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A Meta-Analysis of the Effects and Safety of Pulmonary Surfactants Combined with Budesonide in Bronchopulmonary Dysplasia

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Abstract

Context: The purpose of this analysis was to explore the effects and safety of Pulmonary Surfactants (PS) combined with budesonide in Bronchopulmonary Dysplasia (BPD) by a meta-analysis of Randomized Controlled Trials (RCTs).
Evidence acquisition: Literature searches were performed in PubMed, the Cochrane Library, EMBASE, the China Knowledge Network, and the Wanfang database to collect data from RCTs. The primary outcomes were BPD incidence and BPD-related mortality, while the secondary outcomes were BPD-related complications. Bias was evaluated by the Cochrane risk assessment tool. The RevMan 5.3 software was used for the meta-analysis, and the Egger's test was used for publication bias assessment.
Results: A total of 720 subjects were enrolled from six RCTs, including 352 in the experimental group and 368 in the observation group. The BPD incidence (RR = 0. 42, 95% CI [0. 37, 0. 89], P < 0.001) and BPD-related mortality (RR = 0.54, 95% CI [0.38, 0.89], P < 0.05) differed significantly between the two groups. Significant differences were also found in intraventricular hemorrhage, infection/sepsis, Retinopathy of Prematurity (ROP), and Patent Ductus Arteriosus (PDA). There were no significant differences in the incidence of PDA, Neonatal Necrotizing Enterocolitis (NEC), hyperglycemia, and hypertension.
Conclusions: The intratracheal instillation of pulmonary surfactants with budesonide can reduce the incidence of BPD and BPD-related mortality with no increased risk of short-term complications.

Keywords: Pulmonary Surfactant, Budesonide, Bronchopulmonary Dysplasia, Meta-analysis, Randomized Controlled Trials

1. Context

Bronchopulmonary Dysplasia (BPD) is a chronic pulmonary disorder that occurs during the early stages of neonatal development (1, 2). It is characterized by acute respiratory failure, resulting from a surfactant deficiency at birth (3-5). The latest definition of BPD refers to any oxygen dependence (FiO2) > 21% in newborns aged over 28 days. The pathogenesis and pathological changes in BPD are complex and caused by an array of factors. Genetic susceptibility is the basis of BPD, but other causes include persistent lung injury, abnormal repairs after injury, and pulmonary dysplasia (6, 7).

Since newborns are more vulnerable to drugs, the use of glucocorticoids will likely result in adverse effects (8, 9). Due to the anti-inflammatory effects of glucocorticoids, their postpartum intravenous administration in premature infants can reduce the incidence and severity of BPD (10), but this leads to complications including gastrointestinal bleeding, intestinal perforation, and elevated blood pressure. It is not recommended that patients with high blood sugar levels, infections, or cerebral palsy receive intravenous administration (11).

Animal experiments have confirmed that the intratracheal infusion of Pulmonary Surfactants (PS) combined with budesonide can effectively increase the concentration of budesonide in the alveoli of experimental animals while increasing the anti-inflammatory effects of the drug (12). However, based on the relevant studies in China and other countries, newborns of early gestational age and low birth weight differ in terms of their response and tolerance to pulmonary surfactants when combined with budesonide.

Although prenatal glucocorticoid protocols, postpartum application of PS, and protective ventilation strategies have improved the survival of preterm infants, the incidence of BPD remains high. Light BPD is common in premature infants with a gestational age of < 28 weeks and birth weight < 1,000g; however, BPD remains a common lung disease that leads to premature death and long-term

illness (13). As the local application of glucocorticoids in the airways directly affects the bronchial tubes and lungs, it can replace intravenous infusion to reduce the incidence of BPD in preterm infants. However, these safe and effective drug delivery methods require further analysis.

2. Objectives

This meta-analytic study evaluated the safety and efficacy of pulmonary surfactants in combination with the intratracheal instillation of budesonide to prevent BPD.

