Study Protocol

Official Title of the Study: The Outcomes of Different Dexamethasone Regimens for the Prevention of Bronchopulmonary Dysplasia in Preterm Infants: A Multicenter Randomized Controlled Trial

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I. Research Background

Bronchopulmonary dysplasia (BPD) is a serious chronic pulmonary disease primarily affecting preterm infants, especially those with very low birth weight (VLBW) and extremely low birth weight (ELBW). The pathological features of BPD mainly include simplified alveolar structures and abnormal pulmonary vascular development, which can lead to long-term respiratory disorders, neurodevelopmental impairments, and even death [1,2]. The pathogenesis of BPD is complex and involves multiple factors such as prematurity, mechanical ventilation, oxygen toxicity, infection, and inflammatory responses [3].

As early as the late 1970s to early 1980s, researchers began exploring the use of corticosteroids, particularly dexamethasone (DEX), for the prevention and treatment of neonatal respiratory distress syndrome (RDS) and BPD [4]. Initial studies employed relatively high doses of DEX (0.5–1.0 mg/kg/day) over prolonged treatment courses, showing significant improvements in lung function, reduced duration of mechanical ventilation, and lower incidence of BPD. As a result, DEX became widely used in neonatal intensive care units (NICUs) during the 1990s, entering what was referred to as a “honeymoon period.” However, with the accumulation of long-term follow-up studies, concerns about the safety of DEX began to emerge. In 1998, Yeh et al. reported that early use of DEX in preterm infants significantly increased the incidence of severe neurodevelopmental impairments at 18 months (41% vs. 31%) [5], and was associated with a higher rate of short-term adverse effects, such as gastrointestinal perforation (13% in the DEX group vs. 4% in controls, $P = 0.02$) [6]. Other studies also linked DEX to cerebral palsy, cognitive dysfunction, and reduced brain volume [7,8]. These findings prompted the American Academy of Pediatrics (AAP) to issue a warning statement in 2002, explicitly opposing the routine use of DEX for the prevention or treatment of BPD. Consequently, clinical practice shifted from aggressive use toward more cautious evaluation.

In this context, researchers began exploring safer alternatives or optimized strategies for DEX use. Hydrocortisone (HC), which acts on mineralocorticoid receptors, was considered potentially less neurotoxic. Some studies suggest HC has a milder impact on neurodevelopmental outcomes, but its efficacy in preventing BPD remains controversial [9].

For instance, early administration of HC (within 7–14 days after birth) showed no significant differences compared to placebo in terms of BPD incidence, oxygen use duration, or brain volume [9]. Although prophylactic use of HC (cumulative dose 18–72.5 mg/kg) did not increase the risk of cerebral palsy or neurodevelopmental delay, its overall effectiveness still requires further validation.

Meanwhile, low-dose DEX strategies (e.g., <0.5 mg/kg/day) have been proposed to achieve a balance between efficacy and safety. Some studies have demonstrated that even with low doses of DEX, when initiated between postnatal day 7 and 14, it can effectively reduce the incidence of BPD without increasing adverse neurological outcomes [10,11]. A meta-analysis including 669 participants showed that starting DEX between days 7 and 14 after birth reduced the incidence of BPD or death at both day 28 and 36 weeks postmenstrual age, facilitated earlier extubation, and did not increase the occurrence of severe complications such as hypertension, severe retinopathy of prematurity (ROP), or infections [8]. A Cochrane review (2003) also noted that DEX initiated after three weeks of age could reduce oxygen dependence and extubation failure, without significantly affecting mortality or increasing the risk of infection, necrotizing enterocolitis (NEC), or gastrointestinal bleeding [12].

In recent years, researchers have re-evaluated the role of DEX in BPD prevention and treatment. A large retrospective study (n=1136) found that DEX use between days 7 and 14 after birth was associated with a 6.2% reduction in cerebral palsy and a 6.6% reduction in cognitive impairment. Moreover, DEX administration after 3 weeks of age did not increase the risk of neurodevelopmental delay [10]. In a 2019 study, infants in the high-dose, long-course DEX group demonstrated significantly better functional survival at age 7 compared to those in the moderate-dose, short-course group [13]. A 2021 network meta-analysis further suggested that a moderate cumulative dose of DEX (2–4 mg/kg) may represent the optimal regimen for BPD prevention, achieving a better balance between efficacy and safety, although high-dose strategies are less acceptable in clinical practice [13].

The timing of the first dose is also a key factor in corticosteroid intervention strategies for BPD. In a 1997 RCT conducted in Taiwan involving 262 preterm infants, initiating DEX within 24 hours of birth significantly reduced the incidence of BPD by 50%, but also increased the

rate of severe neurodevelopmental impairment at 18 months [4]. At Brigham and Women's Hospital, initiating DEX within 24 hours after birth was associated with an increased incidence of intestinal perforation by day 14 [4,6]. These findings indicate that although very early administration of DEX may have strong lung-protective effects, the associated adverse events are significant. In contrast, initiating DEX after 7 days of life is considered to have a more favorable risk-benefit profile, particularly for high-risk infants. Recent reviews have pointed out that early systemic use of DEX or HC is not recommended due to adverse effects, while late systemic use of DEX (≥7 days postnatal age) effectively reduces BPD risk without increasing neurodevelopmental impairment in high-risk infants [14,15].

