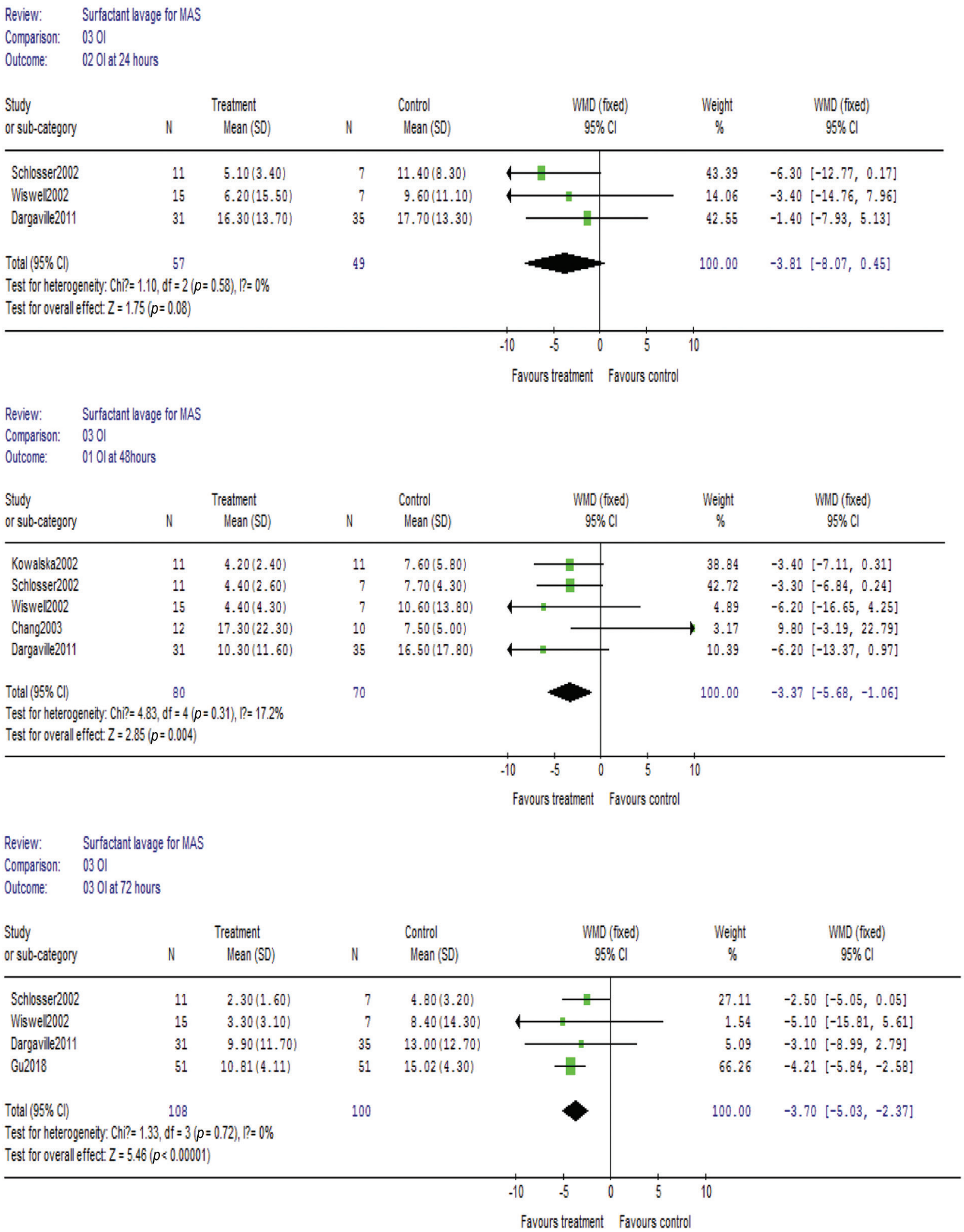

Fig. 2 Effect of surfactant lavage on oxygen index.

Consider the effect of nonrandomization, we analyzed the days of oxygen therapy, which includes two randomized studies. Data also showed no significant difference between surfactant lavage/control groups (WMD = −7.19, 95% CI, −24.14 ~ 9.76; p = 0.41) (Fig. 5).

