Meta-analysis of the efficacy of pulmonary surfactants combined with budesonide for the prevention of bronchopulmonary dysplasia

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Research article

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Abstract

Background Pulmonary surfactants(PS) combined with the intratracheal instillation of budesonide to prevent bronchopulmonary dysplasia (BPD) have been report previously. However, the safety of the use of PS combined with budesonide is still unknown and remains to be clarified. Methods PubMed, the CochraneLibrary, EMBASE, the China Knowledge Network and the Wanfang database were searched for relevant studies. Searches were performed from December 2018, and data from randomized controlled trials (RCTs) were collected. Primary outcome measures were BPD incidence, BPD-related mortality. Secondary outcomes were BPD-related complications. The Cochrane risk assessment tool was used for the evaluation of bias. RevMan5. 3software was employed for meta-analysis. An Egger's test was used for publication bias assessments. Results A total of 720 subjects were enrolled from 6 RCTs, including 352 in the experimental group and 368 in the observation group. A meta-analysis showed that the incidence of BPD [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), $P < 0.05$] significantly differed between the groups. Differences were also observed for intraventricular hemorrhage, infection/sepsis, retinopathy of prematurity (ROP), and patent ductus arteriosus. There were no significant differences in the incidence of PDA, neonatal necrotizing enterocolitis (NEC), hyperglycemia, or hypertension ($P > 0.05$). Conclusion 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. However, considering both sample size and study bias, the safety and efficacy of this treatment plan requires clarification in large-samples, and multi-center clinical RCTs. In addition, the impact of long-term complications such as neurodevelopmental disorders requires further assessment.

Background

Broncho pulmonary dysplasia (BPD) occurs during the early stages of neonatal development. Due to immature lung tissue oxygen inhalation or mechanical ventilation in response to chronic lung injury, BPD impacts neonatal prognosis and pulmonary function[1-3]. The disease was first proposed by northway and colleagues in the 1960s[4]. Due to continual improvements in the diagnosis and treatment of premature infants and critical newborns in China, the survival rates of children with BPD have gradually improved. To-date, a lack of unified norms for clinical diagnosis and disease treatment exist. Clinicians can effectively treat neonatal respiratory disease that is characterized by progressive dyspnea with the prophylactic application of corticosteroids. The pharmacological basis is that glucocorticoids induce newborns to produce pulmonary surfactants, thereby reducing pulmonary resistance and increasing the concentration of other drugs in the alveoli[5]. Considering that premature infants with low birth weights account for more than 50. 5% of children with BPD, methods to reduce its incidence remains an area of intense research interest[6]. Animal experiments have confirmed that the intratracheal infusion of pulmonary surfactants combined with budesonide can effectively increase the concentration of budesonide in the alveoli of experimental animals, increasing the anti-inflammatory effects of the drug[7]. However, based on relevant studies in China and other countries, newborns of small 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, the postpartum application of pulmonary surfactants (PS), and protective ventilation strategies have improved survival in preterm infants, the incidence of BPD remains high. Light BPD is common in immature preterm infants of a gestational age <28 weeks and birth weights <1000 g. BPD remains a common lung disease that leads to premature death and long-term illness [8]. The etiology of BPD is complex, with lung inflammation and host immune responses considered major pathogenic factors. Due to the anti-inflammatory effects of glucocorticoids, their postpartum intravenous administration in premature infants can reduce the incidence and severity of BPD [9], but this leads to complications, including gastrointestinal bleeding, intestinal perforation, and elevated blood pressure. High blood sugar levels, infections, and those with cerebral palsy are not recommended for intravenous administration [10]. As the local application of glucocorticoids in the airways directly affects bronchial tubes and lungs, it can replace intravenous infusion to reduce the incidence of BPD in preterm infants. However, safe and effective drug delivery methods require further analysis. This article evaluates the safety and efficacy of pulmonary surfactants in combination with the intratracheal instillation of budesonide to prevent BPD by meta-analysis.

Methods

Literature inclusion criteria

(1) Type of study: Randomized controlled trial (RCT); (2) Subject: Birth weight < 1500 g and chest radiograph diagnosed as respiratory distress syndrome (RDS); (3) Intervention: Test groups were treated with intratracheal instillation using a mixture of pulmonary surfactants and budesonide. Control groups were treated with intratracheal instillation of pulmonary surfactants.

(4) At least one outcome index set was reported; (5) The language was not limited.

Exclusion criteria

(1) Non-RCTs (reviews, animal experiments, *in vitro* experiments, retrospective studies, observational studies, repeated studies; (2) non-intratracheal instillation: e.g. aerosolized; (3) Research topics were irrelevant and could not be obtained in the literature.