3. Methods

3.1. Literature Inclusion Criteria

The inclusion criteria included

(1) Type of study: randomized controlled trials (RCTs);

(2) Subject: birth weight < 1,500g with a chest radiograph providing a diagnosis of Respiratory Distress Syndrome (RDS);

(3) Intervention: the test group treatment with intratracheal instillation using a mixture of pulmonary surfactants and budesonide and the control group treatment with intratracheal instillation of pulmonary surfactants; and

(4) Outcome: at least one set outcome indicator was reported;

(5) Literature written in a language other than English was also included in this study.

The exclusion criteria included

(1) Non-RCTs (reviews, animal experiments, in vitro experiments, retrospective studies, observational studies, and repeated studies);

(2) Non-intratracheal instillation, e.g., aerosolized; and

(3) Research topics that were irrelevant or could not be obtained in the literature.

3.2. Outcome Indicators

The primary outcome index was the BPD incidence rate and BPD-related mortality. The secondary outcome indicator was the BPD-related complication rate, including intraventricular hemorrhage, infection/sepsis, the Retinopathy of Prematurity (ROP), Patent Ductus Arteriosus (PDA), neonatal Necrotizing Enterocolitis (NEC), hyperglycemia and hypertension.

3.3. Literature Search Strategy

Articles were retrieved from PubMed, the Cochrane Library, EMBASE, the China Knowledge Network, and Wanfang Medical Databases. The search time was from the creation of the database to July 2019. We collected data on the use of pulmonary surfactants combined with budesonide intratracheal instillation to prevent bronchopulmonary dysplasia. The relevant literature on safety and efficacy was also compiled. The search terms included bronchopulmonary dysplasia, chronic lung disease, chronic pulmonary disease, BPD, CLD, and lung dysplasia. The Chinese search terms included bronchopulmonary dysplasia, pulmonary surfactants, glucocorticoids, budesonide, and Pulmicort.

3.4. Document Screening, Data Extraction, and Quality Assessment

The literature was screened by two independent researchers. Data extraction, literature quality assessment, and cross-checking were also performed on the relevant literature. If the researcher's opinions were not uniform, disagreements were resolved through discussions. Duplicated literature was removed, and titles and abstracts were excluded if they were not related to the study subject or included non-RCTs. Full texts were screened to determine inclusion.

The extracted data included (1) first author and year of publication; (2) year of inclusion, inclusion criteria, BPD diagnostic criteria and general information (gestational age, birth body) quality, gender, mode of production, and prenatal use of hormones for pregnancy; (3) intervention methods such as the time of administration and dose; and (4) outcome indicators.

The quality assessment of the clinical trials was performed using the Cochrane risk bias assessment tool. The assessments were based on the following: (1) whether random sequences were generated and correct; (2) whether to distribute concealment; (3) whether to study the blindness of the subjects, and whether the outcome was influenced by the lack of blinding; (4) whether to blind the study results; (5) whether the outcome measures were complete; and (6) whether selective reports, losses of follow-ups or shedding cases were described.

3.5. Statistical Methods

The meta-analyses were performed using the RevMan 5.3 software. Heterogeneity tests were used for the Q assessments and I^2 statistics. If $P \geq 0.1$ and $I^2 \leq 50\%$, no heterogeneity existed between the studies and the combination was a fixed effect. If $P < 0.1$ and $I^2 > 50\%$, heterogeneity was present and merged with a random-effects model. Count

data were expressed as the relative Risk Ratio (RR) and 95% Confidence Intervals (CI). For the two categorical variables, the Odds Ratio (OR) and 95% CI were used to evaluate the safety and efficacy of the intervention. Publication bias assessments were performed using the Egger's tests. A $P < 0.05$ was considered statistically significant.

4. Results

4.1. Literature Search

A total of 512 articles were retrieved, comprising 43 from the China Knowledge Network, 35 from the Wanfang Medical Network, 112 from PubMed, 254 from EMBASE, and 68 from the Cochrane Library. Overall, six trials were included in the meta-analyses. The screening process is shown in Figure 1.

The experimental groups in all six RCTs were intratracheally instilled with PS and budesonide. Only PS was administered into the tracheas of the control group. A total of 720 subjects were included: 352 in the experimental group, and 368 in the control group. The basic information of the subjects is shown in Table 1.

