

Effect of dexamethasone on intelligence and hearing in preterm infants: a meta-analysis

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Abstract

OBJECTIVE: A meta-analysis of published randomized controlled trials investigating the long-term effect of dexamethasone on the nervous system of preterm infants.

DATA SOURCES: Online literature retrieval was conducted using The Cochrane Library (from January 1993 to June 2013), EMBASE (from January 1980 to June 2013), MEDLINE (from January 1963 to June 2013), OVID (from January 1993 to June 2013), Springer (from January 1994 to June 2013) and Chinese Academic Journal Full-text Database (from January 1994 to June 2013). Key words were preterm infants and dexamethasone in English and Chinese.

STUDY SELECTION: Selected studies were randomized controlled trials assessing the effect of intravenous dexamethasone in preterm infants. The quality of the included papers was evaluated and those without the development of the nervous system and animal experiments were excluded. Quality assessment was performed through bias risk evaluation in accordance with Cochrane Handbook 5.1.0 software in the Cochrane Collaboration. The homogeneous studies were analyzed and compared using Revman 5.2.6 software, and then effect model was selected and analyzed. Those papers failed to be included in the meta-analysis were subjected to descriptive analysis.

MAIN OUTCOME MEASURES: Nervous system injury in preterm infants.

RESULTS: Ten randomized controlled trials were screened, involving 1,038 subjects. Among them 512 cases received dexamethasone treatment while 526 cases served as placebo control group and blank control group. Meta-analysis results showed that the incidence of cerebral palsy, visual impairment and hearing loss in preterm infants after dexamethasone treatment within 7 days after birth was similar to that in the control group ($RR = 1.47$, 95%CI: 0.97–2.21; $RR = 1.46$, 95%CI: 0.97–2.20; $RR = 0.80$, 95%CI: 0.54–1.18; $P > 0.05$), but intelligence quotient was significantly decreased compared with the control group ($MD = -3.55$, 95%CI: -6.59 to -0.51; $P = 0.02$). Preterm infants treated with dexamethasone 7 days after birth demonstrated an incidence of cerebral palsy and visual impairment, and changes in intelligence quotient similar to those in the control group ($RR = 1.26$, 95%CI: 0.89–1.79; $RR = 1.37$, 95%CI: 0.73–2.59; $RR = 0.53$, 95%CI: 0.32–0.89; $RR = 1.66$, 95%CI: -4.7 to 8.01; $P > 0.05$). However, the incidence of hearing loss was significantly increased compared with that in the control group ($RR = 0.53$, 95%CI: 0.32–0.89; $P = 0.02$).

CONCLUSION: Dexamethasone may affect the intelligence of preterm infants in the early stages after birth, but may lead to hearing impairment at later stages after birth. More reliable conclusions should be made through large-size, multi-center, well-designed randomized controlled trials.

Key Words: nerve regeneration; systematic review; preterm infants; dexamethasone; glucocorticoids; nervous system development; cerebral palsy; hearing impairment; meta-analysis; randomized controlled trials; the Science and Technology Plan Program of Hunan Province; neural regeneration

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Introduction

Dexamethasone, a glucocorticoid, has been widely used in the prevention and treatment of neonatal respiratory distress syndrome, bronchopulmonary dysplasia and other chronic lung diseases in preterm infants to accelerate the withdrawal of breathing machines and shorten time on oxygen therapy^[1]. Acute adverse reactions of glucocorticoids include high blood pressure, high blood sugar and adrenal insufficiency^[2-3], but the majority of these acute adverse effects are transient. However, glucocorticoids, especially

dexamethasone, have attracted increasing attention because of the long-term effects on the development of the nervous system in preterm infants. Dexamethasone has been reported to increase the risk of cerebral palsy in preterm infants^[4] and affect motor function, cognitive function^[5-6] and academic performance^[7-8] in children at school age. Owing to these potential and serious adverse reactions, the American Academy of Pediatrics and the Canadian Pediatric Society do not recommend postnatal dexamethasone therapy in preterm infants, with exceptions for maintaining essen-

tial oxygenation using large-volume, high concentrations of oxygen^[9]. By contrast, some scholars also found that dexamethasone significantly attenuated lipopolysaccharide-induced inflammation in neonatal rat brain, promoted myelin basic protein expression, inhibited lateral ventricle dilatation, and significantly reduced behavioral abnormalities^[10]. In addition, dexamethasone plays a neuroprotective role through the upregulation of the expression of neurotrophic factors and anti-apoptosis genes, such as nerve growth factor, basic fibroblast growth factor, and vascular endothelial growth factor^[11-12].

We speculate that glucocorticoids have a long-term impact on the development of the nervous system and increase the incidence of cerebral palsy in preterm infants. The existing studies concerning the role of dexamethasone in preterm infants are insufficiently reliable owing to short follow-up periods and small sample sizes in clinical studies, or the absence of randomized controlled trials. The present study aims to quantitatively analyze the long-term effect of dexamethasone on nervous system development in preterm infants through a meta-analysis involving a large sample size in a broader attempt to provide evidence for clinical application of dexamethasone in preterm infants.

Data and Methods

Literature retrieval

A literature search was independently performed by two researchers according to the Handbook RCT search strategy in the Cochrane Collaboration. The searched database included the Cochrane Library (from January 1993 to June 2013), EMBASE (from January 1980 to June 2013), MEDLINE (from January 1963 to June 2013), OVID (from January 1993 to June 2013), and Springer (from January 1994 to June 2013) database. The search terms used were “infant, premature” [MeSH Terms] OR “infant” [All Fields] AND “premature” [All Fields] OR “premature infant” [All Fields] OR “preterm” [All Fields] AND “infant” [All Fields] OR “preterm infant” [All Fields] AND “dexamethasone” [MeSH Terms] OR “dexamethasone” [All Fields] AND Randomized Controlled Trial [ptyp]. The Chinese Academic Journal Full-text database between January 1994 and June 2013 was also retrieved using preterm infants, dexamethasone and randomized controlled trial as the search terms. The presence of bias in the included literature was evaluated by the third researcher. Meanwhile, we manually retrieved all unpublished literature or papers without available full-text, and collected related data from ongoing research or trials. Repetition of the same experiment was excluded.