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), high blood sugar levels and high blood pressure.

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 creating database to July 2019. We collected data on the use of pulmonary surfactants combined with budesonide intratracheal instillation to prevent bronchopulmonary dysplasia. Relevant literature on safety and efficacy were compiled. Search terms included bronchopulmonary dysplasia, chronic lung disease, chronic pulmonary disease, BPD, CLD, and lung dysplasia. Chinese search terms included bronchopulmonary dysplasia, pulmonary surfactants, glucocorticoids, budesonide, and primec.

Document screening, data extraction and quality evaluation

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

Data extraction 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, prenatal use of hormones for pregnancy; (3) intervention methods such as time of administration and dose; (4) Outcome indicators.

Quality evaluation of the clinical trials was performed using the Cochrane risk bias assessment tool. Assessments were based on the following: (1) whether random sequences were generated and are correct; (2) whether to distribute concealment; (3) whether to study 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; (6) whether selective reports, loss of follow-up, or shedding cases are described.

Statistical methods

Meta-analyses were performed using RevMan5. 3 software. Heterogeneity tests were used for Q assessments and I² statistics. If $P \geq 0.1$, $I^2 \leq 50\%$, no heterogeneity existed between the studies, and the combination was a fixed effect; if $P < 0.1$, $I^2 > 50\%$, heterogeneity was present and combined 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 its 95% CI were used to evaluate the safety and efficacy of the intervention. Publication bias assessments were performed using Egger's tests. $P < 0.05$ was considered statistically significant.

Results

Literature Search

A total of 512 articles were retrieved, including 43 articles from the China Knowledge Network, 35 from the Wanfang Medical Network, 112 from PubMed, 254 from EMBASE, and 68 from the Cochrane Library.

Six screens were included. The screening process is shown in Figure 1.

Basic information for study inclusion

All 6 RCTs were intratracheal instilled with PS and budesonide as the experimental group. 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.

Bias assessments

The Cochrane risk assessment tool was used for bias evaluation. The studies were randomized but only two described the correct random method (article [11] uses sealed envelopes, article [12] uses allocation lists) and noted allocation concealment. One of the RCTs was numbered according to the order of admission (high risk), whilst the other three articles referred to the admissions as “random”, producing a higher likelihood of selective bias. In two of the articles, the evaluators were blind so the existence of bias and measurement bias were not excluded. All five articles had no pre-defined outcome indicators. One study had only partial outcome indicators and did not describe the specific incidence. Two of the articles lost children to 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. Bias assessments are shown in Figure 2-3.

Meta Analysis

BDP incidence

Six studies described the incidence of BPD, including a total of 720 children. Heterogeneity tests showed $P=0.31$, $I^2 = 28\%$, suggesting no heterogeneity and so the fixed effect model was used. The analysis showed that differences in the incidence of BPD between the experimental and control groups were statistically significant [RR=0.42, 95% CI (0.37, 0.89), $P < 0.001$].

BDP related mortality

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

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 experimental and control groups. No significant differences were observed but the

systolic blood pressure of the children in the experimental group were higher than those of the control group on the 3rd and 7th day of treatment ($P<0.05$). The diastolic blood pressure of the children in the experimental groups were higher than that the control group on the 3rd and 5th day of treatment ($P<0.05$). A single study [11] performed a follow-up in children aged 2 to 3 years, which showed that the body mass of the experimental and control groups [(11.6±1.4) kg vs (11.4 ±2.6) Kg], height [(85.2 ±6.4) cm vs (87.7±3.9) cm], head circumference [(46.3±1.8) cm vs (47.0 ±3.0)] did not significantly differ between the two groups. There were no significant differences in abnormal neurological manifestations, mental development index scores (MDI) and psychomotor development index scores (PDI) between experimental and control groups ($P>0.05$), but only 50% of the children entered a follow-up study, so a loss of follow-up due to bias existed [17].

Publication bias assessment

Egger's tests showed no significant publication bias in the incidence of BPD [$t = 1.04$, 95% CI (-2.12, 1.86), $P = 0.494$](Fig.6).