4.2. Bias Assessments

The Cochrane, risk assessment tool, was used for the bias evaluation. The studies were randomized, but only two described the correct random method (article (14) used sealed envelopes and article (3) used allocation lists) and noted allocation concealment. One of the RCTs were numbered according to the order of admission (high risk), while the other three articles referred to the admissions as "random," producing a higher likelihood of selection bias. Two of the articles were done by blind evaluation, so the existence of bias and measurement bias was not excluded. None of the five articles had pre-defined outcome indicators. One study only had partial outcome indicators and did not describe the specific incidence. Two of the articles included children not completing their follow-up, which was described by the other four articles. The risk of gender reporting was low, and there was uncertainty regarding bias from other sources. The bias assessments are shown in Figures 2 and 3.

4.3. Meta-Analysis

4.3.1. Bronchopulmonary Dysplasia Incidence

Six studies described the incidence of BPD, including a total sample of 720 children. Heterogeneity tests showed $P = 0.31$ and $I^2 = 28\%$, suggesting no heterogeneity, so the fixed-effect model was used (Figure 4).

The analysis showed that the differences were statistically significant in the incidence of BPD between the experimental and control groups (RR = 0. 42, 95% CI [0.37, 0.89], $P < 0.001$).

4.3.2. Bronchopulmonary Dysplasia-related Mortality

The BPD-related mortality was reported in four studies, including a total number of 571 children. No heterogeneity was observed between the studies ($P = 0.43$, $I^2 = 0\%$), so a fixed-effect model was used. There were significant differences in BPD-related mortality between the experimental and control groups (RR = 0.54, 95% CI [0.38, 0.89], $P < 0.05$) (Figure 5).

4.3.3. Secondary Outcome Indicators

Intraventricular hemorrhage, infection/sepsis, the Retinopathy of Prematurity (ROP), Patent Ductus Arteriosus (PDA), Neonatal Necrotizing Enterocolitis (NEC), hyperglycemia, and hypertension were compared between the experimental and control groups.

As shown in Table 2, no significant differences were observed. However, the systolic blood pressure of children in the experimental groups was higher than that of children in the control groups on the third and seventh days of receiving treatment ($P < 0.05$). The diastolic blood pressure of children in the experimental groups was higher than that of children in the control groups on the third and fifth days of receiving treatment ($P < 0.05$). A single study (14) performed a follow-up on children aged 2 - 3 years, which showed that body mass (11.6 ± 1.4 kg vs. 11.4 ± 2.6 kg), height (85.2 ± 6.4 cm vs. 87.7 ± 3.9 cm), and head circumference (46.3 ± 1.8 cm vs. 47.0 ± 3.0 cm) of children did not differ significantly between the experimental and control groups. There were no significant differences in abnormal neurological manifestations, Mental Development Index (MDI) scores, and Psychomotor Development Index (PDI) scores between the experimental and control groups ($P > 0.05$), but only 50% of the children entered a follow-up study, so a loss of follow-up data due to bias occurred (15).

4.3.4. Publication Bias Assessment

The Egger's tests showed no significant publication bias in the incidence of BPD (t = 1.04, 95% CI [-2.12, 1.86], P = 0. 494) (Figure 6).

5. Discussion

Reducing infection and inflammation is the key to treating BPD. Glucocorticoids have direct and indirect anti-inflammatory effects and can improve lung functioning

