Systematic Evaluation of Early Inhalation of Nitric Oxide for Prevention and Treatment of Bronchopulmonary Dysplasia in Premature Infants

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Bronchopulmonary dysplasia (BPD) is a common chronic lung disease in premature infants, which seriously affects the quality of life of premature infants and may even lead to death of premature infants. At present, there is no unified opinion on the prevention and treatment of BPD, and the mechanism of its occurrence and development is not completely clear in clinical practice. Therefore, finding a better way to prevent and treat BPD is one of the hot spots in clinical practice. The safety of nitric oxide in premature infants with BPD is a focus of clinical attention, but its systematic evaluation has not been reported. In this study, meta-analysis method was used to analysis. The results demonstrated that there were no obvious differences in the incidence, survival, BPD-free survival, and mortality between the inhaled nitric oxide group (iNO group) and the placebo group. The common complications such as toxemia, necrotizing enterocolitis, and visual impairment between the iNO group and the placebo group were not obvious. This suggests that the use of NO to prevent BPD in premature infants has no obvious effect.

Keywords: Inhaled nitric oxide; Bronchopulmonary dysplasia; Premature infants; Meta-analysis
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Bronchopulmonary dysplasia (BPD) is a common disease in preterm infants, which directly affects the prognosis of the premature infants[1, 2]. BPD in premature infants, also known as chronic lung disease (CLD), is a chronic respiratory disease caused by multiple causes. Children with BPD require long-term mechanical ventilation, which not only damages lung function, but also affects long-term physical and intellectual development [3]. Studies have reported [4] that the incidence of BPD in premature infants with a birth weight (BW) of <1.00 kg is 54%; and long-term mechanical ventilation, infection, oxidative stress damage, and lung inflammation may be jointly involved in alveolar dysplasia.

With the advancement of neonatal monitoring technology, the survival rate of premature babies, especially those with very low birth weight (<1.50 kg), has increased obviously, but the incidence of BPD has also increased year by year. With the development of perinatal medicine, the advancement of neonatal monitoring technology and treatment methods, and the continuous development of BPD research, the clinic has a deeper understanding of the cause of BPD [5]. The consensus reached so far is that on the basis of genetic susceptibility, premature delivery, mechanical ventilation, infection, and oxidative stress and other unfavorable factors damage immature lung tissue. Abnormal repair of lung tissue after injury leads to the occurrence of BPD; it can be seen that the immature lung, acute lung tissue injury, and abnormal repair of lung tissue after lung tissue injury are the three key links in the occurrence of BPD [6]. Haliay et al. found that [7], hormone therapy (especially dexamethasone) within 8 days after birth of premature infants can effectively reduce the time of mechanical ventilation and reduce the incidence of CLD, but it may cause complications such as intestinal perforation and hypertension. However, Patra et al.

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[8] found that the premature infant was treated with hydrocortisone for more than 7 days after birth. When he was 1 year old, his language development was affected, and his motor development at 2 years old was also affected. However, Baud et al. [9] started systemic application of low-dose hydrocortisone within 24 hours after birth of premature infants, and continued to use the drug for more than 7 days after birth. Follow-up to 2 years old, their results showed that the children's nervous system was not affected. Other drugs include caffeine, surface active substances, antioxidants, and pulmonary artery dilators. However, clinically, there are still controversies about the effectiveness, pros and cons of related treatments, and there is a lack of unified and standardized prevention and treatment programs.

Recent studies have found [10-13] that pulmonary vascular disease is closely related to BPD, and arterial hypertension is closely linked to the severity and prognosis of BPD. In theory, down-regulating cerebral arterial hypertension is beneficial to prevent BPD. An animal study pointed out that inhaled nitric oxide (iNO) can promote pulmonary vascular regeneration, alleviate complications, inhibit cell death, and reduce oxidative damage. At present, many studies have reported the efficacy of early iNO on BPD in premature infants, but the efficacy reported by different studies is different. Therefore, this study used Meta-analysis to systematically evaluate the correlation of early iNO in the effect and safety of BPD in premature infants, and provide reference for the treatment of BPD in premature infants.

MATERIALS AND METHODS

Search Strategy

Databases such as PubMed(https://pubmed.ncbi.nlm.nih.gov/), EMBASE, and China National Knowledge Infrastructure (CNKI, https://www.cnki.net/) were searched. The search terms are: (1) "Nitric Oxide", "inhaled nitric oxide", "NO", "iNO". (2) "premature", premature baby", "preemy", "premie", "premature infant". (3) "bronchopulmonary dysplasia", "BPD", "chroniclungdisease", "CLD". Combine the above search terms Search (at least two search terms each time).