In summary, there remain numerous unresolved issues regarding the optimal use of DEX in BPD prevention. Early administration shows strong efficacy but carries high neurotoxicity risks; late administration is safer but may miss the optimal intervention window. High-dose regimens offer pronounced benefits but are associated with more side effects, while low-dose regimens are relatively safer but may be less effective. Short-course treatments yield rapid effects, but the sustainability of benefits is unclear, whereas long-course treatments may offer prolonged benefits at the cost of cumulative side effects. Moreover, preterm infants of different gestational ages, birth weights, and disease severities may respond differently to corticosteroid therapy. Despite decades of clinical experience with DEX in BPD prevention and treatment, the AAP still emphasizes the lack of sufficient evidence in its current guidelines and refrains from providing a definitive recommendation [16]. Therefore, there is an urgent need for a well-designed, large-scale, multicenter randomized controlled trial to systematically evaluate the short- and long-term efficacy and safety of different DEX regimens—including dosage, timing, and duration—in preterm infants with high BPD risk.

This research holds significant scientific and clinical value. Currently, there is a severe lack of high-quality evidence regarding the optimal DEX regimen for BPD prevention. This study will help fill that gap and provide clearer guidance for clinical practice. By comparing different DEX strategies, the study aims to identify the optimal balance between efficacy and safety, thereby optimizing preventive strategies for BPD. By assessing the impact of various DEX regimens on long-term neurodevelopmental outcomes, the research will contribute to

reducing BPD-associated neurodevelopmental impairments and improving the long-term quality of life for preterm infants. Ultimately, this study will offer evidence-based recommendations to guide clinicians in the rational use of DEX for BPD prevention, minimizing unnecessary risks, and maximizing potential benefits.

In conclusion, this study will comprehensively explore the complex issues surrounding DEX use in the prevention of BPD in preterm infants. It aims to provide critical evidence to resolve longstanding controversies, with the ultimate goal of improving health outcomes for preterm infants and reducing the long-term burden of BPD on patients and their families.

II. Study Objectives

Primary Objective:

To compare the incidence of BPD and/or BPD-related mortality at a postmenstrual age of 36 weeks in preterm infants meeting the inclusion criteria, treated with two different dexamethasone regimens (the DART regimen versus a medium-dose tapering regimen).

Secondary Objectives:

- To compare the duration of weaning ventilation, total days of ventilator use, and length of hospital stay between the two groups.
- To assess the changes in the Oxygenation Index (OI) on days 0, 3, 7, 10, 14, and 28 of treatment in both groups.
- To compare the incidence of complications at discharge, such as Retinopathy of Prematurity (ROP), Intraventricular Hemorrhage (IVH), Necrotizing Enterocolitis (NEC), infection, and Pulmonary Hypertension, between the two groups.
- To compare the incidence of adverse effects associated with steroid therapy between the two groups.
- To evaluate neurodevelopmental outcomes at a corrected age of 18-24 months using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) Mental Development Index (MDI)/Psychomotor Development Index (PDI) or the Griffith Mental Development Scales.

III. Study Methods

This study is a multicenter, prospective, randomized, parallel-controlled clinical trial.

Study Sites: Multiple hospitals across China with high-level Neonatal Intensive Care Units (NICUs) will participate.

Randomization:

A block randomization method will be used to assign participants to one of two study groups in a 1:1 ratio. Subjects will receive a unique randomization number in the order of enrollment and will be assigned to one of the following treatment groups:

- DART regimen
- Moderate-dose tapering regimen

Blinding:

Blinding will be applied for the assessment of secondary outcomes (e.g., neurodevelopmental outcomes). Evaluators will be from an independent team and will not be involved in the routine clinical care of the infants.

1. DART Regimen Group

Cumulative dose: 0.89 mg/kg over 10 days Intravenous dexamethasone [17], administered as follows:

- 0.075 mg/kg/dose, every 12 hours for 3 days
- 0.05 mg/kg/dose, every 12 hours for 3 days
- 0.025 mg/kg/dose, every 12 hours for 2 days
- 0.01 mg/kg/dose, every 12 hours for 2 days, then discontinue

If extubation is not successful more than or equal to two weeks after completing the treatment ($FiO_2 > 40\%$ and $MAP > 8$ cmH_2O), the DART regimen may be repeated. The number of repeated courses, reasons, and specific timing must be documented.

(Note: According to reference [13], if the infant meets respiratory criteria again at least 72 hours after completing the initial 9-day course, a second 9-day course may be administered. If the infant meets the criteria again during the 42-day observation period, a third course may be considered.)