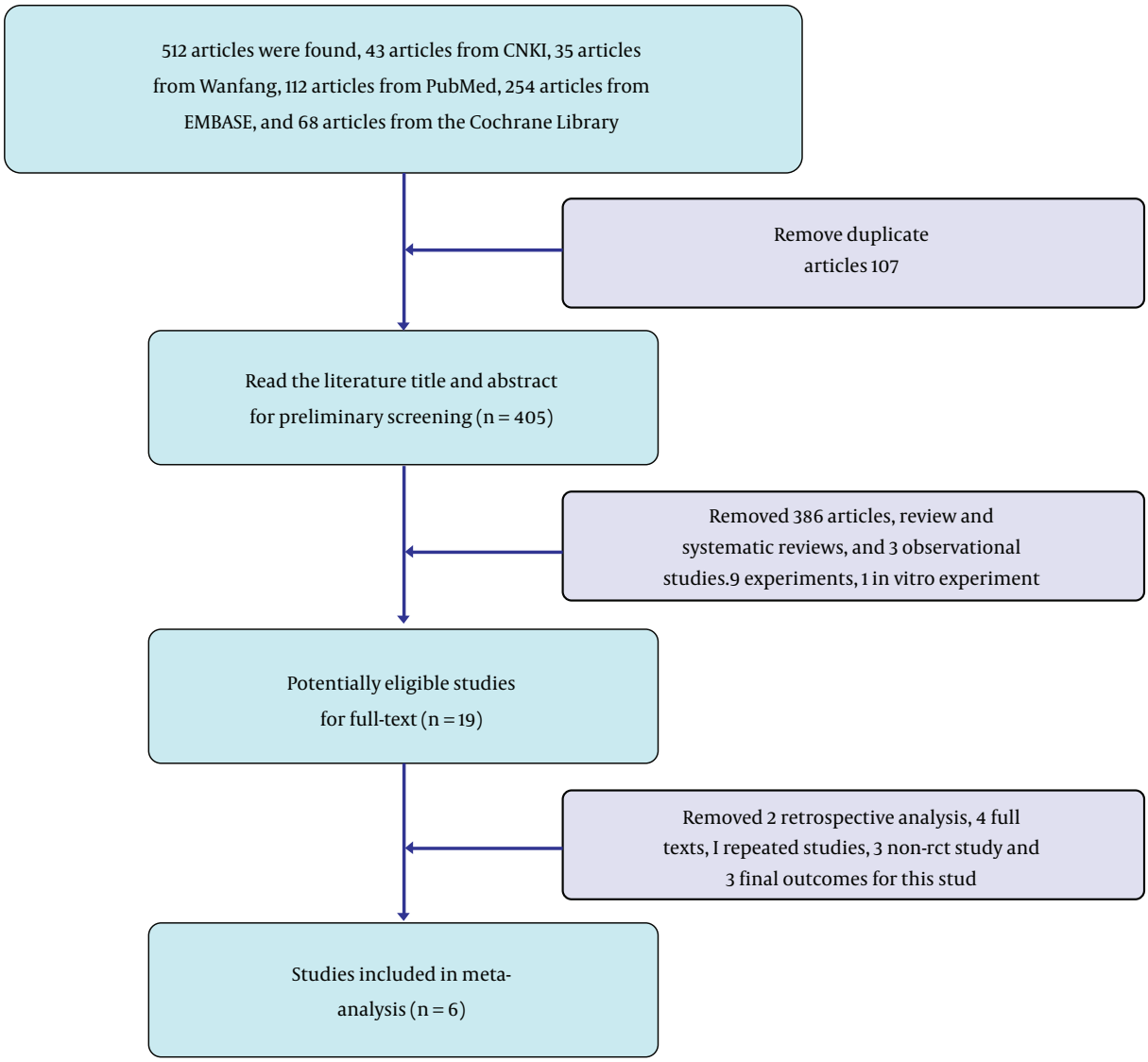

Figure 1. Flow chart of the study selection

through mechanisms that prevent BPD occurrence, including accelerating fetal lung development, reducing pulmonary microvascular permeability, improving gas exchange, and the oxygenation index. Pulmonary edema and intrapulmonary shunts are reduced, and glucocorticoids increase the synthesis of pulmonary surfactants (16-18). These results have also received widespread attention. However, due to an increasing number of studies highlighting how glucocorticoids increase the risk of hyperglycemia, hypertension, cardiac hypertrophy, and gastrointestinal perforation and reduce body mass, their application in premature infants remains controversial. Therefore, further research in this area is required (19).