(5) With respect to hospital stay, data were reported by five trials (surfactant lavage group/control group = 76/65) (Fig. 5). There was no significant heterogeneity among these trials (χ^2 = 6.81, p = 0.15; I^2 = 41.3%). Result showed no significant difference between surfactant

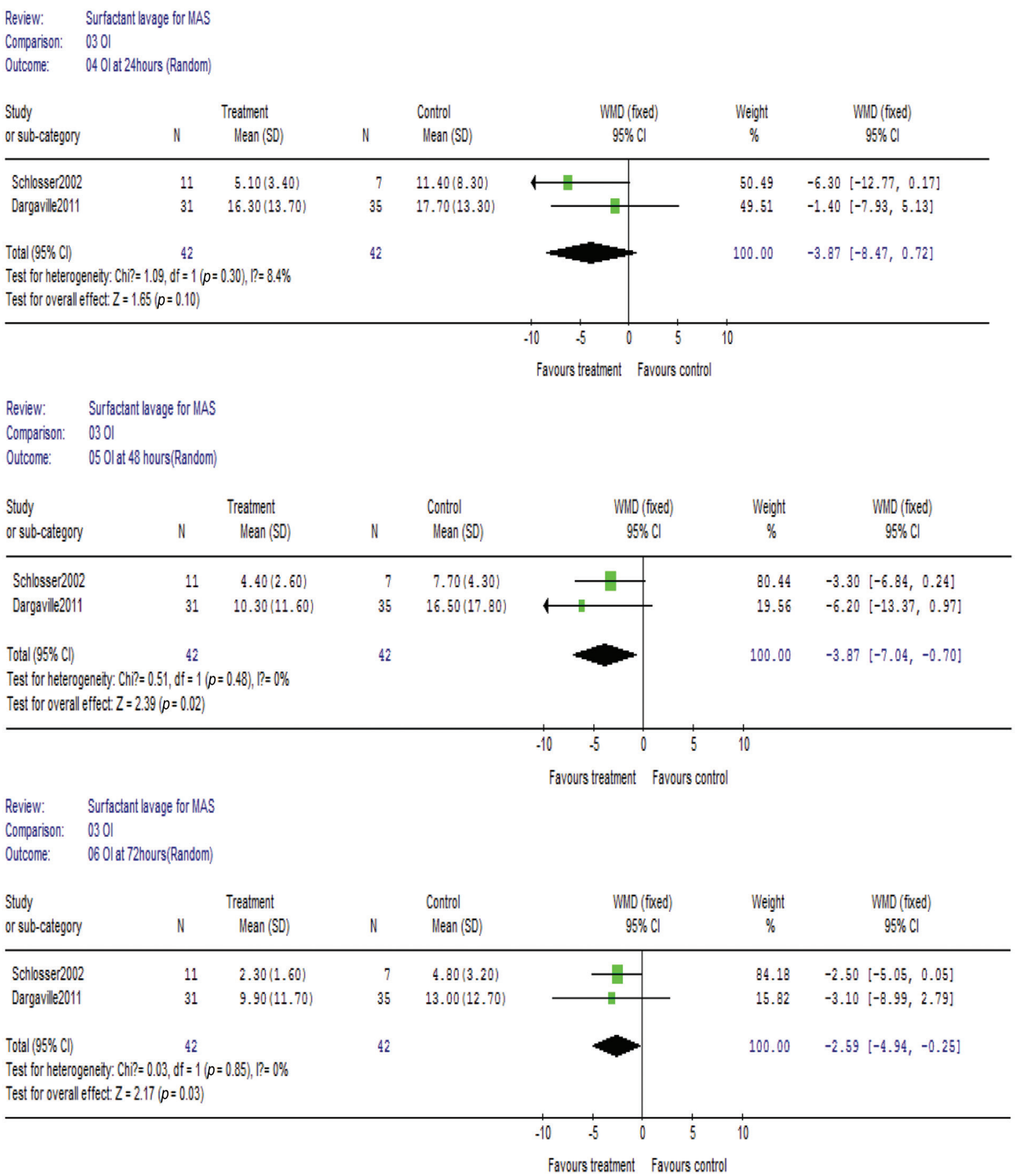

Fig. 3 Effect of surfactant lavage on oxygen index (for randomized studies only).

lavage/control groups (WMD = –0.71, 95% CI, –2.77 ~ 1.36; $p = 0.50$); Nonrandomized studies were included.

3.3. The comparison of possible complications of MAS between surfactant lavage and control groups

(1) Data of mortality between surfactant lavage group and control group were reported by 11 studies (surfactant lavage group/control group = 189/204). There was no significant heterogeneity among these trials ($\chi^2 = 5.69$, $p = 0.58$; $I^2 = 0\%$). The result showed no difference in death between the two groups (OR = 0.64, 95% CI, 0.32 ~ 1.28; $p = 0.21$); Consider the effect of nonrandomization, we analyzed the mortality that includes four randomized studies. Data also showed no significant difference between surfactant lavage/control groups (OR = 0.78, 95% CI, 0.35 ~ 1.72; $p = 0.54$) (Fig. 6).