Inclusion and Exclusion Criteria

Included literature

Inclusion criteria: (1) Publicly published research. (2) The included studies are all related studies of early iNO in the effect and safety of BPD in premature infants. (3) The study included iNO group and control (placebo) group. (4) The research object is premature infants. Exclusion criteria: (1) reviews, conference abstracts, duplicate literatures, unpublished literatures. (2) The data is incomplete, and relevant specific data cannot be obtained for statistical analysis.

Research object

The subjects of the study were live-born babies born before 37 weeks of gestation, called premature babies or immature babies.

Quality Evaluation of the Included Literature

The literature quality evaluation is done independently by two evaluators, and the literature with different opinions is decided after discussion or a third party decides whether to include the literature. The quality of the literatures was evaluated according to Newcastle-Ottawa-Scale (NOS) [13], including: (1) Selection of study subjects (0 to 4 points): The definition of the case and whether the diagnosis is appropriate. Whether the case is representative. The choice and definition of the control group. (2) Comparability between groups (0 to 2 points): Whether the case group and the control group are comparable during the design and statistical analysis. (3) Exposure factor measurement (0 to 4 points): Whether the determination of exposure investigation and assessment methods are the same. Whether the research methods of the case group and the control group are the same. Whether the non-response rate is the same. NOS scale evaluation score 0-10, 10 indicates the highest literature quality. Literatures with a NOS of ≥ 5 points were included in this meta-analysis.

Data Extraction

Two researchers independently searched and included the literatures, and the disputed literature was decided by a third party. Literature screening process: preliminary screening of literature titles and abstracts. Read through the full text for the second screening. Finally, documents that meet the inclusion criteria were included. The content of the literature extraction includes: (1) General information included in the literature: research author, publication year, country, age, sample size of the research object. (2) The results of the case group and the control group.

Statistical Analysis

Selection of effect indicators and clinical significance

Rev Man 5.3 software was used for statistical analysis. The research data is a binary variable, and the results was expressed in odds ratio (OR) and its 95% confidence interval (95% CI).

Heterogeneity test and effect model

The Q test was used to test the heterogeneity first, and $P>0.1$ and $I^2<50\%$ indicated that there was no statistical heterogeneity among the studies, and the fixed effects model (FEM) was used for analysis. If heterogeneity exists, random effects model (REM) was used for analysis.

Sensitivity analysis and publication bias

Sensitivity analysis is to change the analysis model and eliminate one by one to find out the uncertain factors that may have an impact on the combined effect value. Re-combine the effect size to reduce the degree to which it affects the robustness of the result. In this paper, we use the method of eliminating research one by one to analyze the sensitivity of the research results.

At present, the visualization method commonly used to identify publication bias or other biases is the funnel chart method. When the funnel chart is symmetrical, the publication bias is small or non-existent. If the funnel chart is asymmetrical, it indicates that there may be publication bias.

RESULTS AND DISCUSSION

Search Results and Inclusion Process

The preliminary search yielded 577 literatures. By reading the title and abstract, 505 literatures on meta-analysis, review, and animal research were eliminated. Through careful reading of the full text, 26 literatures that did not meet the inclusion requirements, incomplete data, low scores, and duplicate data were eliminated. In the end, a total of 8 qualified literatures were included. Figure 1 shows the detailed literature screening process.

Figure 1
Literatures screening flow chart.

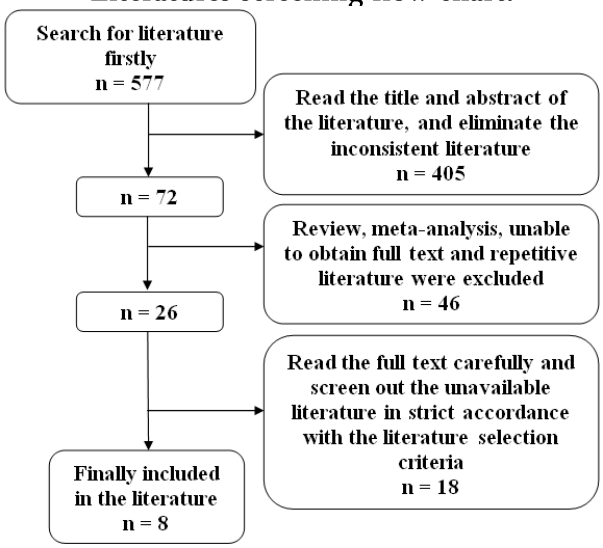


Figure 2
Forest plot of the incidence of BPD in iNO and Placebo group.