Rationale for design:

Due to the rapid physiological changes in preterm infants, early responses to interventions are often evident within short timeframes. The shorter assessment intervals aim to capture early treatment effects more sensitively and dynamically.

Previous exploratory observations indicated that two-week intervals are feasible and safe for evaluating parameters such as weight gain and lab changes, with no significant adverse effects observed.

2. Moderate-Dose Tapering Regimen Group

Cumulative dose: 2.35 mg/kg over 7 days Intravenous dexamethasone [19], administered as follows:

- 0.5 mg/kg/d for 3 days
- 0.25 mg/kg/d for 3 days
- 0.1 mg/kg/d for 1 day

If extubation is not successful more than or equal to two weeks after completing the treatment ($FiO_2 > 40\%$ and MAP > 8 cmH_2O), the same regimen may be repeated. The number of repeated courses, reasons, and specific timing must be documented.

Definition of BPD Severity (based on 2019 consensus criteria):

Clinically, BPD is defined as oxygen and/or respiratory support dependency for at least 28 days or continuing until 36 weeks corrected gestational age in preterm infants born at <32 weeks gestation.

2019 severity classification (Jensen definition)[20]

- Severity is determined by the mode of respiratory support required at **36 weeks PMA**, regardless of FiO_2:Mild BPD (grade I): Requires low flow nasal cannula (<2 L/min)
- Moderate BPD (grade II): Requires CPAP, NIPPV, or nasal cannula flow of ≥2 L/min (including HFNC)
- Severe BPD (grade III): Requires invasive mechanical ventilation

Standardized Supportive Care (applied to all groups):

Respiratory Support:

- Target SpO_2: 90–95%, $PaCO_2$: 45–65 mmHg

Monitoring for Hemodynamically Significant PDA (HsPDA):

- Evaluations on days 3, 7, 14, and 28 using the Iowa PDA score

Table 1 – Iowa PDA score.[1]

Measurement	0	1	2
Pulmonary vein D wave (cm/s)	<30	30-50	≥50
Mitral valve E wave (cm/s)	<45	45-80	≥80
Isovolumetric relaxation time (ms)	>50	30-50	≤30
Left atrium to aortic root ratio	<1.3	1.3-2.2	≥2.2
Left to Right Ventricular output ratio	≤1.5	1.5-2.0	≥2.0
Aortic/Peripheral Doppler flow reversal	Forward/Absent		Reversed
Ductus diameter indexed to weight (mm/kg)	<1.5	1.5-3.0	≥3.0

Nutritional Support:

- Early enteral nutrition + parenteral nutrition

- Caloric goal: 110–130 kcal/kg/day

Infection Monitoring:

- Ureaplasma (airway): DNA tested within 72 hours and again by day 21, with treatment documented

- CMV (urine): CMV DNA tested twice within 21 days, with treatment documented

Fluid Management and Other Supportive Care:

- Includes transfusions, vasoactive medications, etc.

Standardized Ventilator Management Protocol:

Ventilator Mode Selection:

- SIMV, AC, PSV, VG, etc.

Ventilator Parameter Adjustments:

- FiO_2, MAP, PEEP, respiratory rate, tidal volume, etc.

Extubation Criteria:

- Mandatory extubation attempt within 72 hours of starting dexamethasone and again within 24 hours of meeting all of the following conditions:
  - $FiO_2 < 0.40$ to maintain $SpO_2 \geq 88\%$
  - Mean airway pressure (MAP) < 8 cm H_2O
  - Hemodynamically stable as assessed by the clinical care team
- Daily review of ventilator settings by study personnel to ensure protocol adherence

Pre-Extubation Considerations:

- Caffeine use is allowed
- No frequent/severe apnea episodes
- Stable spontaneous breathing

Extubation Method:

- Gradual weaning from ventilator support
- Transition to NIPPV/CPAP or high-flow nasal cannula

Sample Size

In this study, the primary outcome measure is the comparison of the incidence of BPD and/or BPD-related mortality at a postmenstrual age of 36 weeks in preterm infants meeting the inclusion criteria, treated with two different dexamethasone regimens (the DART regimen versus a medium-dose tapering regimen). This is a categorical variable, and intergroup analysis will be performed using the chi-square test. Based on previous literature, it is anticipated that the intervention could reduce this incidence by an absolute difference of 10% in the study population. With a two-sided alpha of 0.05 and a statistical power ($1-\beta$) of 0.80, the calculated required sample size is approximately 388 participants per group, totaling 776 participants. Accounting for an estimated dropout and loss-to-follow-up rate of approximately 20%, the final planned enrollment is approximately 970 infants (485 per group) to ensure adequate study power.