(2) Regarding pneumothorax, there were 9 eligible studies included (surfactant lavage group/control group = 163/186), and no significant heterogeneity was detected among these trials ($\chi^2 = 10.76$, $p = 0.22$; $I^2 = 25.6\%$). The analysis showed that there was significant difference between surfactant lavage group

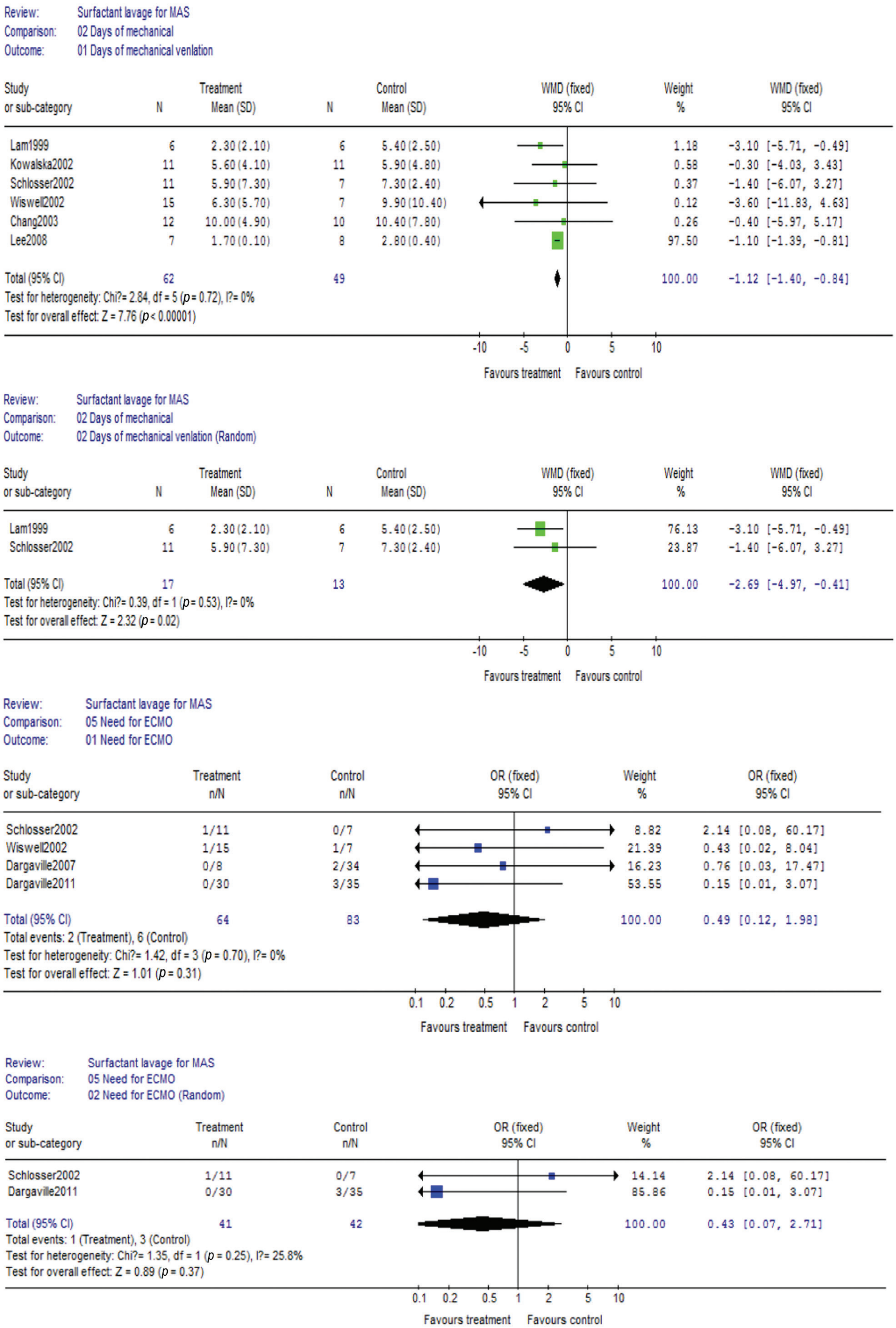

Fig. 4 Effect of surfactant lavage on days of mechanical ventilation and need for ECMO (including randomized studies). ECMO, extracorporeal membrane oxygenation.