As one of the many complex multifunctional substances produced by human alveolar type II epithelial cells, pulmonary surfactants are the most important substances affecting pulmonary autonomic respiratory function (20). The lack of pulmonary surfactants in premature infants can directly lead to a persistent collapse of the alveoli and small airways, resulting in various dyspnea manifestations (hypoxemia and acidosis) shortly after birth, while further affecting the synthesis of pulmonary surfactants (21, 22).

This study included six RCTs and a total of 720 preterm infants who were diagnosed with BPD. The results of the

Table 1. The Main Characteristics of the Five Included Studies

Study and Year	Inclusion Year	Cases	Gestational Age (Weeks)		Birth Weight (g)		Antenatal Treatment with Corticosteroid		Intervention	
		Test and Control Group	Test	Control	Test	Control	Test	Control	Test (B ± PS, mg /kg)	Control (PS, mg/kg)
Ye et al (2008)	2004 - 2008	116 (60, 56)	26. 4 ± 2. 2	26. 7 ± 2. 3	881 ± 245	919 ± 272	46	42	0. 25 ± 100[a]	100[a]
Ye et al (2016)	2009 - 2013	265 (131, 134)	26. 5 ± 1.9	26. 8 ± 2. 0	882 ± 123	935 ± 264	112	106	0. 25 ± 100[b]	100[b]
Pan et al (2017)	2015 - 2016	30 (15, 15)	29. 5 ± 1. 8	30. 0 ± 1. 7	1 260 ± 240	1 360 ± 370	10	9	0.25 ± 70[c]	70[c]
Deng et al (2016)	2014 - 2015	46 (18,28)	29. 45 ± 0. 96	29. 25 ± 1. 40	1 310 ± 180	1 280 ± 220	4	6	0.25 ± 75[d]	150[d]
Ren et al (2019)	2012 - 2015	160 (80, 80)	38. 47 ± 1. 74	38. 64 ± 1. 33	1 648 ± 132	1 228 ± 124	26	29	0.23 ± 65[e]	65[e]
Su et al (2019)	2016 - 2018	98 (48, 50)	29. 68 ± 1.55	29.16 ± 1. 45	1351 ± 337	1211 ± 267	22	24	0.25 ± 200[f]	200[f]

Abbreviations: B, budesonide

[a] Enter the NICU to give the first dose, repeat every 8 h to the child FiO2 ≤ 0.4 or extubation.

[b] Every 8 h repeated administration to the child FiO2 < 0.3, or extubation or 6 times.

[c] If FiO2 > 0.4 or mean arterial pressure > 8 cm H2O, repeat the administration once.

[d, e] Within 8 h of birth, it can be reused every 8 ~ 12 h according to the condition.

[f] It can be repeated once every 6 ~ 12 h after administration.

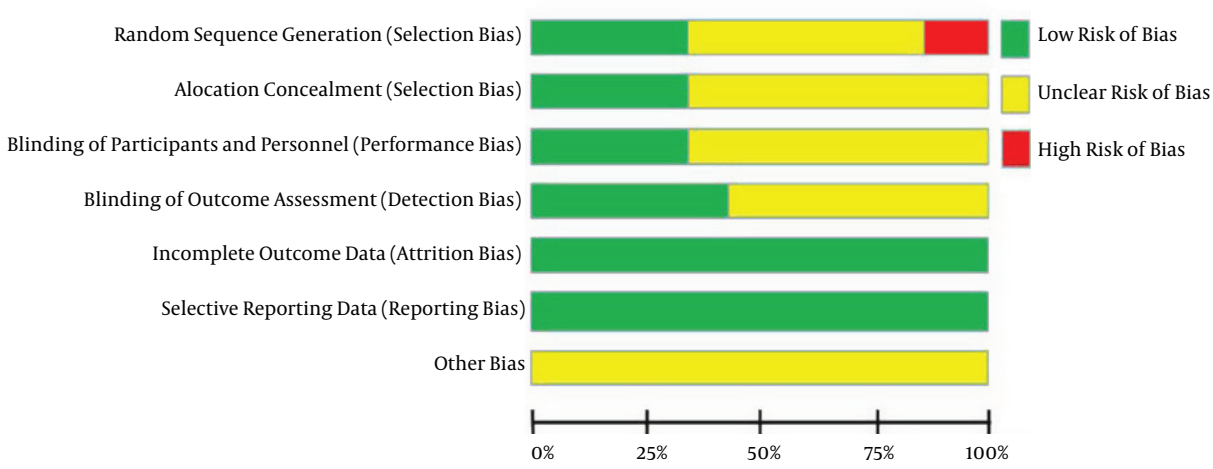

Figure 2. Bias assessment for the included studies

Table 2. A Meta-Analysis of the Incidence of Complications Between Experimental and Control Groups