IV. Study Population

This study aims to enroll preterm infants with a gestational age of 24 weeks to 29 weeks + 6 days who have required invasive mechanical ventilation for at least 14 days after birth and are receiving their first dose of study medication between 14 and 28 days of life. Prior to enrollment, infants must have required an inspired oxygen concentration (FiO_2) > 40% and a mean airway pressure (MAP) > 8 cmH_2O for at least 24 consecutive hours to ensure an adequate level of illness severity. In addition, informed consent must be obtained from the parents or legal guardians, and infants must not have received any other corticosteroid treatment prior to enrollment to avoid potential confounding factors. The goal is to enroll a well-defined population of preterm infants based on strict eligibility criteria.

1. Inclusion Criteria

(All of the following must be met)

1) Gestational age between 24 weeks and 29 weeks + 6 days; Invasive mechanical ventilation for ≥14 days after birth; First dose of study drug administered between 14 and 28 days of life.

2) FiO_2 > 40% and MAP > 8 cmH_2O maintained for at least 24 hours prior to enrollment.

3) Informed consent signed by parent(s) or legal guardian.

4) No use of other corticosteroids prior to enrollment as specified in the inclusion criteria.

2. Exclusion Criteria

(Any of the following will exclude the infant from participation)

1) Presence of ventilator-associated pneumonia (VAP) at the time of enrollment, diagnosed based on clinical signs, imaging, and microbiological findings.

According to the U.S. Centers for Disease Control and Prevention (CDC) and the National Nosocomial Infections Surveillance System (NNIS), VAP is defined as pneumonia occurring at least 48 hours after the initiation of mechanical ventilation [22].

Although the CDC/NNIS definition lacks specific criteria for neonates and preterm infants under 1 year of age, most NICU-based studies on VAP still adopt these criteria [23]. Infants with cytomegalovirus (CMV) pneumonia treated for less than 2 weeks are also excluded.

2) Severe congenital malformations (e.g., complex congenital heart disease, diaphragmatic hernia), or known immunodeficiency.

3) Other severe illnesses with a poor prognosis or short expected survival.

4) Refusal of participation by parents or legal guardians.

3. Withdrawal Criteria

Subjects may voluntarily withdraw from the study at any time and for any reason. In addition, subjects will be withdrawn from the study under any of the following circumstances:

1) The subject experiences a serious adverse event (SAE), and the study physician determines that continued participation poses an unacceptable risk.

2) The subject receives medications or interventions prohibited by the study protocol that may impact the accuracy or safety of the trial results.

3) The subject’s condition deteriorates and requires emergency treatment not aligned with the study protocol.

4) The subject is later found to not meet inclusion criteria or to meet exclusion criteria but

was mistakenly enrolled.

5) The trial monitor or ethics committee recommends the termination of the subject's participation.

6) The parent or legal guardian withdraws informed consent or explicitly requests to discontinue participation.

4. Study Termination Criteria

Study termination refers to the complete discontinuation of the clinical trial before its planned conclusion.

1) A major safety concern arises during the study, necessitating immediate termination.

2) A significant error in protocol design or major deviation in implementation is discovered, making it impossible to evaluate the drug's effect.

3) The sponsor requests termination of the study.

V. Study Procedure

1. Pre-enrollment Screening

Eligible infants will begin screening on day 14 of life. Once eligibility is confirmed, informed consent will be obtained from the parents or legal guardians, and randomization will be performed.

2. Intervention

Participants will be randomly assigned in a 1:1 ratio to receive one of the dexamethasone regimens. Standardized supportive care and ventilator management will be administered concurrently. Monitoring of intervention adherence will be implemented to ensure all treatments are delivered according to protocol.

3. Follow-up and Assessments

- Short-term follow-up: Record extubation outcomes at 72 hours and 7 days; monitor for complications such as intestinal perforation, gastrointestinal bleeding, hyperglycemia,

hypertension, and myocardial hypertrophy.

- Mid-term follow-up: Document the number of steroid treatment courses and related complications.

- Long-term follow-up: At 18–24 months corrected age, conduct neurodevelopmental assessments using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), or the Griffiths Mental Development Scales (GMDS), along with evaluations of hearing, vision, and other developmental outcomes.

VI. Outcome Measures

Primary Outcome Measure:

- Efficacy Indicator:

The incidence of BPD and/or BPD-related mortality at a corrected age of 36 weeks in preterm infants meeting the inclusion criteria, treated with two different dexamethasone regimens (the DART regimen and the medium-dose tapering regimen).

- Incidence and severity of BPD at 36 weeks corrected gestational age, classified according to Jensen criteria:

  - Grade I (mild): Nasal cannula < 2 L/min

  - Grade II (moderate): CPAP, NIPPV, or nasal cannula ⩾ 2 L/min

  - Grade III (severe): Ongoing need for invasive mechanical ventilation

Secondary Outcome Measures:

Short-term Indicators:

- Efficacy Indicator:

Extubation success rate following the first course of treatment, defined as no reintubation within 72 hours and 7 days after initial extubation.

Oxygenation Index (OI) on days 0, 3, 7, 10, 14, and 28 of treatment

(OI = MAP × FiO_2 × 100 / PaO_2)

- Safety Indicators:

Incidence of adverse events, including hyperglycemia, hypertension, infection, gastrointestinal bleeding, etc.