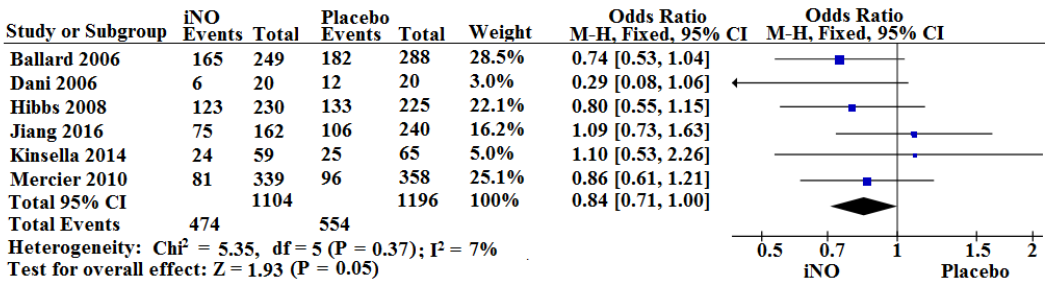
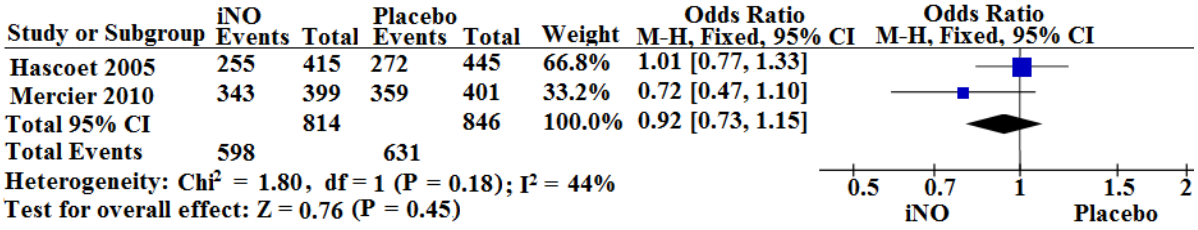


Figure 3
Forest plot of survival rate between iNO and Placebo group..



Features of the Included Literatures

Eight literatures were included in this study [14-21], including 1808 premature infants who used NO to prevent and treat BPD and 1906 premature infants who received placebo. The included literatures were scored on the NOS scale, and the results were all greater than 5 points. Table 1 shows the general information of the included literatures.

Table 1
Features of the included literatures

Literature	Research methods	Research object (birth month age and weight)	Number of cases (Research group/control group)	The intervention of research group	The intervention of control group	Observation index	NOS score
Hascoet 2005 [14]	Randomized control	＜32 week	415/445	Inhaled NO	Placebo	28d survival rate and mortality	7
Ballard 2006 [15]	Randomized double-blind	＜36 week	294/288	Inhaled NO	Placebo	BPD-free survival rate	8
Dani 2006 [16]	Non-blind random	＜30 week	20/20	Inhaled NO	Placebo	BPD incidence, mortality, high frequency ventilation rate	7
Hibbs 2008 [17]	Multi-center, random, double-blind	＜1250g	230/225	Inhaled NO	Placebo	BPD incidence	9
Mercier 2010 [18]	Multi-center, random, double-blind	＜ 29 week, ≥500 g	399/401	Inhaled NO	Placebo	BPD-free survival rate, BPD incidence rate	9
Kinsella 2014 [19]	Multi-center, randomized control	＜ 30 week, 500 – 1250g	59/65	Inhaled NO	Placebo	BPD incidence, mortality, complications	9
Jiang 2016 [20]	Prospective non-randomized control	34 week	162/240	Inhaled NO	Placebo	BPD-free survival rate, BPD incidence, complications	6
Hasan 2017 [21]	Randomized control	＜30 week,＜1250g	229/222	Inhaled NO	Placebo	BPD-free survival rate, BPD severity, survival rate	8

Meta-analysis Results

Meta-analysis of the Incidence of BPD in the iNO Group and the Control Group

Six literatures met the inclusion requirements, and there was no heterogeneity among the research (P = 0.37, I^2 = 7%), so the FEM was used for combined analysis. There was no obvious difference in the incidence of BPD between iNO and placebo group (OR = 0.84, 95% CI: 0.71-1.00, P = 0.05), see Fig 2.