Inclusion and exclusion criteria

Inclusion criteria

(1) Literature type: All published or to-be-published studies in international journals addressing randomized controlled trials about the effect of dexamethasone treatment in preterm infants were included, with language and nation not specified. (2) Subjects: Preterm infants (gestational age is less than 37 weeks) suffering from neonatal respiratory distress syndrome, in urgent need of mechanical ventilation for oxygen support, and at a high risk of chronic lung disease, were included. Those with congenital heart disease and sepsis after birth were excluded. (3) Interventions: Literature concerning a dexamethasone treatment and a blank control or placebo

group were included. (4) Outcome variable or curative effect assessment index: neurological damage in preterm infants at the end of follow-up after dexamethasone treatment, including cerebral palsy, visual impairment, hearing loss and changes in intelligence quotient values. The outcome variables are odds ratio (OR), relative risk (RR) or mean difference (MD) in treatment and control groups at the end of follow-up.

Exclusion criteria

(1) Repeatedly published literature, only pertaining to one paper with long-term follow-up period, large sample volume and full-scale data. (2) Literature was excluded if they met any of the following criteria: prenatal dexamethasone therapy (at late pregnancy or before childbirth); non-intravenous administration of dexamethasone (such as inhalation); no description of long-term prognosis of the nervous system; or non-randomized controlled trials and animal experiments.

Data extraction

Two independent reviewers inspected the titles and abstracts of the included studies, and screened the selected literature according to inclusion and exclusion criteria. Where disputes arose owing to no subject words found in titles and abstracts, we acquired the full report for more detailed scrutiny to assess their relevance to this review. Again, where disagreement occurred we attempted to resolve this through the third researcher or through discussion. The extracted data included author's name, publication year, sample size, interventions, the number of cases at the final follow-up, outcome variables (cerebral palsy, visual impairment, hearing loss and intelligence quotient values), and follow-up time.

Quality assessment

The quality of methodological reporting of selected studies was assessed using bias analysis of randomized controlled trials. Criteria for quality assessment were based on recommendations from the Cochrane Handbook 5.1.0 software^[22], including selection bias, performance bias, attrition bias, publication bias and other biases. The analysis results were defined as “Yes” (low bias), “No” (high bias) and “Unclear” (bias-related information is not clear or bias can not be determined).

Main outcome measurements

The prevalence of nervous system adverse consequences (cerebral palsy, visual impairment, hearing loss) and the development of intelligence (intelligence quotient values) after dexamethasone treatment were detected.

Statistical analysis

Meta-analysis was performed using RevMan 5.2.6 software (Cochrane Collaboration, 2012, <http://ims.cochrane.org/revman>). For binary outcomes, the relative risks of nervous system adverse reactions between treatment and control groups and 95% confidence intervals (CI) were calculated. Continuous variables were represented as MD and 95% CI, and subject to statistical analysis. Heterogeneity was assessed using χ^2 and I^2 tests. When the analysis results showed no heterogeneity ($P \geq 0.10$ or $I^2 < 50\%$), we adopted a fixed-effect model for description of potential publication bias. When the analysis results showed the presence of heterogeneity ($P < 0.10$ or $I^2 \geq 50\%$), we chose a random-effect mod-

Table 1 The characteristics of included studies

Study	Patient		Case (n)	Outcomes				Follow-up	Follow-up rate (%)
	(n)	Intervention		Cerebral palsy (n)	Vision damage (n)	Hearing damage (n)	IQ scores (n)		
Yeh et al. ^[8] , 2004	T 132	0.25 mg/kg, Q12 h×7 d; 0.12 mg/kg, Q12 h×7 d; 0.05 mg/kg, Q12×7 d; 0.02 mg/kg, Q12 h×7 d	72	20	12	18	78.20±15.00	15 years	55.7
	C 130	Placebo	74	14	7	12	84.40±12.60		
Ter Wolbeek et al. ^[13] , 2013	T 63	0.5 mg/kg per day tapering off to 0.1 mg/kg per day over 21 d	63	Unrecorded	Unrecorded	Unrecorded	86.79±16.16	14–17 years	100.0
	C 71	Blank control	71	Unrecorded	Unrecorded	Unrecorded	90.28±15.80		
Doyle et al. ^[14] , 2007	T 35	(0.89 mg/kg total) tapering	29	4	1	2	Unrecorded	2 years	80.0
	C 35	Placebo	27	6	0	4			
O'shea et al. ^[15] , 2007	T 57	42-d tapering course of dex	50	13	Unrecorded	Unrecorded	Unrecorded	4–11 years	80.5
	C 61	Blank control	45	4	Unrecorded	Unrecorded	Unrecorded		
Gross et al. ^[16] , 2005	T 12	42-d tapering course of dex	9	0	3	Unrecorded	85.00±10.00	15 years	58.3
	C 12	Blank control	5	1	2	Unrecorded	73.00±23.00		
Jones et al. ^[17] , 2005	T 124	0.6 mg/kg per day×7 d	71	17	3	4	Unrecorded	13–17 years	61.5
	C 120	Placebo	79	12	2	5	Unrecorded		
Romagnoli et al. ^[18] , 2002	T 15	0.5 mg/kg per day×6 d; 0.25 mg/kg per day×6 d; 0.125 mg/kg per day×2 d	15	2	3	1	84.20±12.40	3 years	100.0
	C 15	Blank control	15	3	1	3	83.00±15.60		
Romagnoli et al. ^[19] , 2002	T 25	0.5 mg/kg per day×3 d; 0.25 mg/kg per day×3 d; 0.125 mg/kg per day×1 d	23	2	2	1	85.80±13.90	3 years	90.0
	C 25	Blank control	22	3	1	4	85.60±16.30		
Shinwell et al. ^[20] , 2000	T 132	0.25 mg/kg, Q12 h×3 d	80	39	17	1	Unrecorded	53±18 months	64.1
	C 116	Blank control	79	12	12	0	Unrecorded		
Jones et al. ^[21] , 1995	T 145	0.6 mg/kg per day×7 d	100	20	8	11	Unrecorded	3 years	72.8
	C 142	Placebo	109	18	8	22	Unrecorded		

