Less invasive surfactant administration in preterm infants with respiratory distress syndrome—an updated meta-analysis

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Abstract

Background: Less invasive surfactant administration (LISA) seems to have a good application prospect both in experimental models and patients with respiratory distress syndrome (RDS). Data regarding the effect of LISA procedure on RDS are conflicting.

Methods: A search was conducted by two investigators involved in this research in PubMed, Embase, and Cochrane databases for studies in English and in Wanfang, VIP, and Cnki databases for Chinese studies (all last launched on December 18, 2018). 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 RDS: (1) with respect to mechanical ventilation (<72 hours) and mechanical ventilation (all time periods). Data showed significant differences between LISA/control groups. (2) With respect to days of mechanical ventilation, data showed no significant differences between LISA/control groups. (3) With respect to bronchopulmonary dysplasia, the analysis showed that there was significant difference between LISA group and control group. (4) Regarding days of supplementary oxygen therapy and hospital stay, no significant differences were found. The comparison of possible complications of RDS: (1) data for mortality, pneumothorax and pulmonary hemorrhage showed no differences in the two groups. (2) Data for retinopathy of preterm comparison showed significant difference between the two groups. (3) Regarding intraventricular hemorrhage/periventricular leukomalacia, significant differences were found between the two groups.

Conclusion: Based on the above evidences, LISA is an effective and safe treatment for preterm infants with RDS.

Keywords: Less invasive surfactant administration; Meta-analysis; Preterm; Respiratory distress syndrome

1. INTRODUCTION

Preterm infants (especially gestational age from $28^{0/7}$ to $32^{6/7}$ weeks) account for a large proportion of inpatients in neonatal intensive care unit. These infants are more likely to develop respiratory distress syndrome (RDS), and often need surfactant treatment and mechanical ventilation compared with term newborns. But, it has been proven that traditional invasive mechanical ventilation after birth, even for a short period, could cause acute or chronic lung injuries.[1,2] Recently, a new, less invasive surfactant administration (LISA) was introduced[3] and is gradually practiced.[4]

LISA has been used as the standard application of surfactant administration originated in German with a wide variation in personal experiences, such as type of delivery catheter, stage of gestational age, etc.[5,6] LISA method was developed to combine the benefits of surfactant and nCPAP.[7] Existing researches have shown that LISA procedure is associated with better pulmonary outcomes, such as less bronchopulmonary dysplasia (BPD) and mechanical ventilation, shorter duration of oxygen supplementation as well as a reduced risk of mortality.[7–9] Besides, researchers have also observed a significantly decreased risk of pneumothorax and severe intraventricular hemorrhage (IVH) for patients treated with LISA procedure.[7]

In the past several years, surfactant administration via INtubation SURfactant Extubation (InSurE) has been suggested as an appropriate surfactant treatment compared with traditional invasive mechanical ventilation.[10] Related rapid intubation-extubation seems effectively reduce the long-term need of mechanical ventilation and further lung injury. The outcomes of InSurE and LISA for preterm infants have been compared in several studies.[11] A large prospective randomized controlled trial (AMV Trial) demonstrated a significant reduction in the use of mechanical ventilation in LISA group compared with standard treatment with InSurE.[12] Another study (Take Care Study) showed that LISA method seems superior to InSurE.[13] However, some of those studies just focused on the respiratory outcomes of preterm infants.

So, in view of the limitation and uncertainty, an updated meta-analysis including the latest literature is performed to evaluate the potential effect of LISA procedure on RDS in preterm babies.

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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] In order 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 and in Wanfang, VIP, and Cnki databases for Chinese studies (databases were last launched on December 18, 2018). The following search terms were employed: "Less invasive surfactant administration," "RDS," "Minimally invasive surfactant therapy," and "Preterm." The inclusion criteria of this meta-analysis were as follows: (1) controlled test involving RDS with LISA procedure; (2) human clinical studies. Hence, cases, reviews, meta-analysis, 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, LISA catheter, criteria for surfactant, application of surfactant, application of mechanical ventilation, primary outcomes, randomization, blinding, Jadad score, and CONSORT items. Subsequently, the outcomes were divided into two parts. First was the comparison of effectiveness of LISA procedure on RDS (including mechanical ventilation needed, supplementary oxygen needed, BPD and hospital stay). Second, with respect to the possible complications of RDS, death, retinopathy of preterm (ROP), IVH, periventricular leukomalacia (PVL), pulmonary hemorrhage and pneumothorax were compared between LISA and control groups.

2.3. Statistical analysis

For each outcome, either odds ratio or weighted mean difference 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 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