Outcome	Studies	Heterogeneity Test	Test	Control	OR (95% CI)	P
Intraventricular hemorrhage	(10-12)	P = 0.48, I^2 = 0%	69/209	75/218	0.96 (0.68, 1.45)	0.95
Infection/Septicemia	(10-13)	P = 0. 66, I^2 = 0%	38/235	48/251	0.73 (0.43, 1.24)	0.36
ROP	(3, 10-12)	P = 0. 36, I^2 = 28%	38/209	46/218	0.86 (0.42, 1.34)	0.57
PDA	(3, 10, 11)	P = 0.17, I^2 = 59%	86/191	98/190	0.74 (0. 46, 1.06)	0.07
NEC	(3, 11, 12, 14)	P = 0.78, I^2 = 0%	8/182	18/197	0.75 (0.31, 1.58)	0.52
Hyperglycaemia	(3)	-	1/18	1/20	0.53 (0.04, 6.39)	0.62
Hypertension	(3)	-	1/33	1/35	1.12 (0.06, 19.28)	0.94

meta-analysis showed that pulmonary surfactants combined with budesonide intratracheal instillation reduced the incidence of BPD in preterm infants and their associated mortality but did not increase the incidence of complications such as infection, intraventricular hemorrhage, the retinopathy of prematurity, and patent ductus arterio-