T: The number of cases initially recruited in treatment group; C: the number of cases initially recruited in placebo control group; case (n): the number of cases at the end of follow-ups; IQ scores: Wechsler Intelligence test scores, normal 90–109, moderate to fair 110–119, excellent 120–139, extremely excellent over 140, fair to poor 80–89, critical 70–79, mental defect less than 69. d: Days; h: hours.

Table 2 Results of bias risk of included literature

Risk of bias	Interpretation	With in a study	Across studies
Low	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key domains	Most information is from studies at low risk of bias
Unclear	Plausible bias that raise some doubt about the results	Unclear risk of bias for one or more key domains	Most information is from studies at low or unclear risk of bias
High	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains	The proportion of information from studies at high risk of bias to affect the interpretation of results

el. Meanwhile the sensitivity of analysis results was detected. Meta regression analysis is selected if the heterogeneity could accurately measure and explain all variations, while we applied meta regression analysis + mixed-effect model when the heterogeneity could not explain variations. Only 10 studies were included in this study, so we did not choose meta regression analysis + a mixed-effect model.

Results

Data retrieval

After preliminary retrieval, 1,669 studies addressing dexamethasone treatment in preterm infants were initially identified through electronic and manual searches. After reading their titles, abstracts and full-text, ten randomized controlled trials were considered potentially relevant for further inspection

[8, 13–21]. They were all published in English. Data retrieval procedures are shown in Figure 1.

Characteristics of included studies and methodological quality estimation

Table 1 summarizes the characteristics from each study included. Among 10 studies, random allocation method and random number were introduced in detail in four studies^[14, 17, 20–21]; other documents only mentioned random allocation, leaving the allocation method unclear. Another five studies^[8, 15, 17, 20–21] recorded allocation concealment method. All studies, bar one^[8], gave a description of blinding method. The loss to follow-up, the number of lost cases, and the reasons for dropout were recorded. The loss to follow-up reached over 30% in some studies^[8, 16–17, 20]. According to the Cochrane Handbook 5.1.0 for Interventions in the Cochrane Collaboration^[22] (Table 2),