Discussion

There is no definitive definition of bronchopulmonary dysplasia (BPD). In 1979, Tooley recommended that BPD should be defined as requiring oxygen therapy 28 days after birth [18]. In 1988, Shennan et al. [19] proposed that BPD should be defined as requiring clinical oxygen at 36 weeks of gestational age, which was further confirmed by Shennan and colleagues, and is now accepted in clinical practice. The latest definition of BPD refers to any oxygen dependence (FiO_2)>21% in newborns aged over 28 days. The pathogenesis and pathological changes of 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 repair after injury, and pulmonary dysplasia [20,21]. With the application of pulmonary surfactants, the pathological changes of new BPD are characterized by pulmonary microvascular and alveolar dysplasia. At present, there is no definitive and effective BPD treatment and its control is based on prevention. Commonly used methods include protective ventilation strategies, NO inhalation, the restriction of liquids and diuretics, caffeine, and vitamin A, active substances, glucocorticoids, and nutritional support. Since intrauterine infections such as chorioamnionitis produce inflammatory mediators during preterm birth, postnatal exposure to infections or iatrogenic factors (such as mechanical ventilation and oxygen therapy) can lead to inflammatory reactions, infections, lung dysplasia, and developmental cessation [22]. Infection and inflammation are key to BPD. Glucocorticoids have direct and indirect anti-inflammatory effects, and improve lung function through an array of 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 [23] which have received widespread attention. However, due to an increasing number of studies highlighting how glucocorticoids increase the risk of hyperglycemia, hypertension, cardiac hypertrophy, gastrointestinal perforation, and the reduction

of body mass, their application in premature infants remains controversial. Further research in this area is required [24].

BPD primarily occurs in premature infants, as is more obvious at a lower gestational age. Previous studies have shown that the incidence of neonatal respiratory distress syndrome in premature infants aged 23 to 31 weeks decreases with increasing gestational age[25]. 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[26]. Surfactants are composed of lipids and proteins and influence lung maintenance and neonatal lung surface gradient tension. To-date, four types of surfactant proteins have been isolated, amongst which proteins B and C interact with phospholipids to reduce the tension of the lung surface[27]. 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, further affecting the synthesis of pulmonary surfactants[28]. With continuous improvements in perinatal medical technology, a higher number of premature infants with very low birth weights can be cured and survive BPD caused by hypoplastic lungs after air pressure injury and inflammatory factors[28]. It is thus important to prevent the occurrence of BPD in the clinic.

This study included 6 RCTs and a total of 720 preterm infants diagnosed with BPD. The results 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 arteriosus. These results are consistent with the meta-analysis of Venkataraman et al [23]. Previous studies [11] showed that pulmonary surfactants combined with intratracheal budesonide had no significant effects on growth and nervous system development in children. Nimmo et al [29] showed that pulmonary surfactants act as effective carriers of glucocorticoids in the lungs of mice.

Strengths and limitations

The limitations of this study included: the use of only 5 RCTs of which the total sample sizes were small. Four studies were from mainland China, 1 was from Taiwan, and 1 was from a multi-center research centre in Taiwan, China and Chicago, USA, so ethnic limitations existed. The ratio of pulmonary surfactants and budesonide included in the studies varied but subgroup analysis was not performed due to the small sample size. Only a single RCT was followed up, and long-term outcomes such as growth levels and nervous system development were compared. There was therefore a possibility of loss of follow-up bias and the effects of pulmonary surfactants and budesonide on the long-term development of the nervous system were unclear.

Implication for research

The efficacy and safety of PS+budesonide mixtures and intratracheal instillation with PS were not compared to other modes of administration. The scope of the study was therefore limited. In future

studies, minimally invasive and non-invasive drug delivery methods such as nebulization should be employed to identify the optimal route of administration.

Conclusions

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

Abbreviations

PS:Pulmonary surfactants; BPD:Bronchopulmonary dysplasia; RCTs: Randomized controlled trials; ROP: Retinopathy of prematurity; PDA:Patent ductus arteriosus; NEC:neonatal necrotizing enterocolitis; RDS: Respiratory distress syndrome; CI:Confidence intervals; MDI:Development index scores; RR:Relative risk ratio; PDI: Psychomotor development index scores.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materia

Supporting data can be obtained from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The conception and design of the study was provided by Guosheng Liu; acquisition of papers, analysis and interpretation were led by Jiayong Zhuang and Boran Ye; the manuscript was first drafted by Bingbin He; all the authors were involved in reviewing the draft. All authors have read and approved the final

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Figures

Figure 1

screening process

Figure 2

bias assessment

Ye et al(2008)	+	+	+	+	+	+	?
Ye et al(2016)	+	+	+	+	+	+	?
Pan et al(2017)	?	?	?	?	+	+	?
Deng et al(2016)	?	?	?	?	+	+	?
Ren et al(2019)	-	?	?	?	+	+	?
Su et al(2019)	?	?	?	+	+	+	?
Random sequence generation(selection bias)							
Allocation concealment(selection bias)							
Blinding of participants and personnel(performance bias)							
Blinding of outcome assessment(detection bias)							
Incomplete outcome data(attrition bias)							
Selective reporting data(reporting bias)							
Other bias							

Figure 3

bias assessment

Figure 4

Figure 5

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

Figure 6

publication bias assessment

Supplementary Files

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