Indicators During Total Hospitalization:

- Efficacy Indicators:
  - Incidence of complications at discharge, including:

Retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), infections, pulmonary hypertension, and growth retardation

  - Total days on mechanical ventilation
  - Total length of hospital stay

Long-term Indicators:

- Safety Indicator:

Neurodevelopmental outcomes at 18–24 months corrected age, assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III MDI/PDI), or the Griffiths Mental Development Scales (GMDS).

VII. Risk Prevention and Management

This study involves preterm infants, a population with inherent risks related to medication use and clinical interventions. To ensure the highest level of participant safety, the research team has established comprehensive risk prevention and response strategies. These include strict inclusion and exclusion criteria, standardized treatment protocols, an adverse event monitoring system, and oversight by an independent Data and Safety Monitoring Board (DSMB). These measures aim to minimize risks and safeguard the well-being of all participants.

Strict Inclusion and Exclusion Criteria to Ensure Safety: The inclusion criteria require that participants be in stable condition, while those with severe infections, major congenital anomalies, or other high-risk conditions are excluded. The use of other corticosteroids prior to enrollment is strictly prohibited to eliminate confounding factors.

Standardized Medication and Treatment Protocols: All medications and interventions will be administered strictly in accordance with the study protocol by experienced neonatologists. Each administration will be preceded by an evaluation to assess contraindications or high-risk factors. Medication may be withheld or discontinued if safety concerns arise.

An adverse event monitoring system will be implemented, including daily assessments of

blood glucose, blood pressure, weight changes, and other relevant parameters. A Data and Safety Monitoring Board (DSMB) will conduct regular reviews of safety data. In the event of a serious adverse event (SAE), the incident will be immediately reported to the Ethics Committee and relevant authorities, and an evaluation will be conducted to determine whether the study should be suspended.

Clear Withdrawal and Termination Mechanisms: Explicit criteria for withdrawal are in place (e.g., clinical deterioration, use of prohibited medications, withdrawal of parental consent). If any withdrawal or termination criteria are met, the intervention will be stopped immediately, and the infant will receive optimal clinical care.

Protection of Participant Privacy: All data collection and management will be handled using coded identifiers. Data storage and transmission will be encrypted to prevent any breach of personal information.

Enhanced Informed Consent Process: Trained research staff will communicate thoroughly with parents or legal guardians, using clear and accessible language to explain the study procedures and associated risks. Written materials will be provided, and families will have ample time to make an informed decision. During the study, parents may consult with the research team at any time, provide feedback, or withdraw from the study without penalty.

VIII. Adverse Event Recording and Reporting

During the study, investigators must closely monitor for the occurrence of adverse events (AEs). Upon the occurrence of any AE, including significant adverse events, the investigator is responsible for analyzing its cause, making a clinical judgment, and documenting the following: time of occurrence, symptoms, severity, duration, treatment measures, and outcome, as well as assessing the event's relevance to the study intervention. All relevant medical documentation, including laboratory reports, must be recorded in the source documents.

In the event of a serious adverse event (SAE), immediate protective measures must be taken to safeguard the participant. Investigators must promptly complete a Serious Adverse Event Report Form and notify the Ethics Committee within 24 hours. The affected participant must be followed closely, and the event must be documented continuously until resolution,

stabilization, or death.

IX. Data Management

- Completion of Case Report Forms (CRFs):

CRFs will be completed by clinical investigators.

- Data Entry and Modification:

Dr. Chen Zheng is responsible for data entry and management. Data will be entered and managed using the Rien Electronic Data Capture (EDC) System for clinical trials. To ensure data accuracy, dual data entry will be performed independently by two data managers, followed by cross-verification.

- Database Locking:

Once the accuracy and completeness of the database are confirmed, the Principal Investigator and the statistical analysis team will jointly lock the database.

X. Statistical Analysis Methods

Data analysis will be conducted using SPSS, R, or other statistical software.

Baseline Data Analysis:

Descriptive statistical analysis will be conducted on the baseline characteristics of each group (e.g., gestational age, birth weight, sex, antenatal steroid use, etc.). Continuous variables will be compared using analysis of variance (ANOVA) or the Kruskal-Wallis test, while categorical variables will be compared using the chi-square test or Fisher's exact test to assess the balance between groups.

Primary Outcome Analysis:

The 72-hour and 7-day extubation success rates will be compared among groups using the chi-square test or logistic regression analysis.

Secondary Outcome Analysis:

For continuous variables (e.g., time to extubation, oxygenation index [OI]), ANOVA or the Kruskal-Wallis test will be used. For categorical variables (e.g., incidence of bronchopulmonary dysplasia [BPD], incidence of complications), the chi-square test or Fisher's exact test will be applied. Repeated measures ANOVA will be used to assess changes in OI at different time points (days 0, 3, 7, 10, 14, and 28). Linear regression analysis will be employed to assess the relationship between dexamethasone dosage and neurodevelopmental outcomes (MDI/PDI).