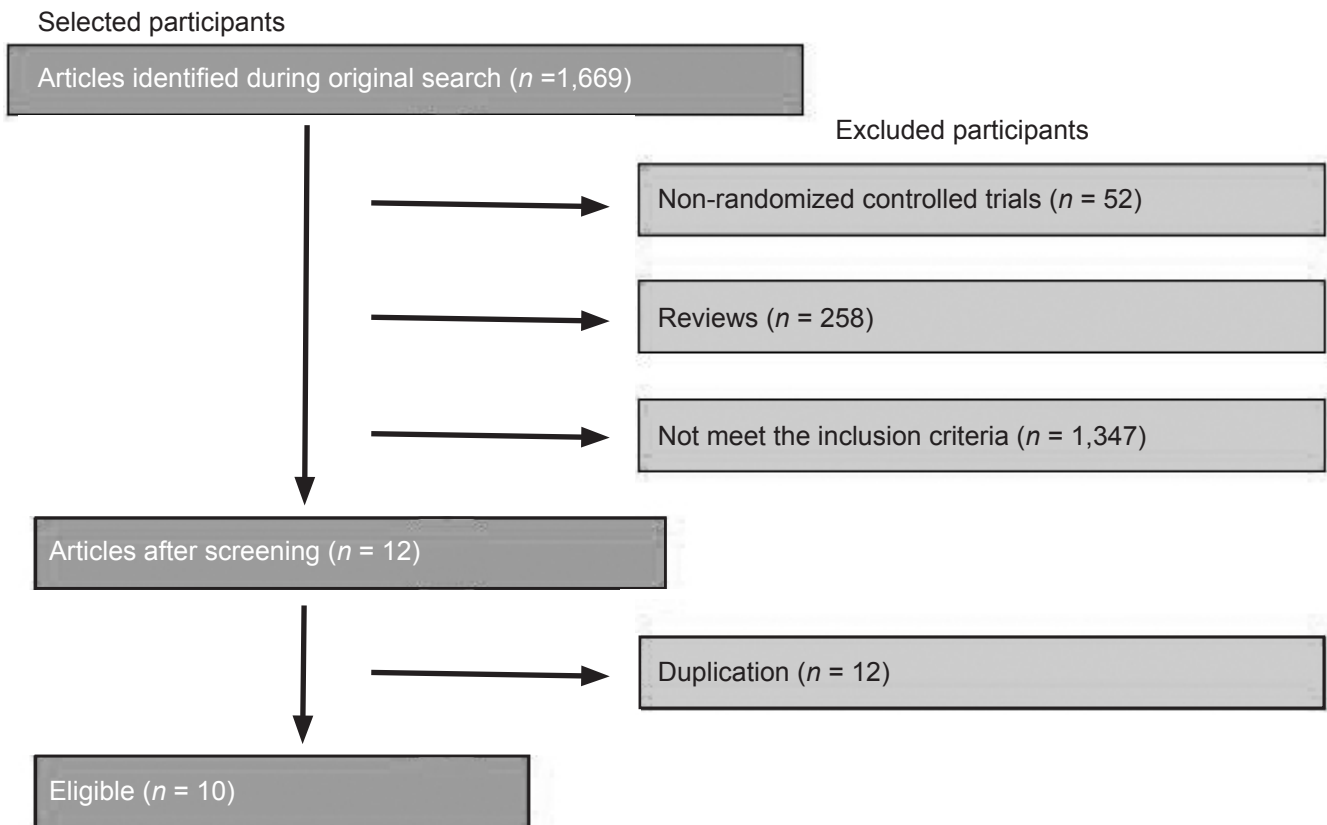


Figure 1 Flow-chart of literature screening.

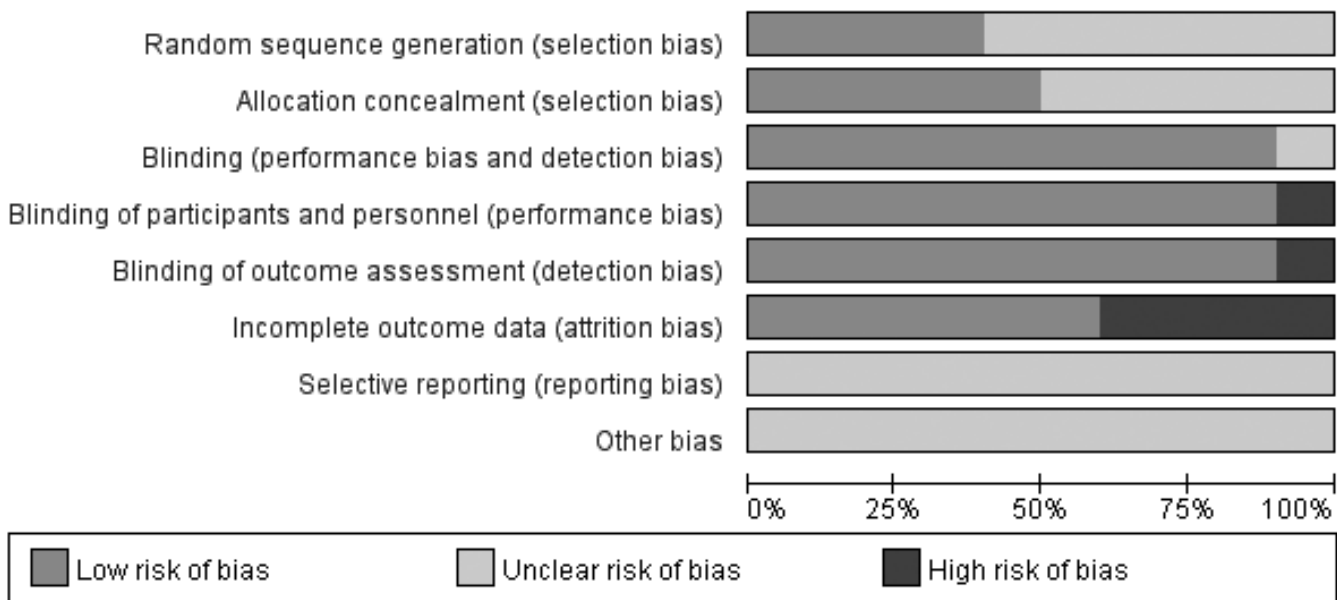


Figure 2 Distribution of bias in the included studies.

According to the Evaluation Criteria of Bias Risk of Randomized Controlled Trials in Cochrane Handbook, green refers to “yes” (low bias), red refers to “no” (high bias), and yellow refers to “unclear” (bias-related information is not clear or bias cannot be determined).

the quality of random allocation, quality of random concealment, blinding and data integrity were considered the four critical domains. The results showed high biases in five studies^[8, 16-17, 19-20], low bias in one study^[21], and moderate bias in four studies^[13-15, 18] (Figures 2, 3).

Ten randomized controlled trials were included in this review, involving 1,038 cases. Among them, 512 cases received dexamethasone treatment (cerebral palsy in 117 cases, visual impairment in 49 cases and hearing loss in 38 cases), while 526 cases served as the control group (cerebral palsy in 73

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Doyle,L W 2007	+	?	+	+	+	+	?	?
Jones,R 1995	+	+	+	+	+	+	?	?
Jones,R A 2005	+	+	+	+	+	+	?	?
Romagnoli,C 2002	?	?	+	+	+	+	?	?
Romagnoli,C 2002	?	?	?	+	+	+	?	?
Shinwell,E S 2000	+	+	+	+	+	+	?	?
Steven J.Gross 2005	?	?	+	+	+	+	?	?
T.Michael O'shea 2007	?	+	+	+	+	+	?	?
Ter Wolbeek,M 2013	?	?	+	+	+	+	?	?
Yeh,T F 2004	?	+	+	+	+	+	?	?

Figure 3 Risk of bias in the included literature. According to the Evaluation Criteria of Bias Risk of Randomized Controlled Trials in Cochrane Handbook, green refers to “yes” (low bias)^[21], red refers to “no” (high bias)^[8, 16-17, 19-20], and yellow refers to “unclear” (bias-related information is not clear or bias cannot be determined)^[13-15, 18].

cases, visual impairment in 33 cases and hearing loss in 50 cases). In addition, five studies^[8, 13, 16, 18-19] described changes in intelligence quotient values.