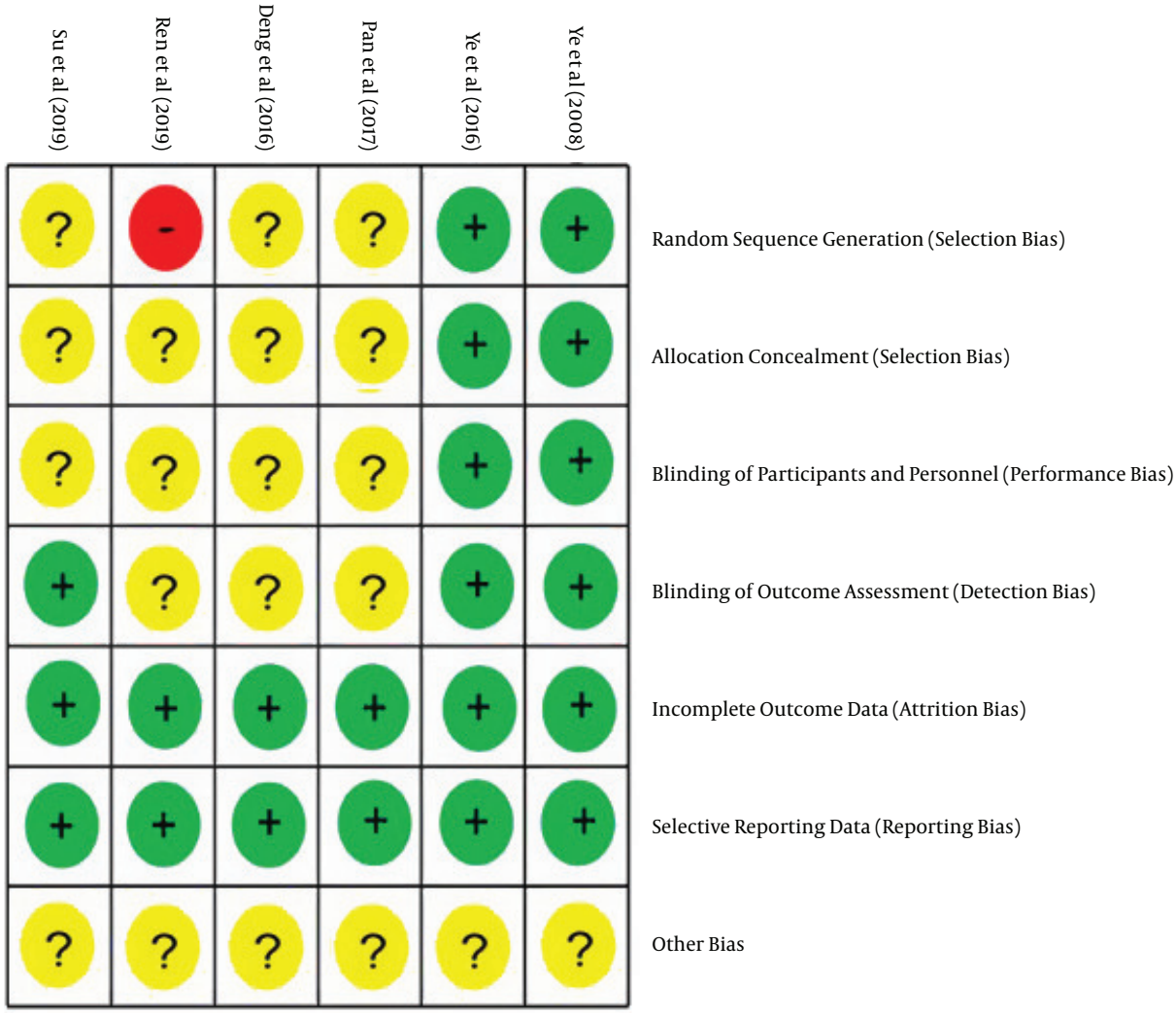

Figure 3. Quality evaluation of the included studies

sus. These results are consistent with a meta-analysis by Venkataraman et al., whose study showed that although mortality was not different between the experimental and control groups (OR: 0.61; 95% CI: 0.34 - 1.04), a 40% reduction was observed in the composite outcome of death or BPD in the budesonide-surfactant group. Thus, the intratracheal administration of a budesonide-surfactant combination was associated with the decreased incidence of BPD alone or the composite outcome of death or BPD in VLBW infants, though there is a need for larger trials before this treatment can be recommended as a standard of care (23). A previous study showed that pulmonary surfactants combined with intratracheal budesonide had no significant effects on the growth and nervous system development in children and that the treatment significantly improved the combined outcome of death or chronic lung disease in small premature infants (24). Nimmo et al. showed that pulmonary surfactants act as effective carriers of glucocorticoids in the lungs of mice, and the prophylactic intratracheal administration of glucocorticoids administered shortly after birth may prevent inflammatory insult to the lungs, and so reduce the likelihood of chronic lung disease developing in patients (25).

5.1. Strengths and Limitations

The limitations of this study included the use of only six RCTs in which the total sample size was small. Four studies were from mainland China, one was from Taiwan, and one was from a multi-center research center in Taiwan, China, and Chicago, USA, so ethnic limitations existed. The