Meta-analysis of the Survival Rate of iNO Group and Control Group

Two literatures met the inclusion requirements, and there was no heterogeneity between the research (P = 0.18, I^2 = 44%), so the FEM was used for combined analysis. There was no obvious difference in survival between iNO and placebo group (OR = 0.92, 95% CI: 0.73-1.15, P = 0.45), see Fig 3.

Meta-analysis of BPD-free survival rate in iNO group and control group

Four literatures met the inclusion requirements, and there was heterogeneity among the research (P = 0.05, I^2 = 61%). Therefore, a REM was used for combined analysis. There was no obvious difference in BPD-free survival between iNO and placebo group (OR = 1.02, 95% CI: 0.76-1.35, P = 0.92), see Fig 4.

Figure 4
Forest plot of BPD-free survival rate between iNO and Placebo group.

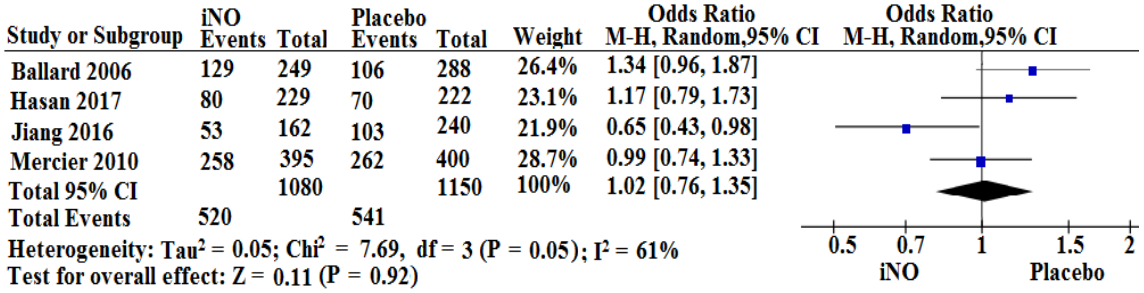


Figure 5
Forest plots of mortality in iNO and Placebo group.

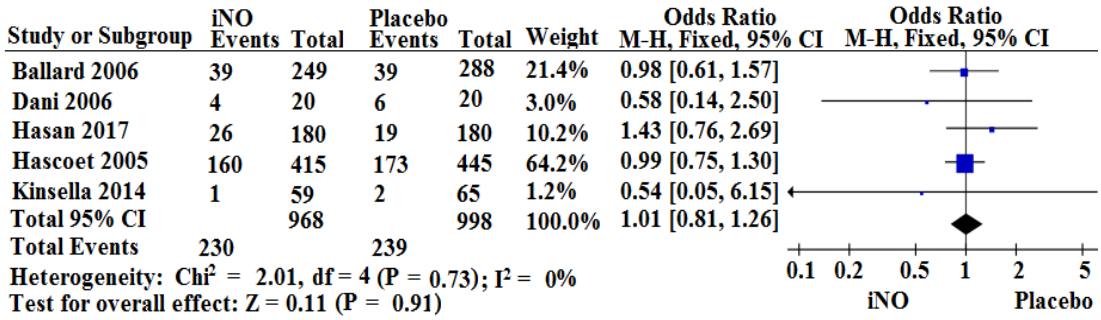
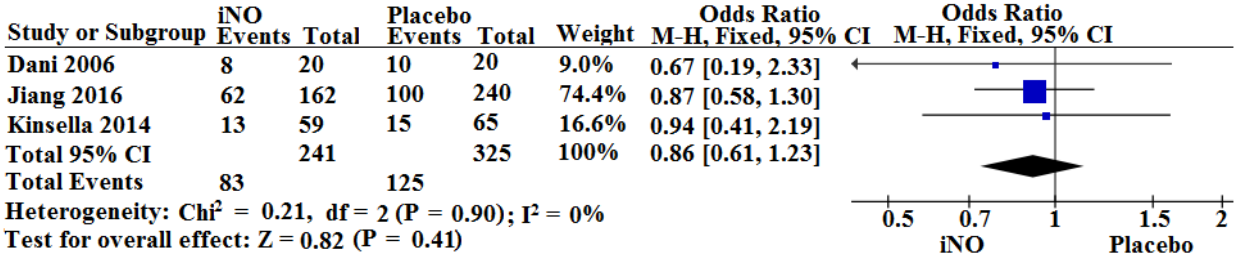


Figure 6
Forest plot of toxemia in iNO and Placebo group.