Meta-analysis results

Comparison of the incidence of cerebral palsy in preterm infants after dexamethasone treatment

Nine studies^[8, 14-21] reported the effects of dexamethasone on the incidence of cerebral palsy. The heterogeneity test results showed that $\chi^2 = 14.68$, $P = 0.07$, $I^2 = 45\%$, indicating significant heterogeneity among studies. The random effect model was used for analysis. Meta-analysis results showed the combined $RR = 1.47$ and $95\%CI: 0.97-2.21$, indicating that there was no significant difference in the incidence of cerebral palsy in preterm infants between the dexamethasone treatment and the control group ($Z = 1.68$, $P = 0.07$; Figure 4A).

Comparison of the incidence of visual impairment in preterm infants after dexamethasone treatment

Eight studies^[8, 14, 16-21] reported the effects of dexamethasone

on the incidence of visual impairment. The heterogeneity test results showed that $\chi^2 = 1.83$, $P = 0.07$, $I^2 = 0\%$, indicating no significant heterogeneity among studies. The fixed effect model was used for analysis. Meta-analysis results showed the combined $RR = 1.46$ and $95\%CI: 0.97-2.20$, indicating that there was no significant difference in the incidence of visual impairment in preterm infants between the dexamethasone treatment group and the control group ($Z = 1.83$, $P = 0.07$; Figure 4B).

Comparison of the incidence of hearing loss in preterm infants after dexamethasone treatment

Seven studies^[8, 14, 17-21] reported the effects of dexamethasone on the incidence of hearing loss. The heterogeneity test results showed that $\chi^2 = 8.01$, $P = 0.24$, $I^2 = 25\%$, indicating no significant heterogeneity among studies. The fixed effect model was used for analysis. Meta-analysis results showed the combined $RR = 0.80$ and $95\%CI: 0.54-1.18$, indicating that there was no significant difference in the incidence of hearing loss in preterm infants between the dexamethasone treatment group and the control group ($Z = 1.12$, $P = 0.26$; Figure 4C).

Changes in intelligence quotient values in preterm infants after dexamethasone treatment

Five studies^[8, 13, 16, 18-19] reported the effects of dexamethasone on intelligence quotient. The heterogeneity test results showed that $\chi^2 = 4.94$, $P = 0.29$, $I^2 = 19\%$, indicating no significant heterogeneity among studies. The fixed effect model was used for analysis. Meta-analysis results showed the combined $MD = -3.55$, $95\%CI: -6.59$ to -0.51 , indicating that the intelligence quotient of preterm infants after dexamethasone treatment was significantly decreased compared with that in the control group ($Z = 2.29$, $P = 0.02$; Figure 4D).

Sensitivity analysis results

The methodology of the included studies was evaluated according to the Cochrane Handbook 5.1.0 software, and bias evaluation results indicate that the risk of bias was the highest in reference 19, which was then excluded. When comparing the treatment group and control group before and after treatment, the incidence of cerebral palsy RR ($95\%CI$) was 1.47 (0.97-2.21) and 1.53 (1.00-2.33) respectively, whilst the incidence of visual impairment RR ($95\%CI$) was 1.46 (0.97-2.20) and 1.45 (0.96-2.19). Furthermore, the incidence of hearing loss RR ($95\%CI$) was respectively 0.80 (0.54-1.18) and 0.85 (0.57-1.27) and the intelligence quotient value MD ($95\%CI$) was -3.55 (-6.59 to -0.51) and -4.05 (-7.29 to -0.81), suggesting a significant difference in intelligence quotient value between the two groups ($P = 0.01$; Figure 5).

Meta-analysis on the effect of dexamethasone on the nervous system of preterm infants at a later stage after birth

Ten studies were included in the meta-analysis. Among them, three studies^[8, 13, 20] introduced early use of dexamethasone in preterm infants (within 7 days after birth) and seven studies^[8, 14, 16-19, 21] introduced later use of dexamethasone in preterm infants (after 7 days after birth). Owing to a small number and small sample size of randomized controlled trials addressing early postnatal dexamethasone therapy, we failed to perform subgroup analysis. Therefore, we only analyzed the literature concerning the use of later postnatal dexamethasone (after 7 days). Meta-analysis results showed that when