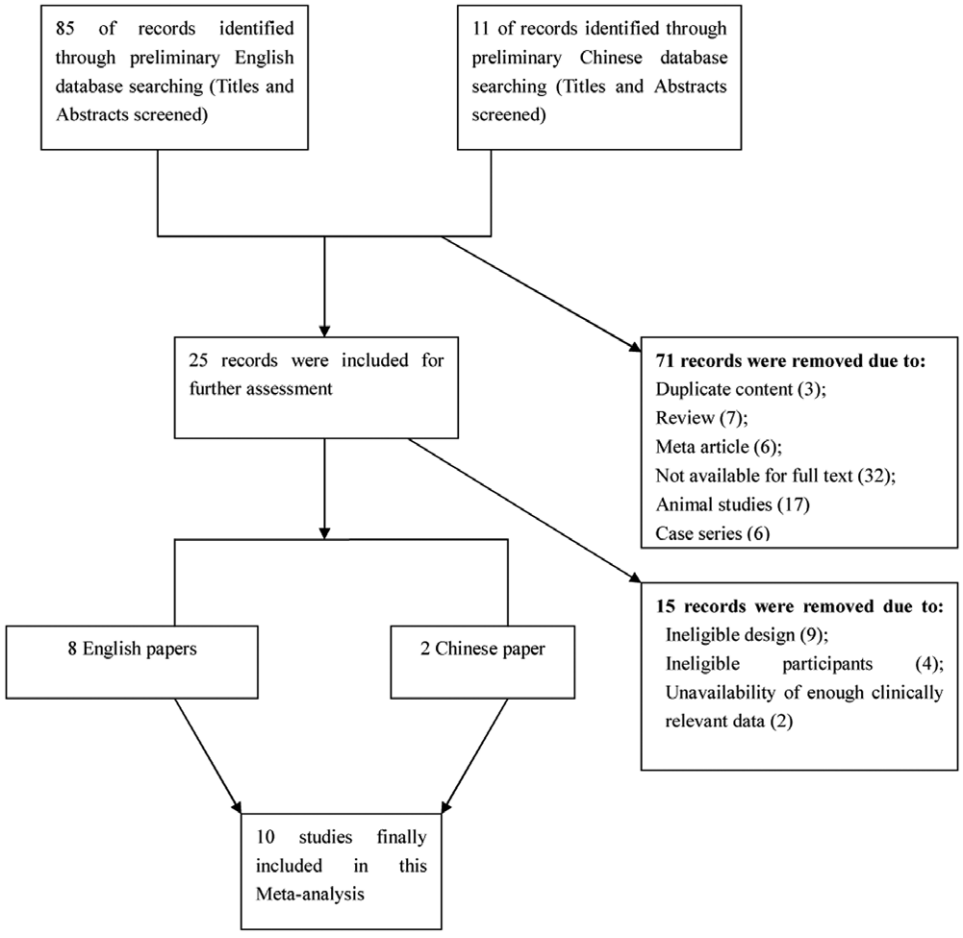

Fig. 1. Flow diagram of selection of studies for inclusion in the meta-analysis.

Table 1

Demographic characteristics of trials included in the meta-analysis.

Study	Population (Experiment / Control)	Gestational Age (Experiment / Control)	LISA Catheter	Criteria for Surfactant	Application of Surfactant (First dose)	Control Group	Application of Mechanical Ventilation	Primary Outcomes
Kanmaz et al.,[13] 2013	100/100	28 ± 2/ 28.3 ± 2	5F nasogastric tube	CPAP with FiO_2 >0.4	Curosurf 100 mg/kg	InSurE; CPAP	CPAP > 7 cmH_2O; FiO_2>0.6	Surfactant administration time; Radiologic scoring; MV duration; Supplementary O_2; Complications
Mirnia et al.,[18] 2013	66/70	29.6 ± 1.7/ 29.6 ± 1.7	5F feeding tube	CPAP with FiO_2 >0.3	Curosurf 200 mg/kg	InSurE; CPAP	PCO_2>50–60 mmHg and PH<7.2 under CPAP	MVrequirement; Supplementary O_2; Complications
Bao et al.,[4] 2015	47/43	29.1 ± 1.5/ 29.3 ± 1.6	16 gauge, 130 mm vascular catheter	CPAP with FiO_2 ≥0.3 (28–29 wks) or ≥0.35 (30–32wks)	Curosurf 200 mg/kg	CPAP	FiO_2≥0.5 or PH<7.2 or significant apnea	MVrequirement; Supplementary O_2; Complications
Göpel et al.,[19] 2015	1103/1103	28 (26.7–29.4)/ 28 (26.7–29.4)	2.5–5F catheter	CPAP with FiO_2 ≥0.3 for LISA group and variable FiO_2 for control group	Curosurf/bovine 100 mg/kg	Not mentioned	Not mentioned	Postnatal steroid treatment; Dexamethasone treatment; MVrequirement; Complications
Kribs et al.,[9] 2015	107/104	25.3 ± 1.1/ 25.2 ± 0.91	4F catheter	CPAP with FiO_2 ≥0.3 or RDS (Silverman score ≥5)	Curosurf 100 mg/kg	Mechanical ventilation (intubated)	FiO_2≥0.45 or respiratory acidosis with PH< 7.15 or severe apnea	Respiratory stimulants; Pulmonary outcome; Complications
Mohammadizadeh et al.,[20] 2015	19/19	30 ± 2/ 31 ± 2	4F feeding tube	CPAP with FiO_2 ≥0.3 or RDS (Silverman score ≥5)	Curosurf 200 mg/kg	CPAP	FiO_2≥0.7 for >2 hs or FiO_2≥0.4 for >12 hs or PH<7.2 or PCO_2>65 mmHg or significant apnea	MVrequirement; Supplementary O_2; Complications
Li et al.,[21] 2016	22/22	29.5 ± 1.3/ 29.3 ± 1.6	Gastric feeding tube (1.3 mm diameter)	Not mentioned	Curosurf (119.5 versus 136 mg/kg)	InSurE; CPAP	Not mentioned	Supplementary O_2; Complications; ScO_2; MABP
Lu et al.,[22] 2016	38/34	31.0 ± 1.6/ 30.7 ± 1.9	6F gastric tube	CPAP with FiO_2 ≥0.4 or PaO_2<50mmHg	Curosurf 200 mg/kg	InSurE; CPAP	FiO_2≥0.6 or PH< 7.2 or PCO_2>65 mmHg or significant apnea	Complications; MVrequirement
Langhammer et al.,[23] 2018	148/148	28 (26–29)/ 28 (26–29)	Not mentioned	Not mentioned	Curosurf or beractant (dosage is unknown)	CPAP	Not mentioned	Complications; MVrequirement; Supplementary O_2;
Zheng et al.,[24] 2018	34/50	31.52 ± 1.38/ 31.36 ± 1.48	6F gastric tube	CPAP with FiO_2 ≥0.4 or PaO_2<50mmHg	Curosurf 200 mg/kg	InSurE; CPAP	Not mentioned	Complications; MVrequirement; Supplementary O_2; Follow up

