Randomized Trial of 42-Day Compared with 9-Day Courses of Dexamethasone for the Treatment of Evolving Bronchopulmonary Dysplasia in Extremely Preterm Infants

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Objective To compare pulmonary and neurodevelopmental outcomes in extremely preterm infants with evolving bronchopulmonary dysplasia treated with either a 42-day course of dexamethasone or 9-day course(s) of dexamethasone.

Study design This was a prospective, randomized study in 59 infants ≤27 weeks of gestation born between October 2006 and December 2010, who at day 10-21 of life had ventilatory support with mean airway pressure ≥8 cm H_2O and FiO_2 ≥60%. Infants received dexamethasone 0.5 mg/k/day × 3 days followed by a slow taper (42-day group, n = 30) or dexamethasone 0.5 mg/k/day followed by a rapid taper (9-day group, n = 29). Infants in the 9-day group received additional 9-day courses if they again required entry support. The primary outcome was intact survival (normal neurologic examination, IQ >70, and functioning in school without supplemental educational support) at 7 years of age.

Results The 42-day and 9-day groups were similar for mean gestational age (25 weeks) and all baseline characteristics. Nineteen of 29 infants (66%) in the 9-day group received only 1 course of dexamethasone; therefore, the total steroid dose for the 42-day group (7.56 mg/kg) was significantly greater than that for the 9-day group (4.04 mg/kg), $P < .001$. Infants in the 42-day group had shorter duration of ventilation (25 vs 37 days), $P < .005$, received fewer transfusions (2 vs 3.5), $P < .01$, and reached full enteral feeds earlier (40 vs 46 days), $P < .05$. Intact survival at school age was significantly increased in the 42-day group (75%) compared with the 9-day group (34%), $P < .005$.

Conclusion A 42-day tapering course of dexamethasone in extremely preterm infants at high risk for bronchopulmonary dysplasia decreased hospital morbidities and increased rate of survival without handicap compared with a treatment protocol that attempted to minimize steroid exposure. (J Pediatr 2019;211:20-6).

Several clinical trials have shown that dexamethasone treatment for perterm infants who are ventilator-dependent results in improvement in lung function, earlier weaning from mechanical ventilation, and reduced incidence of bronchopulmonary dysplasia (BPD).[1-4] However, later reports raised concerns of potential adverse neurodevelopmental effects of postnatal corticosteroids,[5-7] which prompted theAmerican Academy of Pediatrics to publish a policy statement in 2002 concluding that dexamethasone for the prevention and treatment of BPD could not be recommended as routine therapy and that, outside of clinical trials, use of dexamethasone for this purpose should be limited to exceptional clinical circumstances.[8] The use of corticosteroids declined precipitously thereafter, but neurosensory and cognitive outcomes in extremely preterm infants remained unchanged.[9,10] A systematic review published in 2005 suggested that the beneficial effects of dexamethasone in reducing lung disease, a risk factor for neurodevelopmental impairment, may exceed potential negative effects in the most immature infants with the highest risk of BPD.[11] This same relationship was shown with greater statistical significance in an updated analysis, including data from a greater number of randomized controlled trials.[12]

Data on optimum dosing and duration of corticosteroid therapy are inconclusive.[13] Meta-analyses have suggested that higher cumulative doses of dexamethasone are associated with reduced risk of BPD or of the combined outcome of mortality and BPD.[14-16] The relationship between cumulative dose and mortality and cerebral palsy seems to be modified by the timing of treatment. In those infants treated moderately early (7-21 days of age), the risk of combined mortality and cerebral palsy has an inverse relationship, with higher doses being associated with lower risk of poor outcome.[15,16] The opposite has been reported in infants treated late (>21 days of age), with higher doses being associated with a higher relative risk of mortality and cerebral palsy.[15,16] An 18- to 22-month adjusted age follow-up study suggested that there is no "safe" window for steroid use in extremely low birth weight infants and that each 1 mg/kg dose exposure was associated with a 2.0-point reduction in Mental Developmental Index and a 40% increased risk for disabling cerebral palsy.[17] However, that study included a large number of infants who were treated late

BPD	Bronchopulmonary dysplasia
IEP	Individualized education program

and the relationship was found to be modified by the risk of BPD, with those at highest risk experiencing less harm.[17]