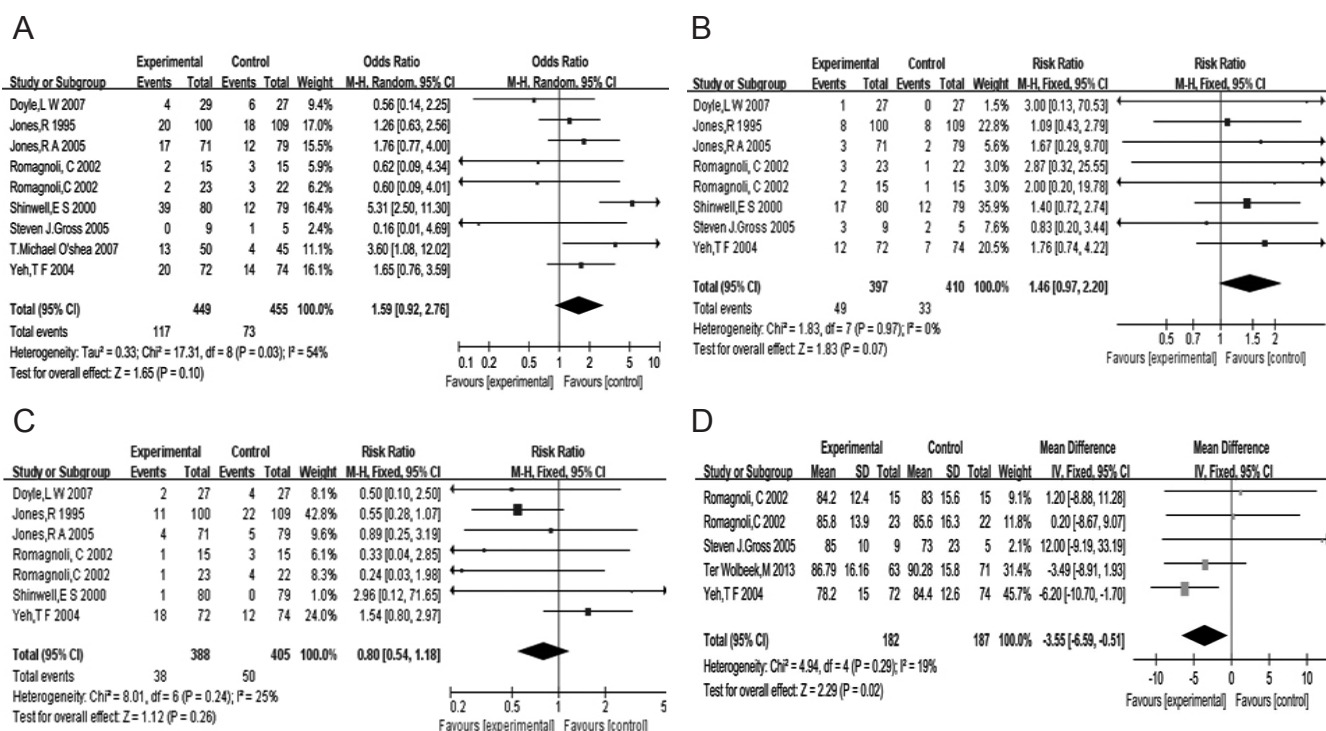


Figure 4 Meta-analysis on the long-term effect of dexamethasone on nervous system development in preterm infants.

(A–C) Meta-analysis results on the incidence of cerebral palsy (nine studies^[8,14,21]), visual impairment (eight studies^[8,14,16,21]), and hearing loss (seven studies^[8,14,17,21]) in preterm infants after dexamethasone treatment. There was no significant difference in the incidence of cerebral palsy between treatment and control groups. (D) Meta-analysis results of intelligence quotient value in preterm infants after dexamethasone treatment (five studies^[8,13,16,18-19]). The intelligence quotient value of preterm infants in the treatment group was significantly lower compared with that in the control group.

comparing treatment and control groups, the incidence of cerebral palsy *RR* (95%*CI*) was 1.26 (0.89–1.79), the incidence of visual impairment *RR* (95%*CI*) was 1.37 (0.73–2.59), the incidence of hearing loss *RR* (95%*CI*) was 0.53 (0.32–0.89), and intelligence quotient *MD* (95%*CI*) was 1.66 (–4.7 to 8.01). This is evidence that later postnatal dexamethasone therapy significantly affected the hearing of preterm infants ($P = 0.02$) while early dexamethasone has no impact on the incidence of cerebral palsy and visual impairment, as well as intelligence quotient values in the treatment group compared with that in the control group ($P > 0.05$; Figure 6).

Analysis of publication bias

Among the included studies ($n = 10$), eight studies^[8,14,16-21] reported visual impairment, indicating the homogeneity of related studies. The publication bias of these eight papers was analyzed (Figure 7). The obtained funnel plot was asymmetrical on both sides, suggesting the presence of publication bias among the selected studies.

Discussion

Children receiving perinatal glucocorticoids have a high risk of periventricular leukomalacia, cerebral palsy and abnormal behavior, and pubertal motor and cognitive levels may also be reduced^[15-6,13,23]. Brain MRI examination detected decreased brain surface area and brain mantle index, with the

affected region being mainly gray matter, while white matter, basal ganglia and cerebellum were also involved^[24]. In children with Cushing's syndrome, brain size was significantly reduced, brain ventricles dilated, and reduction of hippocampal size was more apparent. After 1 year of treatment, brain volume recovered, but intelligence quotient was still significantly lower than normal levels^[25-26]. In animal experiments, dexamethasone administration in pregnant rats induced the apoptosis of amygdala neurons in pups^[27]. After newborn rats were treated with dexamethasone, the number of astrocytes in the hippocampus and corpus callosum was significantly reduced. Long-term potentiation of nerve cells in adolescence was also damaged, and long-term depression was enhanced, thus affecting long-term memory and leading to susceptibility to anxiety and fear behavior in response to stress^[28-29]. However, existing clinical observations and follow-up fail to clearly demonstrate the long-term effect of dexamethasone on nervous system development of preterm infants.

Meta-analysis is an evaluation means that focuses on contrasting and combining results from different studies and has the potential to provide the highest level of evidence. This analysis is considered an objective, quantitative method for combining evidence from separate but similar studies in an objective and systematic manner, so statistical test efficacy is improved^[30]. In the present study, we collected the related literature surrounding the application of dexamethasone in preterm infants through meta-analysis, and further detected neurolog-