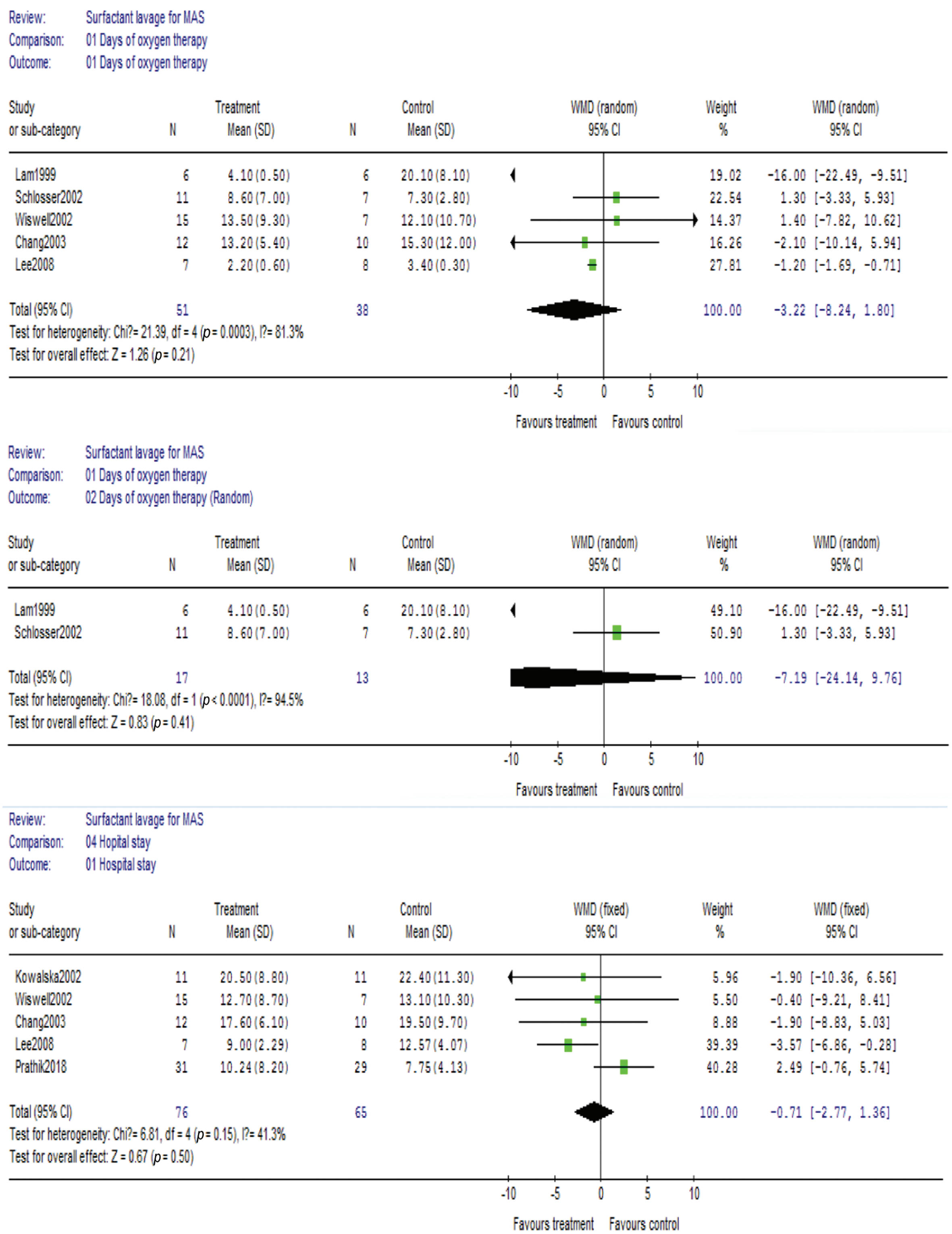

Fig. 5 Effect of surfactant lavage on days of oxygen and hospital stay (including randomized studies).

and control group (OR = 0.46, 95% CI, 0.24 ~ 0.85; p = 0.01); Consider the effect of nonrandomization, we analyzed the pneumothorax which includes four randomized studies. Data showed no significant difference between surfactant lavage/control groups (OR = 0.76, 95% CI, 0.33 ~ 1.75; p = 0.51) (Fig. 7).

(3) Persist pulmonary hypertension was compared in five researches (surfactant lavage group/control group = 103/128). There was no significant heterogeneity among the trials (χ^2 = 6.96, p = 0.14; I^2 = 42.6%). Therefore, a fixed effects model was applied. No significant difference was found between the two groups