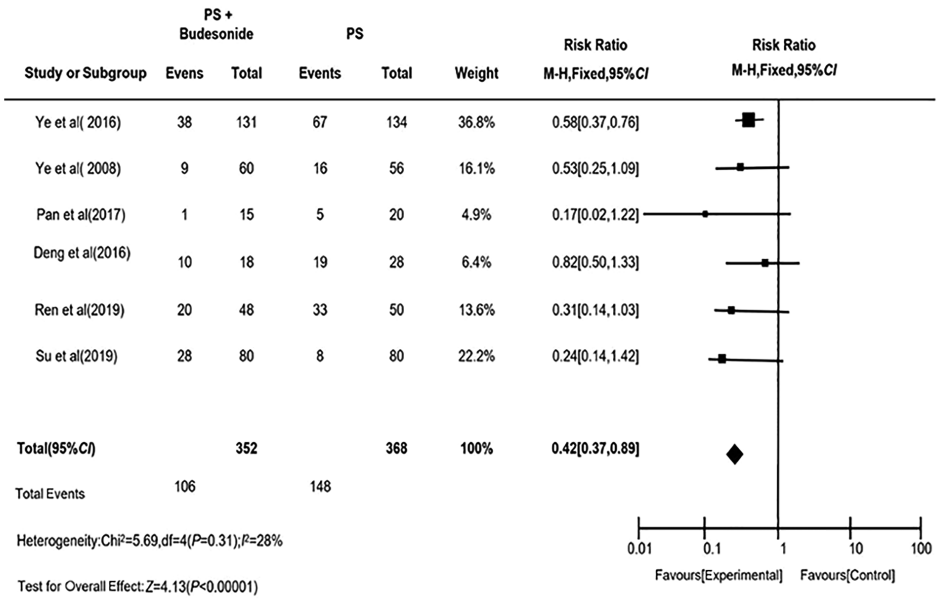

Figure 4. A meta-analysis of the incidence of BPD between experimental and control groups

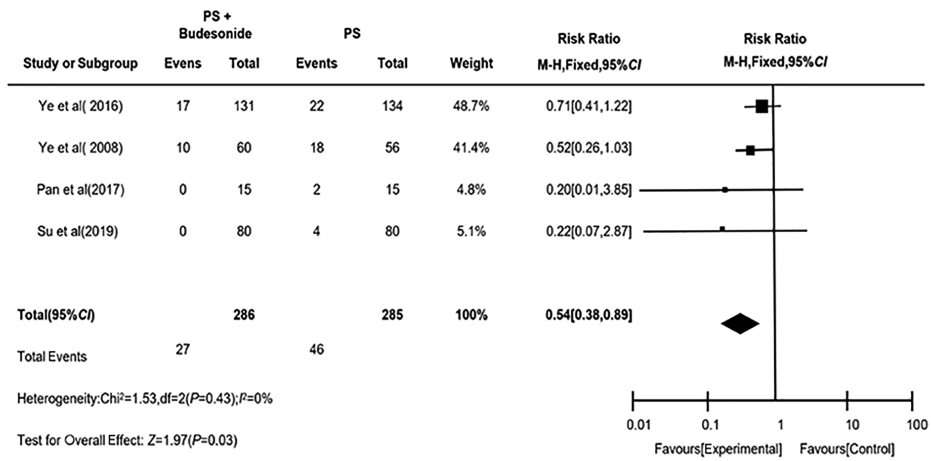

Figure 5. A meta-analysis of BPD-related mortality in experimental and control groups

ratio of pulmonary surfactants and budesonide included in the studies varied, but a subgroup analysis was not performed due to the small sample size. Only a single RCT used follow-ups, and the long-term outcomes such as growth levels and nervous system development were compared. There was, therefore, the possibility of bias due to loss of follow-up, and the effects of pulmonary surfactants and budesonide on the long-term development of the nervous system were unclear.

5.2. Implications for Research

The efficacy and safety of PS + budesonide mixtures and intratracheal instillation with PS were not compared to other modes of administration, so the scopes of the study were limited. In future studies, minimally invasive and non-invasive drug delivery methods such as nebulization should be used to identify the optimal route of administration.

Number of studies=6 Root MSE = 1.023

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% conf.	Interval]
Slope	-.1241723	.48953	-0.27	0.862	-1.482572	1.24571
Bias	1.32586	1.509625	1.04	0.494	-2.119845	1.86432

Test of H0:no small-study effect P= 0.494

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Figure 6. Publication bias assessment analysis by Egger's tests

6. Conclusions

Pulmonary surfactants, combined with the intratracheal instillation of budesonide can reduce the incidence of BPD and its related mortality and decrease the risk of short-term complications. However, their impact on long-term complications such as neurodevelopmental disorders requires further studies of higher quality that contain large sample sizes and multi-center clinical randomization.

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Footnotes

Authors' Contribution: The conception and design of the study were provided by GSL. Acquisition of papers, analysis, and interpretation were led by JYZ and BRY. The manuscript was first drafted by BBH. All the authors were involved in reviewing the draft. All authors have read and approved the final manuscript.

Conflict of Interests: The authors declare that they have no conflict of interest.

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