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, 96 potentially relevant studies were obtained. Details of the searching process are shown in Figure 1. A search of other aforementioned databases did not identify any additional eligible studies. Ultimately, we identified 10 original studies (eight in English and two in Chinese),[4,9,13,18–24] including the LISA group (n = 1666) and the control group (n = 1675) (Table. 1). The quality of all studies included in this meta-analysis was assessed by Jadad score and CONSORT items (Table. 2). And the score in parenthesis of Tables 1 and 2 indicates the quality of reference.

3.2. The comparison of effectiveness of LISA procedure on RDS

As far as mechanical ventilation is concerned, it will be discussed in three aspects: With respect to mechanical ventilation (<72 hours after birth), data were reported by five trials (LISA group/control group = 238/246) (Fig. 2). There wasn't heterogeneity ($\chi^2 = 0.92$, $p = 0.92$; $I^2 = 0\%$). Data showed significant difference between LISA/control groups (95% CI, 0.35–0.79; $p = 0.002$); With respect to mechanical ventilation (all time periods after birth), data were reported by four trials (LISA group/control group = 1458/1455) (Fig. 2). There was significant heterogeneity ($\chi^2 = 39.24$, $p < 0.00001$; $I^2 = 92.4\%$). Meta-analysis showed significant difference between LISA/control groups (95% CI, 0.08–0.58; $p = 0.002$); With respect to duration of mechanical ventilation, data were reported by three trials (LISA group/control group = 132/132) (Fig. 2). There was significant heterogeneity ($\chi^2 = 24.00$, $p < 0.00001$; $I^2 = 91.7\%$). Meta-analysis showed no significant difference between LISA/control groups (95% CI, –4.01 to 1.20; $p = 0.29$).

Regarding BPD and days of supplementary oxygen therapy, 10 and 3 studies were included into this meta-analysis (LISA group/control group = 1666/1675 and 100/112). Compared with BPD, there was significant heterogeneity among the trials in supplementary oxygen therapy comparison ($\chi^2 = 24.34$, $p < 0.00001$; $I^2 = 91.8\%$). The analysis showed that there was significant difference in BPD comparison between LISA group and control group (95%CI, 0.50–0.74; $p < 0.00001$) (Fig. 3), but no significant difference in the comparison of days of supplementary oxygen therapy between LISA group and control group (95%CI, 0.50–0.74; $p < 0.00001$) (Fig. 4).

With respect to hospital stay, data were reported by two trials (LISA group/control group = 81/93) (Fig. 4). There was no significant heterogeneity among these trials ($\chi^2 = 0.21$, $p = 0.65$; $I^2 = 0\%$). Result showed no significant difference between LISA/control groups (95% CI, –8.11 to 1.75; $p = 0.21$).

3.3. The comparison of possible complications of RDS between LISA and control groups

Data for mortality between LISA group and control group were reported by eight studies (LISA group/control group = 1502/1495). There was no significant heterogeneity among these trials ($\chi^2 = 6.95$, $p = 0.43$; $I^2 = 0\%$). The result showed no difference for death in the two groups (95%CI, 0.52–1.01; $p = 0.06$) (Fig. 5).

Regarding pulmonary outcomes (including pneumothorax and pulmonary hemorrhage), there were eight and three eligible studies included (LISA group/control group = 1641/1651 and 241/254, respectively), and no significant heterogeneity was detected among these trials ($\chi^2 = 3.26$, $p = 0.86$; $I^2 = 0\%$ and $\chi^2 = 0.02$, $p = 0.99$; $I^2 = 0\%$). The analysis showed that there were no significant differences between LISA group and control group (95%CI, 0.48–1.11; $p = 0.14$ and 95%CI, 0.30–1.54; $p = 0.35$) (Fig. 6).

Regarding extra-pulmonary complications, data for ROP comparison were reported in seven researches (LISA group/control group = 462/471). There was no significant heterogeneity among the trials ($\chi^2 = 4.98$, $p = 0.42$; $I^2 = 0\%$). Therefore, a fixed-effects model was applied. Significant difference was found between the two groups (95%CI, 0.29–0.95; $p = 0.03$) (Fig. 6).

(4) In addition to ROP, as far as IVH/PVL is concerned, there were eight and six eligible studies included (LISA group/control group = 1550/1543 and 1442/1444), and no significant heterogeneities were detected among these trials ($\chi^2 = 4.95$, $p = 0.67$; $I^2 = 0\%$ and $\chi^2 = 2.11$, $p = 0.83$; $I^2 = 0\%$). Significant differences were found between the two groups (95%CI, 0.41–0.89; $p = 0.01$ and 95%CI, 0.41–0.96; $p = 0.03$) (Fig. 7).