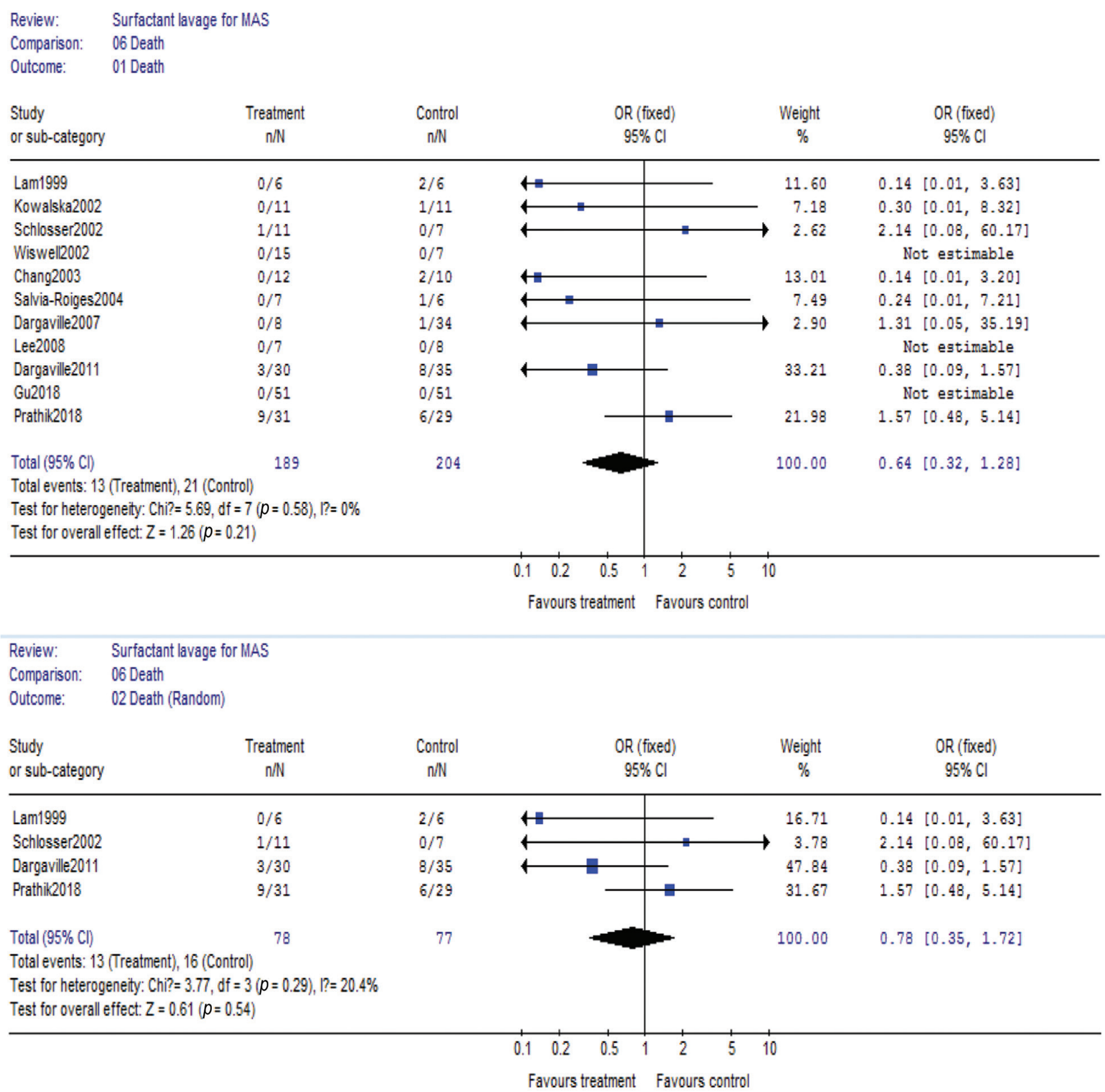

Fig. 6 Effect of surfactant lavage on mortality (including randomized studies).

(OR = 0.63, 95% CI, 0.25 ~ 1.59; w*p* = 0.33). Consider the effect of nonrandomization, we analyzed the persist pulmonary hypertension, which includes two randomized studies. Data also showed no significant difference between surfactant lavage/control groups (OR = 0.21, 95% CI, 0.03 ~ 1.36; *p* = 0.10) (Fig. 8).

(4) Regarding pulmonary hemorrhage, there were two eligible studies included (surfactant lavage group/control group = 59/85), and no significant heterogeneity was detected among these trials (χ^2 = 0.30, *p* = 0.59; I^2 = 0%). No significant difference was found between the two groups (OR = 0.37, 95% CI, 0.06 ~ 2.21; *p* = 0.27); Nonrandomized studies were included (Fig. 8).

3.4. Publication bias

All trials included in the meta-analysis had Jadad quality scores ≥3. A funnel plot was performed to assess the potential publication bias in this meta-analysis. In analyzing the effect of surfactant lavage treatment on mortality, we visually evaluated the symmetry of funnel plot shape and did not find obvious evidence of asymmetry (Fig. 9).

4. DISCUSSION

In the past several years, surfactant therapy has been gradually tried in neonates with MAS to reduce the complications and shorten the course.[10] It has been generally considered safe. Systematic reviews evaluated the efficacy of surfactant lavage in MAS and also found this therapy significantly decreased the incidence of death and the need for extracorporeal membrane oxygenation,[13] another meta-analysis showed that surfactant lavage shorten the duration of hospital stay and mechanical ventilation.[29] However, the evaluation results of the above two reviews are not entirely consistent, such as in the need for ECMO.