Multivariate Analysis:

Multivariate logistic regression or Cox regression analysis will be conducted to control for potential confounding factors (e.g., gestational age, birth weight, antenatal steroid use) and to evaluate the independent effect of dexamethasone regimens on outcomes such as extubation success rate and incidence of BPD.

XI. Dissemination of Research Findings

Upon completion of the study, the research team will prepare manuscripts based on the data and submit them to high-quality national and international journals for publication. The manuscripts will include primary findings, subgroup analyses, monitoring of adverse events, and long-term follow-up outcomes.

Additionally, the results will be presented at national and international conferences in the fields of pediatrics and neonatology to enhance the academic impact of the study. If funding is obtained, a final report will be submitted in accordance with the funding agency's requirements.

The findings from this study will serve as an important reference for optimizing hormonal interventions during extubation in neonates and may contribute to the development of relevant clinical guidelines or expert consensus. Research data, subject to ethical approval, may be shared and used for subsequent analyses in future studies.

XII. Ethical Considerations

1. Risks and Benefits

Participants in this study may face drug-related risks. Dexamethasone is a glucocorticoid that may lead to a range of side effects during short-term use, including but not limited to hyperglycemia, hypertension, gastrointestinal bleeding, increased risk of infection, intestinal perforation, and myocardial hypertrophy. Although the study uses tapering regimens at different doses to mitigate these risks, adverse effects cannot be completely ruled out.

Participants may not directly benefit from this study. However, the information obtained from this research could provide valuable insights into the risk factors associated with prematurity and may benefit future patients facing similar conditions.

2. Protection of Participant Privacy

Only research personnel involved in this study will have access to participants' medical records, and they are bound by confidentiality agreements or researcher declarations. Ethics committees and regulatory authorities have the right to review clinical trial records. Data will be anonymized during processing, omitting any identifying personal information. Publication of results will not disclose individual participant identities. Medical records will be securely stored in the archives of the Children's Hospital, Zhejiang University School of Medicine, under strict confidentiality measures.

3. Informed Consent and Consent Form Signing

Before the clinical study begins, investigators must provide the participant's legal guardians with detailed information about the study, including its nature, purpose, potential benefits, and risks, ensuring that they fully understand the research. The study can only commence once the informed consent form has been signed.

Each participant's contact details (address and phone number) will be collected, and the attending physician will provide their own contact information to ensure participants can reach the research team at any time.

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Statistical Analysis Plan

Official Title of the Study: The Outcomes of Different Dexamethasone Regimens for the Prevention of Bronchopulmonary Dysplasia in Preterm Infants: A Multicenter Randomized Controlled Trial

NCT Number: NCT07052201

Date of the Document: September 26, 2025

Sample Size

In this study, the primary outcome measure is the comparison of the incidence of BPD and/or BPD-related mortality at a postmenstrual age of 36 weeks in preterm infants meeting the inclusion criteria, treated with two different dexamethasone regimens (the DART regimen versus a medium-dose tapering regimen). This is a categorical variable, and intergroup analysis will be performed using the chi-square test. Based on previous literature, it is anticipated that the intervention could reduce this incidence by an absolute difference of 10% in the study population. With a two-sided alpha of 0.05 and a statistical power ($1-\beta$) of 0.80, the calculated required sample size is approximately 388 participants per group, totaling 776 participants. Accounting for an estimated dropout and loss-to-follow-up rate of approximately 20%, the final planned enrollment is approximately 970 infants (485 per group) to ensure adequate study power.

Statistical Analysis Methods

Data analysis will be conducted using SPSS, R, or other statistical software.

Baseline Data Analysis:

Descriptive statistical analysis will be conducted on the baseline characteristics of each group (e.g., gestational age, birth weight, sex, antenatal steroid use, etc.). Continuous variables will be compared using analysis of variance (ANOVA) or the Kruskal-Wallis test, while categorical variables will be compared using the chi-square test or Fisher's exact test to assess the balance between groups.

Primary Outcome Analysis:

To compare the incidence of BPD and/or BPD-related mortality at a postmenstrual age of 36 weeks in preterm infants meeting the inclusion criteria, treated with two different dexamethasone regimens (the DART regimen versus a medium-dose tapering regimen).

Secondary Outcome Analysis:

For continuous variables (e.g., time to extubation, oxygenation index [OI]), ANOVA or the Kruskal-Wallis test will be used. For categorical variables (e.g., incidence of complications), the chi-square test or Fisher's exact test will be applied. Repeated measures ANOVA will be used to assess changes in OI at different time points (days 0, 3, 7, 10, 14, and 28). Linear regression

analysis will be employed to assess the relationship between dexamethasone dosage and neurodevelopmental outcomes (MDI/PDI).