Meta-analysis of mortality in iNO group and control group

Five literatures met the inclusion requirements and there was no heterogeneity among the research (P = 0.345, I^2 = 11%), so a fixed-effect model was used for combined analysis. There was no obvious difference in mortality between the iNO and placebo group (OR = 1.01, 95% CI: 0.81-1.26, P = 0.91), see Fig 5.

Meta-analysis of 3 common complications in iNO group and control group

Three literatures met the inclusion requirements, and there was no heterogeneity among the research (P = 0.90, I^2 = 0%); therefore, the FEM was used for combined analysis. There was no obvious difference in toxemia between iNO and placebo group (OR = 0.86, 95% CI: 0.61-1.23, P = 0.41), see Fig 6.

Two literatures met the inclusion requirements, and there was no heterogeneity between the research (P = 0.20, I^2 = 40%), so the FEM was used for combined analysis. There was no obvious difference in necrotizing enterocolitis between iNOand placebo group (OR = 0.97, 95% CI: 0.57-1.68, P = 0.92), see Fig 7.

Two literatures met the inclusion requirements, and there was no heterogeneity between the research (P = 0.57, I^2 = 0%), so the FEM was used for combined analysis. There was no obvious difference in visual impairment between iNO and placebo group (OR = 1.05, 95% CI: 0.74-1.49, P = 0.79), see Fig 8.

Figure 7
Forest plot of necrotizing enterocolitis in iNO and Placebo group.

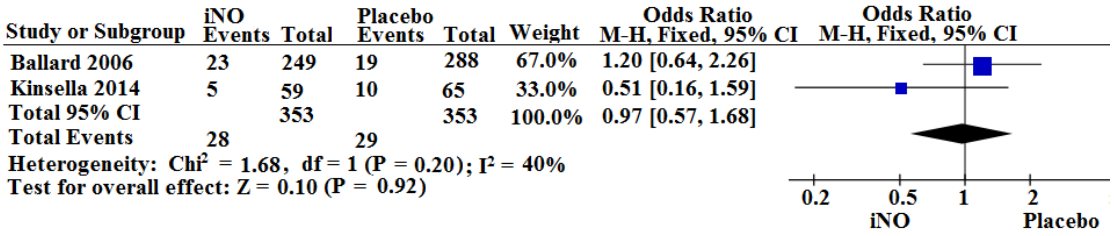
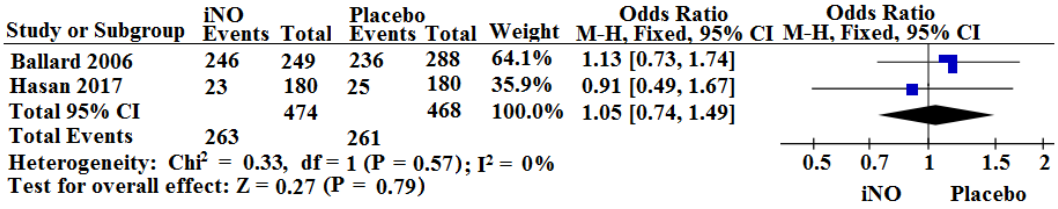


Figure 8
Forest plot of visual impairment in iNO and Placebo group.



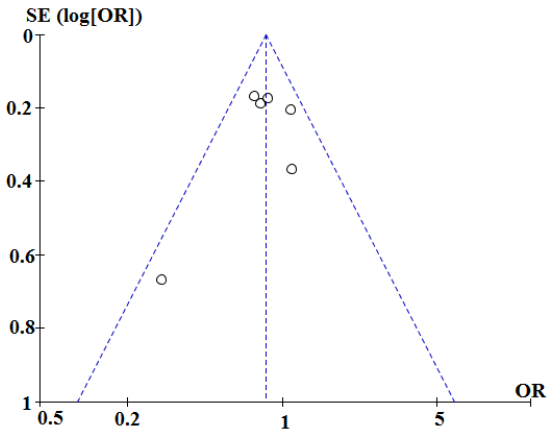
Sensitivity Analysis

The meta-analysis of BPD-free survival rate between iNO group and control group is heterogeneous. In order to eliminate the influence of heterogeneity, the sensitivity analysis was carried out by the method of exclusion one by one. We found that Jiang 2016 [20] is the source of its heterogeneity. After excluding the literature, the difference in BPD-free survival between iNO and placebo group is still not obvious.