MAS has been one of the most devastating diseases in the NICU of developing countries, with postmature infants of amniotic fluid contamination at greatest risk. Recent experimental

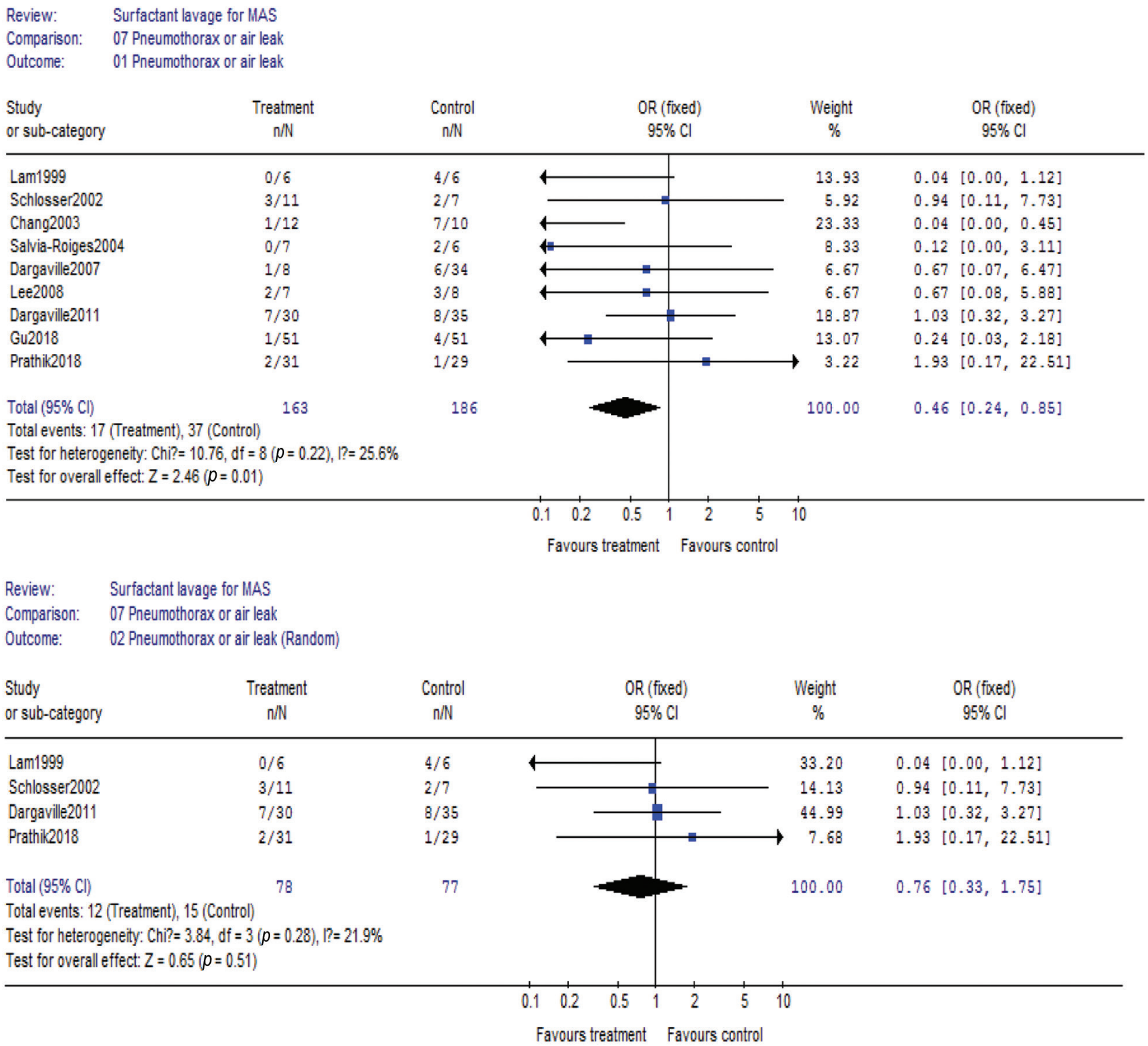

Fig. 7 Effect of surfactant lavage on pneumothorax (including randomized studies).

studies have suggested that lung lavage can remove meconium from the lungs in MAS, and as a result can improve lung function. In animal models of MAS, lung lavage has resulted in considerable improvement in oxygenation and/or pulmonary mechanics, associated with removal of one-third to one-half of the meconium lodged in the airspaces.[30,31] Saline, surfactant, and perfluorocarbon have been studied as potential lavage fluids. Comparative data suggest that exogenous surfactant, whether at full strength[30] or diluted in saline,[19] is a more effective lavage fluid than saline alone, in terms of both pulmonary function post lavage and removal of meconium from the lung.

4.1. The comparison of effectiveness of surfactant lavage treatment on MAS

With respect to oxygen index, surfactant lavage group is significant lower at both 48 and 72 hours (WMD = −3.37, 95% CI, −5.68 ~ −1.06; $p = 0.004$; WMD = −3.70, 95% CI, −5.03 ~ −2.37; $p < 0.00001$). This result is consistent with previous meta-report.[32] Meanwhile, regarding days on mechanical ventilation, the analysis showed that surfactant lavage group has shortened the course of mechanical ventilation compared with the control group (WMD = −1.12, 95% CI, −1.40 ~ −0.84; $p < 0.00001$). So from this perspective, lung lavage could be a potentially effective treatment for MAS by virtue of improving oxygenation, removing meconium from the airspaces and altering the natural course of the disease. However, our meta-analysis found surfactant lavage doesn't eventually shorten days of oxygen therapy and hospital stay (WMD = −3.22, 95% CI, −8.24 ~ 1.80; $p = 0.21$; WMD = −0.71, 95% CI, −2.77 ~ 1.36; $p = 0.50$).