3.4. Publication bias

All trials included in the meta-analysis had Jadad quality scores ≥ 3. A funnel plot was performed in order to assess the potential publication bias in this meta-analysis. In analyzing the outcome of BPD, we visually evaluated the symmetry of funnel plot shape and did not find obvious evidence of asymmetry (Fig. 8).

4. DISCUSSION

Surfactant therapy is an effective treatment for RDS in preterm infants. The best practice to cure this disease is to give

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)
Kanmaz et al.,[13] 2013	Yes	Yes	Yes	Yes	No	No	20	4
Mirnia et al.,[18] 2013	Yes	No	Yes	Yes	No	No	19	3
Bao et al.,[4] 2015	Yes	Yes	Yes	Yes	No	No	21	4
Göpel et al.,[19] 2015	Yes	No	Yes	Yes	No	No	20	4
Kribs et al.,[9] 2015	Yes	Yes	Yes	Yes	No	No	20	4
Mohammadizadeh et al.,[20] 2015	Yes	Yes	Yes	Yes	Yes	No	21	4
Li et al.,[21] 2016	Yes	No	Yes	Yes	No	No	19	4
Lu et al.,[22] 2016	Yes	No	Yes	Yes	No	No	18	4
Langhammer et al.,[23] 2018	Yes	Yes	Yes	Yes	No	No	20	4
Zheng et al.,[24] 2018	Yes	No	Yes	No	No	Yes	16	3

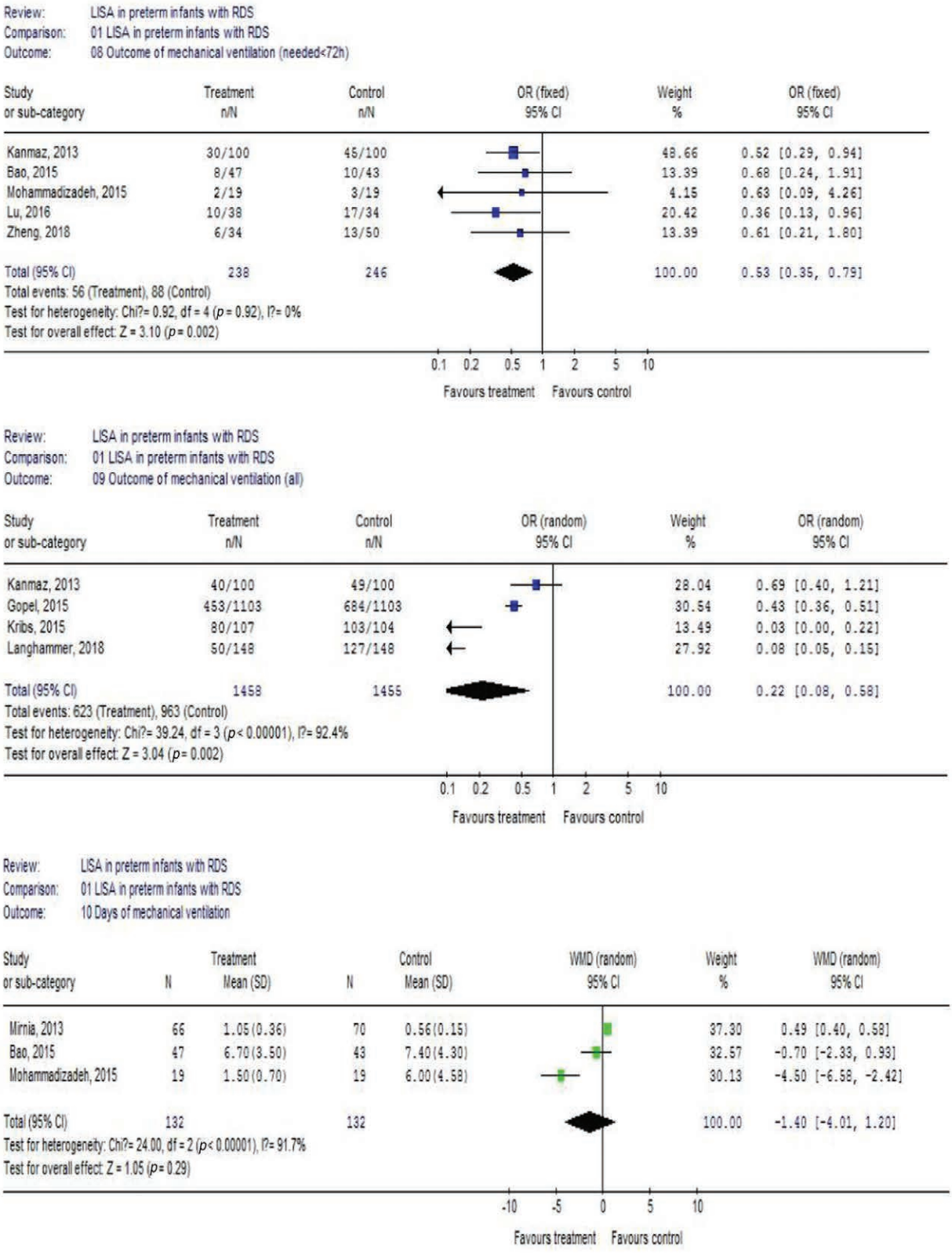

Fig. 2. Effect of LISA procedure on mechanical ventilation.