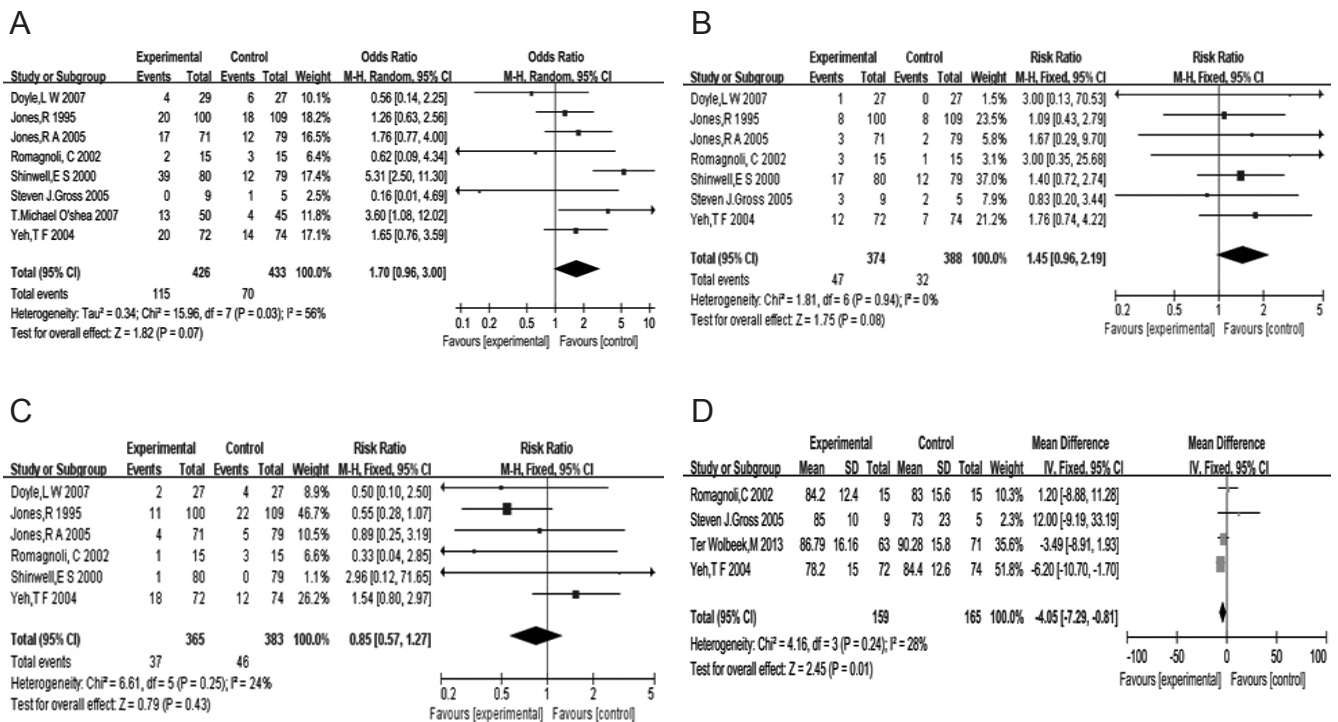


Figure 5 Sensitivity analysis of meta-analysis results of nervous system development in preterm infants after dexamethasone treatment. (A–C) Sensitivity analysis of meta-analysis results on the incidence of cerebral palsy (eight studies^[8, 14–18, 20–21]), visual impairment (seven studies^[8, 14, 16–18, 20–21]), hearing loss (six studies^[8, 14, 17–18, 20–21]) in preterm infants after dexamethasone treatment. There was no significant difference in the incidence of hearing loss between treatment group and control group. (D) Sensitivity analysis of meta-analysis results on intelligence quotient value of preterm infants after dexamethasone treatment (four studies^[8, 15, 16, 18]). There were significant differences in intelligence quotient values of preterm infants between the treatment and control groups (P = 0.01).

ical impairment index at the end of follow-up: cerebral palsy, visual impairment, hearing loss and intelligence quotient values for statistical analysis. The included 10 studies have listed dexamethasone dosage and administration approach. The results of the selected studies showed that, postnatal dexamethasone affects the development of the nervous system in preterm infants. Early dexamethasone application has long-term impact on intelligence quotient value, while later application produces apparent impact on hearing. This finding is different from other systematic reviews and meta-analysis, which point out that dexamethasone increases the incidence of cerebral palsy in preterm children^[31–32]. This discrepancy can be explained by the difference of inclusion criteria. In addition, there are many types of glucocorticoids and derivatives, which exhibit varied impacts on the nervous system. For example, long term hydrocortisone treatment cannot influence the development of the nervous system^[31]. We suggest distinguishing the impact of different glucocorticoid derivatives on the nervous system, otherwise bias will inevitably occur.

The included 10 studies are all randomized controlled trials, and also adopted blinding methods to evaluate the development of the nervous system at follow-up. Sensitivity analysis of these papers showed no difference, so our results are reliable. Our findings showed that dexamethasone had long-term impact on nervous system development in preterm children, although the available evidence cannot prove that dexamethasone may increase the incidence of

cerebral palsy and visual impairment in preterm children. Dexamethasone was shown to affect hearing and intelligence quotient values. After the dexamethasone was withdrawn, assisted ventilation could be reduced by pulmonary surfactant management, nasal ventilation and permissive hypercapnia, but dexamethasone can shorten the time on ventilator in preterm children, correct the incidence of oxygen dependence in preterm children after gestational age of 36 weeks, and lower incidental medical expenses^[4]. In areas with decreased medical treatment options, physicians may selectively prescribe dexamethasone. Increasing evidence confirms that dexamethasone can improve lung function in preterm children within a short period after birth, but the application prospects may be reduced owing to the absence of long-term stability of dexamethasone benefits. Further randomized controlled studies are required to explore certain types of glucocorticoid hormones or a small dosage of dexamethasone in preterm children after birth, which can not only improve lung function but also maintain long-term effects on the nervous system.