In our opinion, this contradiction can be explained by other pathophysiological mechanisms of MAS, such as chemical pneumonia, PPHN, congenital heart disease, etc. After all, surfactant is mainly used for improving alveolar compliance. Theoretically, surfactant is also effective for relieving pulmonary hypertension and reducing the application of ventilation. Former meta-analysis showed that surfactant lavage significantly decreased the death or need for extracorporeal membrane oxygenation (RR 0.34, 95% CI 0.11, 0.99).[13] But our results didn't find this significant difference. Regarding the need for ECMO, compared with the previous meta-analysis which included just two studies (surfactant lavage group/control group = 26/21),[32] there were four eligible studies included in ours (surfactant lavage/control = 64/83). And no significant differences were found between the two groups (OR = 0.49, 95% CI, 0.12 ~ 1.98; $p = 0.31$). This

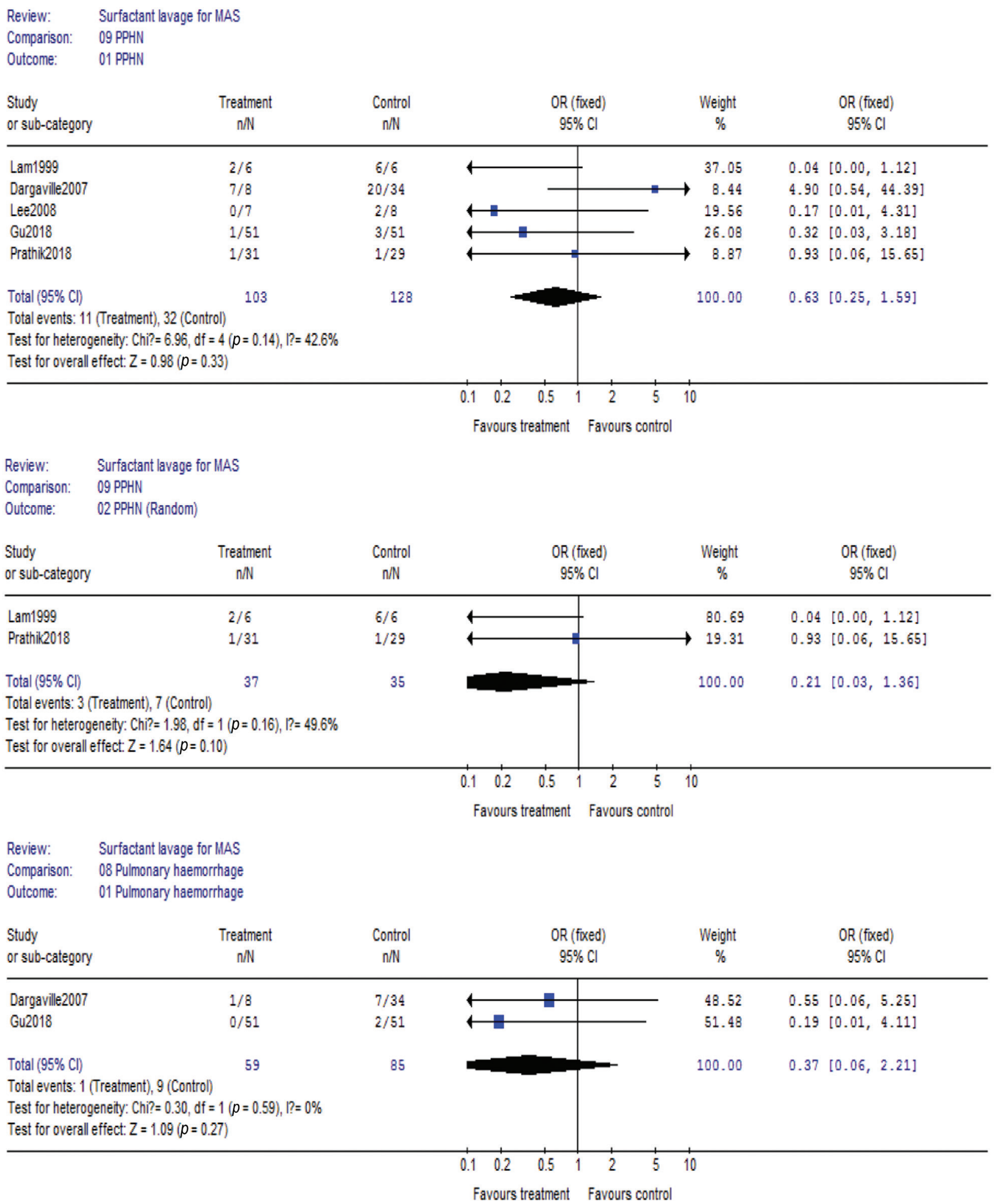

Fig. 8 Effect of surfactant lavage on persist pulmonary hypertension (PPHN) and pulmonary hemorrhage (including randomized studies).

result reflects from a side view that surfactant maybe couldn't decrease pulmonary hypertension ultimately. Perhaps further large sample research is needed. After all, the current sample size of single center clinical study is too small.