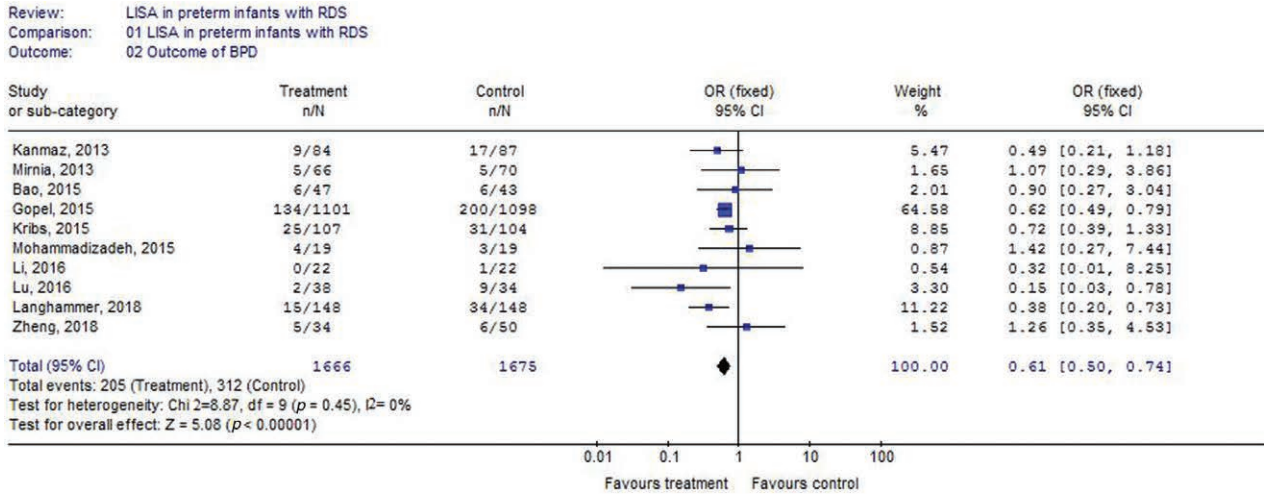

Fig. 3. Effect of LISA procedure on BPD.

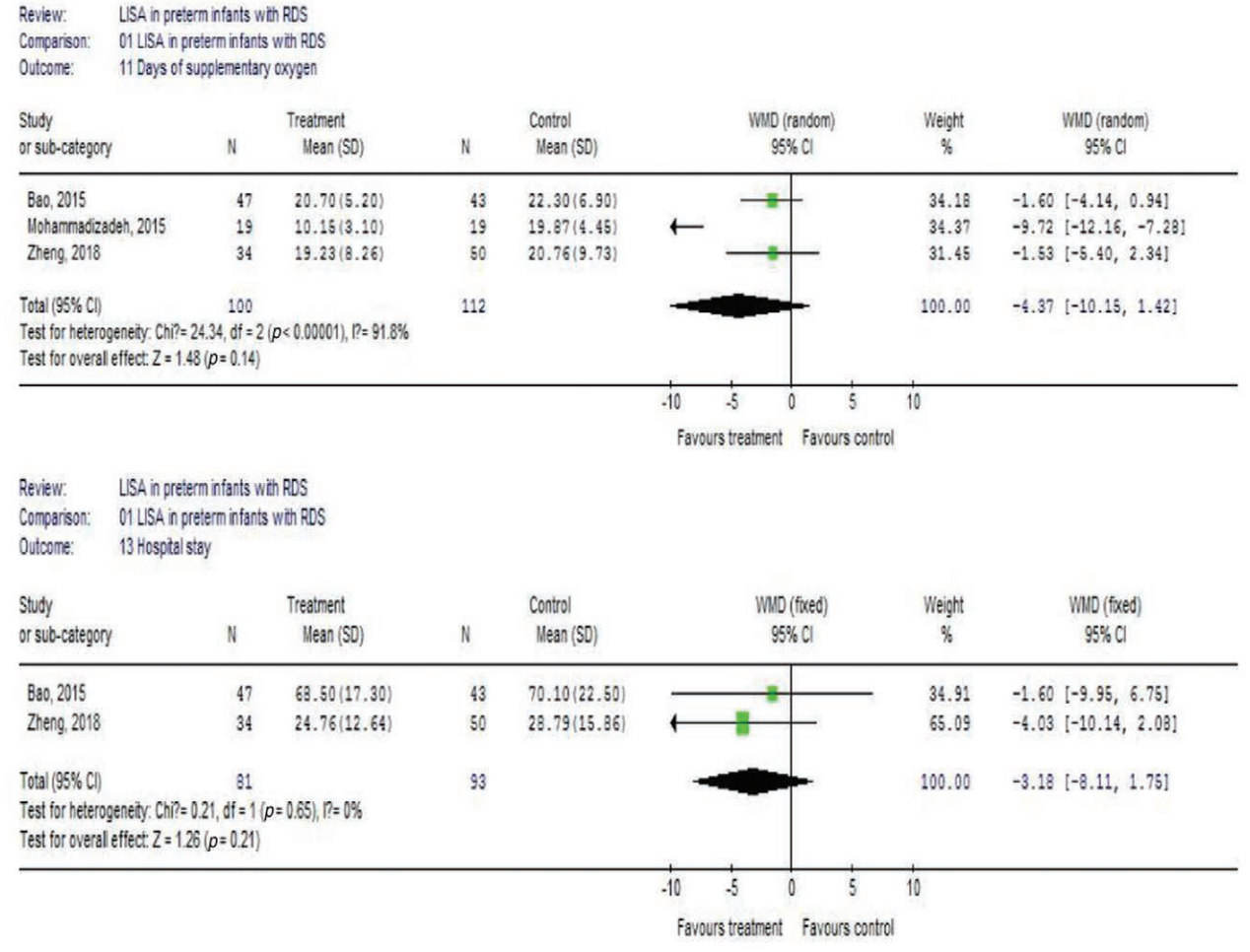

Fig. 4. Effect of LISA procedure on days of supplementary oxygen therapy and hospital stay.