The 10 included studies^[8, 13–21] showed that, systematic application of dexamethasone in preterm children exhibits no significant long-term benefits on the nervous system. Some limitations of this study should be noted: (1) Literature of large sample size and positive results are preferentially published, thus inevitably causing publication bias. The included studies also have publication bias, which reduce

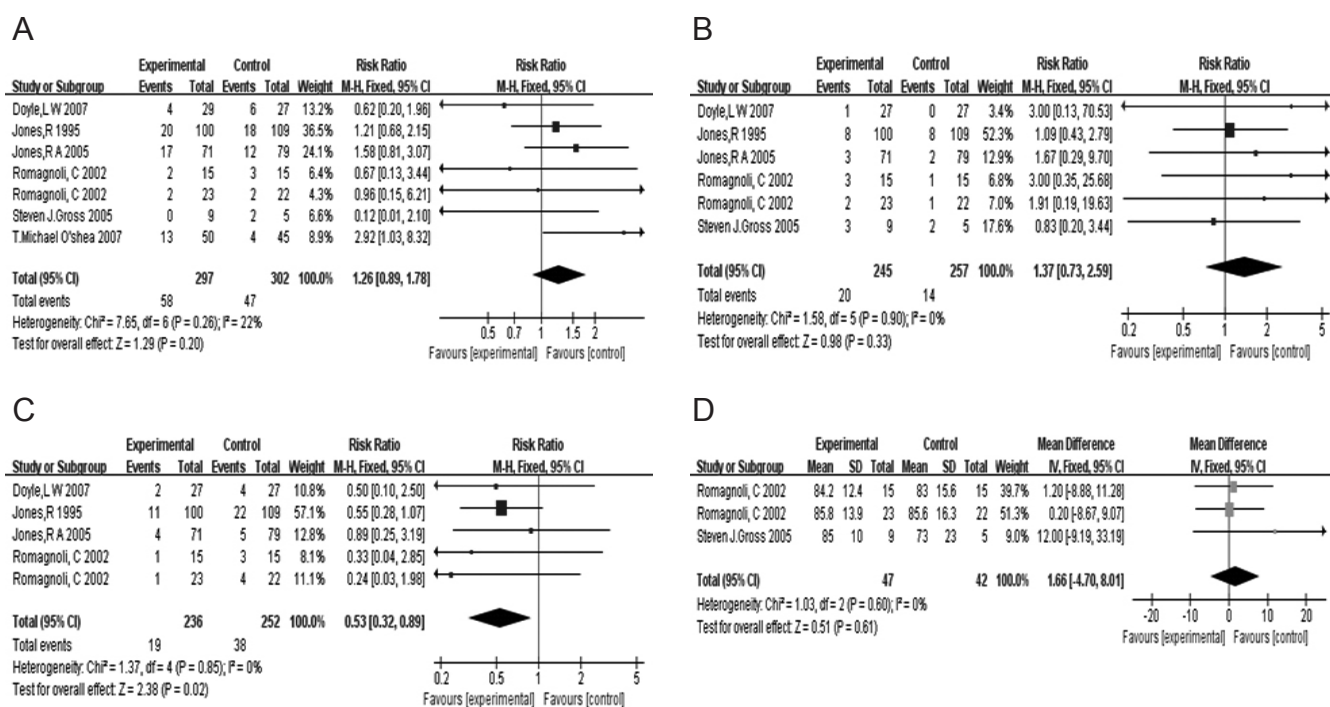


Figure 6 Meta-analysis on the effect of later postnatal dexamethasone in the nervous system of preterm infants. (A, B, D) Meta-analysis results on the incidence of cerebral palsy (seven studies^[14-19, 21]), visual impairment (six studies^[14, 16-19, 21]), and intelligence quotient (three studies^[16, 18-19]) in preterm infants after later postnatal dexamethasone treatment. There was no significant difference between treatment and control groups. (C) Meta-analysis results on the incidence of hearing loss in preterm infants after later postnatal dexamethasone treatment (five studies^[14, 17-19, 21]). The incidence of hearing loss in the treatment group was increased compared with that in the control group ($P = 0.02$).

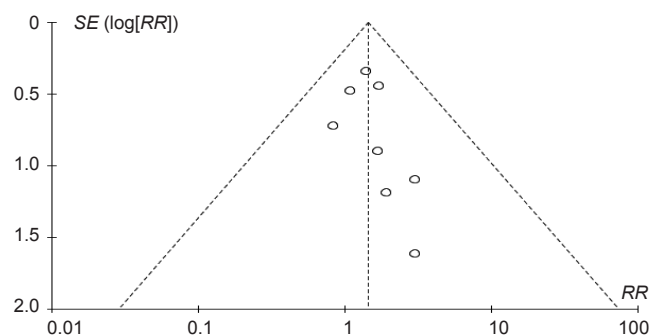


Figure 7 Funnel plot of the visual impairment incidence among eight studies^[8, 14, 16-21]. The funnel plot was asymmetrical on both sides, suggesting the presence of publication bias among the selected studies. SE: Standard error; RR: relative risk.

the reliability of the results. (2) The follow-up period greatly varied, from 18 months to 17 years, four studies recorded a high loss rate, which lead to bias in the results. (3) The sample size in some randomized controlled trials was relatively small. No grants or sponsors from commercial companies are mentioned, so bias could be avoided to some extent. Large-scale, well-designed randomized controlled trials, as well as follow-up, to evaluate the pros and cons of the use of dexamethasone are further required.

Author contributions: Li J and Bo T were responsible for the study concept and design. Shen L and Luo SL assisted the data retrieval. Zhang RL supervised the included literatures, performed

statistical analysis, and wrote the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest: None declared.

Peer review: This study systemically evaluated the effect of postnatal dexamethasone treatment in preterm infants. The results showed that early dexamethasone treatment exhibited long-term impact on intelligence quotient values, later dexamethasone treatment contributes to the hearing impairment in preterm infants. Our findings will provide evidence for clinical physicians.

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