4.2. The comparison of possible complications of MAS between surfactant lavage and control groups

Data for mortality between surfactant lavage group and control group were reported by 11 studies (surfactant lavage group/control group = 189/204). The result showed no difference in mortality between the two groups (OR = 0.64, 95% CI, 0.32 ~ 1.28; p = 0.21). This result is consistent with previous meta-reports.[13,32] From the report by Hahn et al.[32], they found no difference between surfactant lavage group and control group (including two studies, intervention vs. control = 46/42; p = 0.17). Another meta-analysis studied by Choi et al.[13] showed similar conclusion (including 10 studies, intervention vs. control = 124/141; overall effect: 0.44 [0.18, 1.04]).

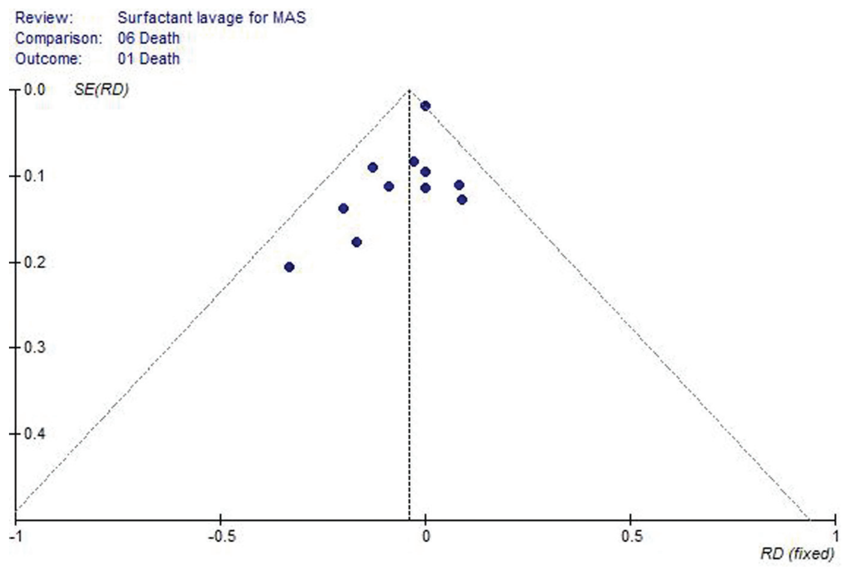

Fig. 9 Funnel plot to assess publication bias.

Except mortality, we also evaluated PPHN and pulmonary hemorrhage. And we found surfactant lavage doesn't increase the risk of these two complications (OR = 0.63, 95% CI, 0.25 ~ 1.59; p = 0.33 and OR = 0.37, 95% CI, 0.06 ~ 2.21; p = 0.27). Pneumothorax is another important issue of concern to us. There were nine eligible studies included (surfactant lavage group/control group = 163/186). Our updated analysis showed that there was significant difference between surfactant lavage group and control group (OR = 0.46, 95% CI, 0.24 ~ 0.85; p = 0.01). The above shows this therapy is relatively safe and does not increase the incidence of common complications.

In addition to the aforementioned concerns, we must note additional limitations to some recent researches. For example, data from some available studies were showed by median and quartile range because of skewed distribution.[21,23,26] These data are discarded because they may affect the overall conclusion. In addition, methods of specific randomization and detailed blinding are generally not included in published reports. In view of this point, we evaluated and analyzed the randomized studies included into this meta-analysis. And we found that the results are similar except for pneumothorax (all studies: OR = 0.46, 95% CI, 0.24 ~ 0.85; p = 0.01 vs. randomized studies: OR = 0.76, 95% CI, 0.33 ~ 1.75; p = 0.51). Maybe more randomized controlled trials are still needed. Besides, three studies (Wiswell et al.[21], Lee et al.[25], and Gu[27]) used different surfactants (Surfaxin, Newfactan, and Curosurf, respectively) from Survanta. In theory, they are equally effective, but detailed researche is yet to be performed. Given these limitations, perhaps the focus of future studies should rather explore in better designed, perspective controlled studies.

In conclusion, with respect to oxygen index and days on mechanical ventilation, surfactant lavage is significantly effective compared with control group, though it didn't eventually shorten days of oxygen therapy and hospital stay. In addition, our meta-analysis showed that surfactant lavage does not increase the risk of related complications. So from this perspective, lung lavage is a potentially effective and safe treatment for MAS.

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