Multivariate Analysis:

Multivariate logistic regression or Cox regression analysis will be conducted to control for potential confounding factors (e.g., gestational age, birth weight, antenatal steroid use) and to evaluate the independent effect of dexamethasone regimens on outcomes such as extubation success rate and incidence of BPD.

Informed Consent Form

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NCT Number: NCT07052201

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Dear Parent or Legal Guardian,

Your child is invited to participate in a research study titled: “The Outcomes of Different Dexamethasone Regimens for the Prevention of Bronchopulmonary Dysplasia in Preterm Infants: A Multicenter Randomized Controlled Trial.” Participation in this study is entirely voluntary. This informed consent form is intended to provide you with important information about the study. Please read it carefully before deciding whether to allow your child to participate. If you have any questions or do not understand any part of the form, please ask the study doctor. The research team will answer all your questions.

This study is being conducted by Dr. Chen Zheng and his team from the Neonatal Intensive Care Unit (NICU) of the Children's Hospital, Zhejiang University School of Medicine. The study has been reviewed and approved by the Medical Ethics Committee of the Children's Hospital, Zhejiang University School of Medicine.

1. Why is this study being conducted?

Background: With advances in perinatal medicine and neonatal intensive care, the survival rate of extremely and very preterm infants has significantly increased. However, both short- and long-term prognoses remain challenging. The presence and severity of bronchopulmonary dysplasia (BPD) can greatly affect the long-term outcomes of preterm infants. Glucocorticoids, such as dexamethasone, are commonly used to prevent and treat BPD. On one hand, dexamethasone can improve respiratory outcomes by reducing inflammation, decreasing pulmonary edema, and promoting alveolar development. On the other hand, there are concerns about its potential negative effects on the nervous system, growth, and metabolism of preterm infants. Currently, there is no consensus on the optimal timing, dosage, and duration of dexamethasone therapy. This study aims to evaluate the impact of dexamethasone regimens on the incidence of BPD and/or BPD-related mortality in preterm infants meeting the inclusion criteria at a postmenstrual age of 36 weeks. The goal is to provide an evidence-based foundation for optimizing dexamethasone therapy in preterm infants and to improve their long-term outcomes.

The primary objective is to compare the effects of two dexamethasone regimens (the DART regimen versus the medium-dose tapering regimen) on the incidence of BPD at 36 weeks' postmenstrual age in eligible preterm infants.

2. What needs to be done before participating in the study?

If you and your child decide to participate, we will ask you to sign this informed consent form before conducting any study-related procedures. If a new version of the consent form is issued during the study, we will ask you to sign the updated version as well.

3. How will the study be conducted?

This study will be conducted at 24 hospitals and will involve 970 patients in total. Enrollment is competitive across centers, and our hospital aims to recruit at least 100 patients.

After signing this consent form, your child will undergo a screening process.

Inclusion criteria:

- Gestational age between 24 weeks and 29 weeks + 6 days
- Requires invasive mechanical ventilation for at least 14 days after birth
- First dose of dexamethasone administered between 14 and 28 days of life
- Before enrollment, your child must have required more than 40% oxygen ($FiO_2 > 40\%$) and a mean airway pressure (MAP) > 8 cmH_2O for at least 24 hours
- Parents must sign the informed consent form
- No prior use of other corticosteroids

Exclusion criteria:

- Ventilator-associated pneumonia (VAP) at the time of enrollment (based on clinical symptoms, imaging, and microbiological tests)
- Severe congenital malformations (e.g., major cardiac defects, diaphragmatic hernia)
- Known immunodeficiency
- Other severe illnesses with poor prognosis or limited life expectancy

The purpose of the screening is to determine whether your child meets the inclusion criteria. After the screening, the study physician will inform you whether your child is eligible to continue in the study. If your child is not eligible, the physician will explain the reason and discuss alternative treatment options with you.

The total duration of participation in the study is approximately 24 months.

If enrolled, your child will undergo the following procedures:

1. Randomization:

Your child will be randomly assigned to one of two groups (1:1 ratio):

- DART regimen group
- Medium-dose tapering regimen group

Dexamethasone will be administered before the first planned extubation attempt.

2. Short-term follow-up:

We will monitor for outcomes such as extubation success at 72 hours and 7 days, intestinal perforation, gastrointestinal bleeding, hyperglycemia, hypertension, and myocardial hypertrophy.

3. Mid-term follow-up:

We will track the number of steroid treatment courses, BPD incidence, and related complications.

4. Long-term follow-up:

At 18–24 months corrected age, we will evaluate your child's neurodevelopment using the Bayley III or Griffiths Developmental Scales, as well as assess hearing and vision.

4. What are the risks or discomforts of participating in this study? Are there any protective measures?

Dexamethasone used in this study may cause side effects such as infections, peptic ulcers or

gastrointestinal perforation, electrolyte imbalance, and high blood pressure. We will closely monitor for these complications during treatment.

This study only involves the collection of clinical data and does not alter the standard care or treatment procedures your child would otherwise receive. Therefore, participation will not result in additional risks related to examinations or treatments.