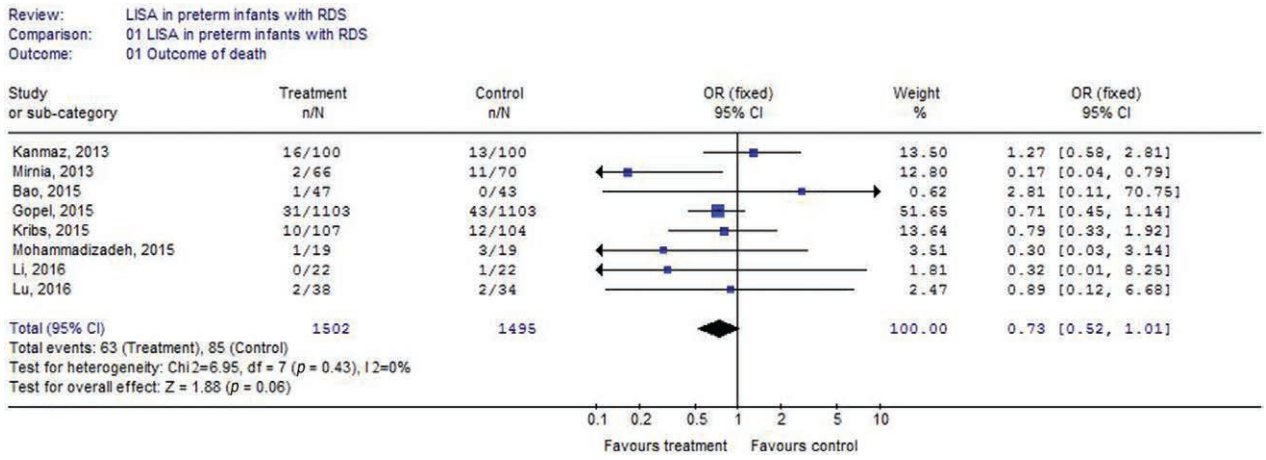

Fig. 5. Effect of LISA procedure on mortality.

surfactant as soon as early after birth, especially in those with gestation age <28 weeks.[25] Hence recent studies advocate a gentler early surfactant administration after birth, which could avoid intubation in preterm babies.[26–28] But almost half of these enrolled preterm infants had treatment failure on nCPAP. This failure, generally defined as need for intubation before 72 hours after birth, is associated with a higher risk of adverse outcomes.

For instance, those infants who were intubated <72 hours had a substantially longer duration of respiratory support than those in whom CPAP was successful. Furthermore, at 25–28 weeks, infants failing CPAP had a higher risk of mortality, BPD, and necrotizing enterocolitis.[29] So in the past several years, more and more pediatricians use InSurE technique so as not to deprive the advantages of early surfactant. But, this still requires intubation and enough ventilation to prompt inflammation for lung damage to possible chronic lung disease, such as BPD. And even with the InSurE method, a brief period of positive pressure ventilation is still required and at times, extubation cannot be rapidly performed.[30,31]

One of these alternative methods is LISA via a thin endotracheal catheter during spontaneous breathing with CPAP. Usage of LISA allows administration of surfactant while avoiding positive pressure ventilation. The results from the previous study suggest that this modified technique for administering surfactant using orogastric tube and without endotracheal intubation and positive pressure ventilation is well tolerated by preterm infants on CPAP for the treatment of RDS. From our meta-analysis, we found LISA procedure significantly reduced the incidence of invasive mechanical ventilation, not only before 72 hours after birth but also during the whole hospitalization (95% CI, 0.35–0.79; p = 0.002 and 95% CI, 0.08–0.58; p = 0.002). Besides, this method significantly decreased the incidence of BPD (95%CI, 0.50–0.74; p < 0.00001). Interestingly, our results showed that LISA procedure did not shorten the course of mechanical ventilation and supplementary oxygen inhalation, as well as hospital stay. Maybe it is because the LISA therapy is less effective for infants with severe RDS. These infants generally need longer invasive mechanical ventilation and hospital stay. In addition, some severe complications could influence the course of supplementary oxygen, such as patent ductus arteriosus and systemic infection.

Currently, avoidance of intubation is one of the main targets in respiratory management among preterm infants, especially in the first few hours of life, due to the association between ventilator-induced lung injury and BPD.[32] In addition, early surfactant administration improves respiratory outcomes compared with later use in patients with RDS.[33,34] The decision to apply surfactant in a patient with spontaneous breathing is difficult and is occasionally delayed to avoid intubation and invasive ventilation through the endotracheal tube. LISA procedure could avoid this problem in theory. However, previously, there were some concerns about its safety. As for the possible complications of LISA procedure, we found the LISA therapy did not increase the risks of death, pulmonary hemorrhage, and pneumothorax. In contrast, this method significantly reduced the incidences of ROP, IVH, and PVL (95%CI, 0.29–0.95, p = 0.03; 95%CI, 0.41–0.89, p = 0.01, and 95%CI, 0.41–0.96, p = 0.03). This may be because LISA method could avoid the hemodynamic fluctuation and high concentration oxygen inhalation during mechanical ventilation.