Risk of Bias

Draw a funnel chart based on 6 studies with the incidence of BPD (see Fig 9). One of the studies is at the bottom of the funnel, but inside the funnel line. This shows that the risk of bias is small.

Figure 9
Funnel chart.



Discussion

Premature babies, especially younger than 28 weeks, often have difficulty breathing after birth due to immature lung tissue development, and may develop respiratory failure. This requires prolonged assisted ventilation, but long-term mechanical ventilation usually leads to a chronic lung injury [22]. The pathological features of this lung injury

include: impaired pulmonary blood vessel and alveolar development, excessive alveolar expansion, and increased responsiveness of pulmonary artery and bronchial smooth muscle. These pathological features are related to the high resistance of the pulmonary circulation and conduction airway and the blood flow of the pulmonary vascular bed through the respiratory tract, especially during expiration [23]. However, the etiology of these changes is unknown, and may be related to the chronic inflammatory response and the development of oxygen-enriched gas in the lungs of premature infants exposed to repeated stretches, and may also be related to the infection of the trachea and lung tissues. These reasons may be the reason why premature infants are prone to BPD。

At present, there is no unified opinion based on the prevention and treatment of BPD, and the mechanism of its occurrence and development is not completely clear clinically. Therefore, finding a better way to prevent and treat BPD is one of the clinical concerns. The prevention and treatment of NO in premature infants with BPD is currently a focus, but its systematic evaluation has not been reported. This study used meta-analysis methods and included a total of 8 articles, including 1808 preterm infants who used NO to prevent and treat BPD and 1906 preterm infants who received placebo. The results demonstrated that there was no obvious difference in BPD incidence, survival rate, BPD-free survival rate, and mortality rate between iNO group and placebo group. The common complications of toxemia, necrotizing enterocolitis, and visual impairment between the iNO group and the placebo group were not obvious. This suggests that the use of NO to prevent BPD in premature infants has no obvious effect. In the retrospective analysis of non-random use of vitamin A by Gadhia et al. [24], combined iNO + vitamin A treatment can reduce the incidence of BPD in premature infants with a BW of 750-999 g, and improve the incidence of premature infants with a BW of 500-749 g for 1 year Post-neurocognitive prognosis. This suggests that this study should be divided into different body weights for subgroup analysis. However, since most of the included studies did not use body weight for subgroup analysis, this meta-analysis obtains all the data of the included study cases, pending further subgroup analysis. In addition, Gadhia et al. [24] combined iNO and vitamins, suggesting that the combined effect may be better than iNO alone. This part needs to be systematically evaluated. The results of Kilbride et al. [25] demonstrated that there was no overall difference in lung function or exercise capacity of children treated with neonatal iNO compared with the placebo group. The Fractional exhaled NO level showed greater variability among patients, but it was often lower in the iNO treatment group. This suggests that premature infants with NO may have a milder inflammatory response. This speculation and its clinical significance need to be further studied. In addition, from the results of this study and previous studies, premature infants with BPD may require various treatments, including respiratory support, nutrition, bronchiectasis, diuresis, infection control, and early start of artificial or breastfeeding.

There is heterogeneity in the meta-analysis of BPD-free survival rate in this study. After excluding Jiang 2016 (a source of heterogeneity), the difference in BPD-free survival between the iNO group and the placebo group was still not obvious. In addition, drawing a funnel chart with 6 studies with data on the incidence of BPD shows that the risk of bias is small.

Limitations and deficiencies of this study: Only 8 literatures were included in this analysis, and the total sample size was small, which may cause the risk of bias to the results. Moreover, only 6 studies are randomized controlled studies, including 3 double-blind and 2 multi-center randomized controlled studies. Therefore, the conclusions of this study need to be supported and verified by the inclusion of more studies. Most of the literature included in this meta-analysis has not undergone further subgroup analysis and discussion, so it cannot be ruled out that certain influencing factors may affect the final conclusion. Most of the research results of the literature included in this article are published articles, and some unpublished articles cannot be excluded, so there may be a certain publication offset. Therefore, a larger sample and higher quality prospective research is still needed to improve the accuracy of the results.

CONCLUSION

There was no obvious difference in BPD incidence, survival rate, BPD-free survival rate, and mortality rate between iNO group and placebo group. The common complications of toxemia, necrotizing enterocolitis, and visual impairment between the iNO group and the placebo group were not obvious. This suggests that the use of NO to prevent BPD in premature infants has no obvious effect.

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