5. What are the benefits of participating in this study?

Participation in this study may improve your child's respiratory outcome, but it is also possible that there will be no benefit. However, the valuable data provided by your child will contribute to future research on bronchopulmonary dysplasia (BPD) in preterm infants.

6. Are there other treatment options besides participating in this study?

Yes. If you choose not to participate, your child may still receive dexamethasone treatment before extubation during hospitalization, depending on their clinical condition. It is also possible that your child will not receive dexamethasone at all or may be extubated directly without steroid use once extubation criteria are met.

7. What if my child is injured as a result of participating in the study?

If your child experiences any injury or adverse event related to participation in this study or during the course of treatment, please contact your study doctor immediately. Your child will receive timely medical treatment.

If the injury is determined to be related to the study, the Neonatal Intensive Care Unit (NICU) of the Children's Hospital, Zhejiang University School of Medicine, will cover the medical expenses and provide appropriate compensation in accordance with national laws and regulations.

Even after signing this informed consent form, you still retain all your legal rights.

8. Are there any costs for participating in this study?

There are no additional costs for participating in this study. You will only be responsible for

the regular hospitalization and medical treatment expenses.

9. Will I be compensated for participating in this study?

No. You will not receive any financial compensation for participating in this study.

10. Is participation mandatory? Can I withdraw after joining?

No, participation in this study is entirely voluntary. You may choose not to allow your child to participate. You may also withdraw your child from the study at any time, for any reason. Choosing to withdraw will not result in any penalty, discrimination, or retaliation and will not affect your child's future medical care or rights. If you decide to withdraw your child from the study, please inform us. We will ensure your child exits the study in the safest manner possible.

11. Under what circumstances might my child be withdrawn from the study?

Your child may be withdrawn from the study by the research doctor under the following conditions:

- You or your child do not follow the instructions of the study team or show poor compliance;
- The study doctor determines that continuing participation may pose unnecessary risks to your child;
- The study is terminated by the Ethics Committee or a regulatory authority.

12. What happens if new information becomes available during the study?

If any new information arises during the study that could affect your decision to continue participation, the study doctor will inform you promptly. You will be given ample time to consider whether to continue participation.

After the study ends, relevant results will be communicated to you and your child.

13. Will my child's information be kept confidential?

Yes. All documents related to your child will be coded to protect identity. Any published

reports or presentations from this study will not include any personal information about you or your child. All data and related codes will be securely stored by the research institution. Study data will be retained for at least 10 years. Your child's medical records may be reviewed by the researchers, the Ethics Committee of the Children's Hospital, Zhejiang University School of Medicine, and relevant government regulatory authorities.

14. Who can I contact if I have questions about the study?

If you have any questions or concerns about any part of this study, the research team will be available to answer them. If you feel your questions are not fully answered or you do not understand the responses, please continue to ask until you are satisfied.

Principal Investigator: Dr. Chen Zheng; Dr. Yanping

Phone Number: +86 13857151000

If you have concerns about your child's rights as a research participant, or if you have any complaints or concerns about the research process, you may contact the Ethics Committee:

Name: Ethics Committee of the Children's Hospital, Zhejiang University School of Medicine

Address: No. 3333 Binsheng Road, Binjiang District, Hangzhou, Zhejiang Province, China

Phone Number: +86 571-86670076

Informed Consent Signature Page

I have read and understood the information in this informed consent form. I have asked questions and am satisfied with the answers provided by the study physician. I have been given sufficient time and opportunity to inquire about the details of the study and to consider whether to allow my child to participate.

I voluntarily agree to allow my child to participate in this study.

Signing this informed consent form does not mean I give up any of my legal rights.

I have been informed that I will receive a signed copy of this document.

I authorize study personnel, the ethics committee, and government regulatory authorities to review my child's medical records.

I ☐ Agree / ☐ Disagree that my child's data from this study may be used in other research.

Participant's Name (Print): _____

Guardian's Name (Print): _____

Relationship to Participant: _____

Guardian's Signature: _____

Date and Time of Signature: _____

Contact Phone Number: _____

(Only one guardian's signature is required for this study)

Statement of Person Obtaining Informed Consent:

I confirm that I have explained the details of this study to the participant's guardian, including their rights and the possible benefits and risks. I have answered the guardian's questions and provided them with a signed copy of the informed consent form.

Name of Person Obtaining Consent (Print): _____

Signature of Person Obtaining Consent: _____

Date and Time of Signature: _____

Contact Phone Number: _____

Impartial Witness Statement (if applicable):

I confirm that the study doctor accurately explained the contents of the informed consent form to the participant's guardian, and that a discussion was held with the guardian. The guardian was given the opportunity to ask questions and voluntarily agreed to allow their child to participate in the study.

Impartial Witness Name (Print): _____

Impartial Witness Signature: _____

Date and Time of Signature: _____

Contact Phone Number: _____

(An impartial witness signature is required if the participant or their guardian is illiterate.)