In addition to the aforementioned concerns, we must note additional limitations to some recent researches. For example, data from few available studies were showed by median and quartile range because of skewed distribution. 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. Some studies include the declaration that the research to date is not adequate to draw precise conclusions. Given these limitations, perhaps the focus of future studies should rather explore in better designed, perspective controlled studies.

In conclusion, we found LISA procedure significantly reduced the incidence of invasive mechanical ventilation, not only before 72 hours after birth but also during hospitalization. Besides, this method significantly decreased the incidence of BPD. We also found the LISA therapy did not increase the risks of death, pulmonary hemorrhage, and pneumothorax. In contrast, LISA procedure significantly reduced the incidences of ROP and IVH/PVL. So, from this perspective, LISA is an effective and safe treatment for preterm infants with RDS.

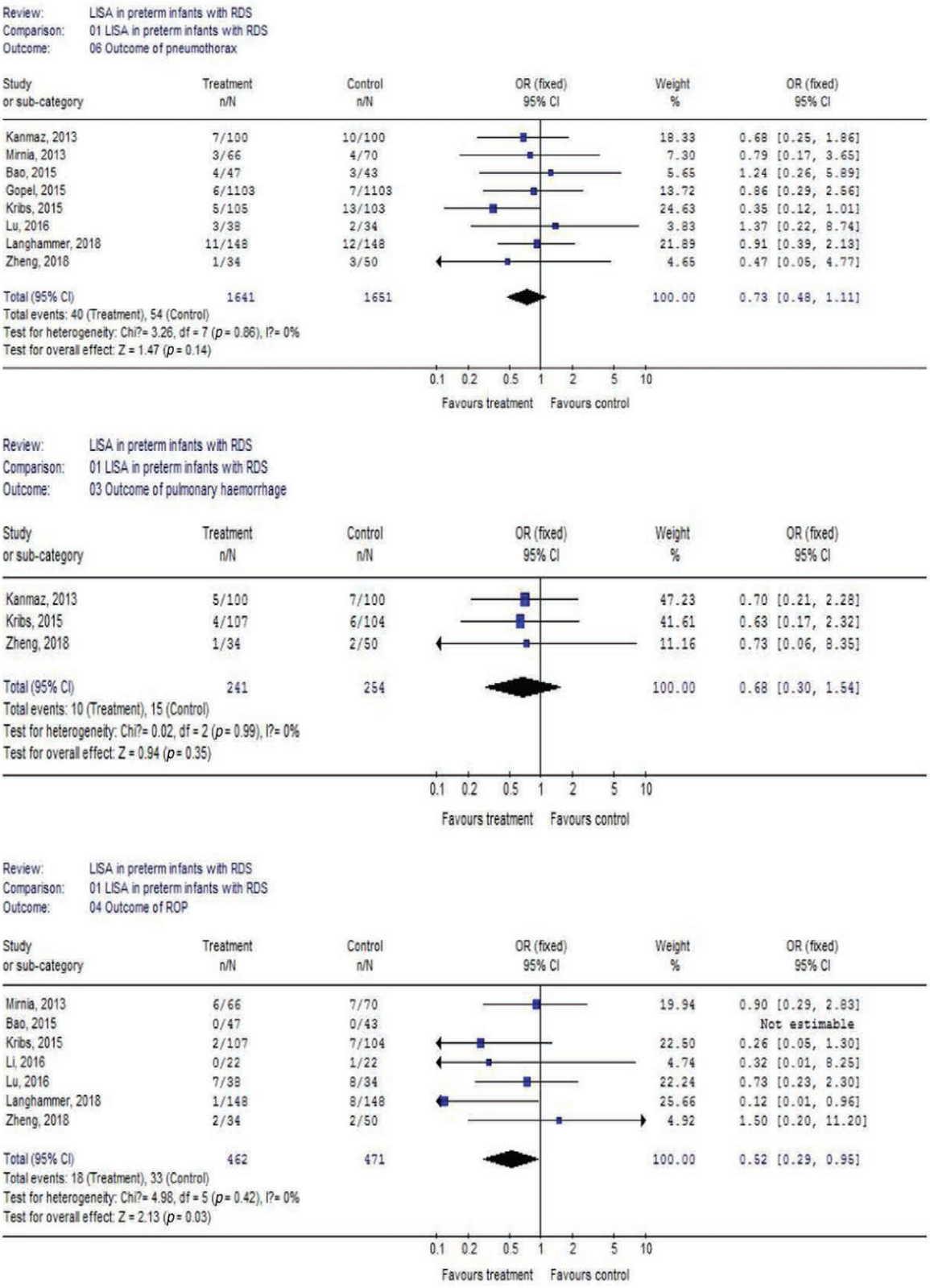

Fig. 6. Effect of LISA procedure on pneumothorax, pulmonary hemorrhage, and ROP.

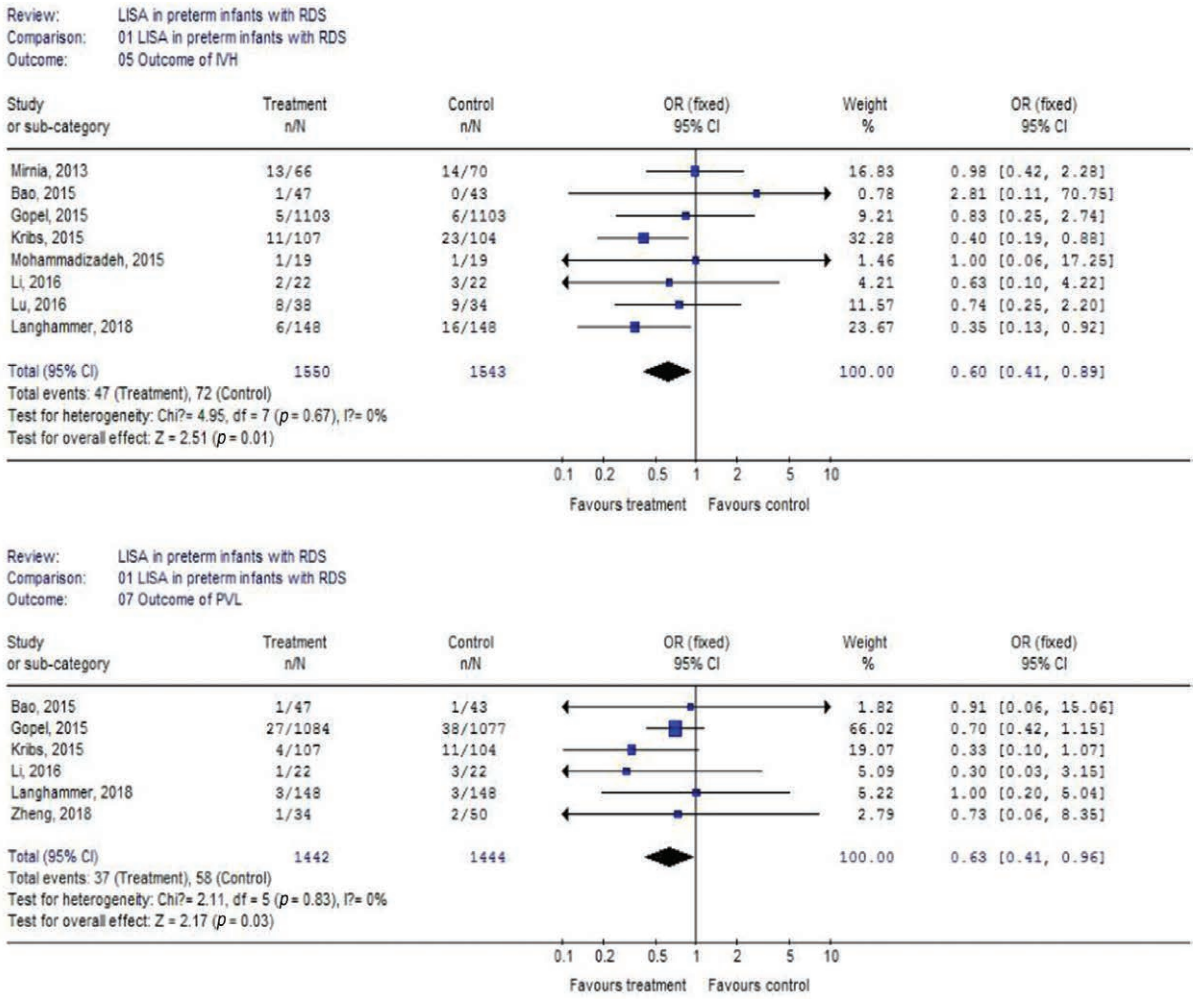

Fig. 7. Effect of LISA procedure on IVH and PVL. IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia.

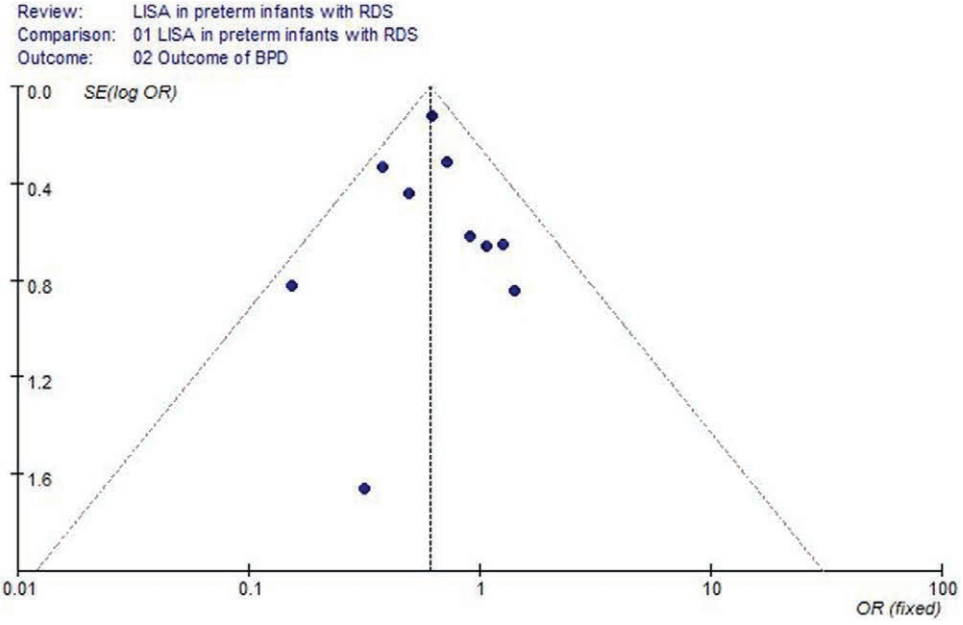

Fig. 8. Funnel plot to assess publication bias.

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