We previously reported a randomized, double-blind, placebo-controlled trial in infants ≤30 weeks of gestational age showing that a 42-day course of dexamethasone resulted in both improved pulmonary and neurodevelopmental outcomes compared with an 18-day course or placebo.[4,18] In that trial, long course and short course therapies were assigned randomly and not modified by clinical response. To further address dose exposure and provide data toward optimizing therapy, we designed a prospective randomized trial that allowed the clinical course of each infant to dictate the extent of steroid exposure. We compared outcomes in ventilated extremely preterm infants with evolving moderate-severe BPD treated moderately early with 2 therapeutic regimens: a 42-day tapering course of dexamethasone vs 9-day rapidly tapering course(s) of dexamethasone, with the number of 9-day courses received modified by the infant's respiratory support requirement. We hypothesized that infants in the repeatable 9-day group would receive significantly less steroid exposure without compromise of respiratory and long-term neurologic outcomes.

Methods

Study candidates were selected from infants admitted to the neonatal intensive care unit of Crouse Hospital (Syracuse, NY), which serves as the regional center for Central New York and cares for all infants <28 weeks of gestational age born in its 17 county area. Infants were eligible for study if they were born at 24-27 weeks of gestational age and at 10-21 postnatal days, met defined respiratory criteria. These criteria included radiographic findings consistent with the diagnosis of evolving BPD and ventilator support with sustained (≥18 hours) FiO_2 ≥60% and mean airway pressure ≥8 cm H_2O. Infants were excluded from study if they had pre-existing conditions with known increased risk for neurodevelopmental impairment; these included a birthweight or head circumference <10th percentile for gestational age, significant congenital malformations including chromosomal anomalies and congenital heart disease, grade IV intracranial hemorrhage, a 5-minute Apgar score <3, or a history of seizures or base deficit of >15. Infants with sepsis or significant patent ductus arteriosus became study eligible if these issues were treated before the end of the enrollment window. Informed consent was obtained from a parent or guardian of each infant. Assent for school-age follow-up was obtained from each child. This protocol was approved by the Institutional Review Board of Crouse Hospital.

Study Design

Figure 3 (available at www.jpeds.com) provides the CONSORT flowchart for the study. Infants were assigned randomly by computerized allocation sequence to receive either a 42-day tapering course of dexamethasone (42-day group) or a 9-day tapering course of dexamethasone (9-day group). The infants in the 42-day group received dexamethasone 0.5 mg

per kilogram per day for the first 3 days and 0.3 mg per kilogram per day for the next 3 days. The dose of dexamethasone was then reduced by 10% every 3 days until a dose of 0.1 mg per kilogram was reached on day 34. Thereafter, this dose of dexamethasone was maintained for 3 days, alternated daily with saline placebo for 1 week, and then discontinued.[4] Infants in the 9-day group received dexamethasone 0.5 mg/kg/day for the first 3 days, 0.25 mg/kg/day for the next 3 days and then 0.125 mg/kg/day for 3 days, followed by saline placebo. After a minimum of 72 hours from completion of the initial 9-day course, if entry respiratory criteria were again met, infants received a second 9-day course, followed by saline placebo. Infants who completed a second 9-day course and subsequently met respiratory criteria within the 42-day study window received a third 9-day course. The clinical status of each infant was transmitted to the study pharmacist on a daily basis in the form of a coded flowsheet. If an infant assigned to the 42-day group again met respiratory criteria during the 42-day study period the pharmacist made no changes.

During the study period, infants in the 42-day group received a total dexamethasone dose of 7.98 mg/kg. Infants in the 9-day group received a total dexamethasone dose of 2.63, 5.25, or 7.88 mg/kg depending upon the number of 9-day courses (1, 2, or 3) received. An individual not involved with the study generated the random allocation sequence. Access to this sequence and all protocol assignments was limited to 2 study pharmacists. All investigators and care givers remained blinded to treatment group.

Infants were managed to maintain oxygen saturations between 88% and 94% and arterial pH between 7.25 and 7.35. Respiratory support was provided with either time-cycled pressure limited (Dräger Medical, Lubeck, Germany) or high frequency oscillatory (Sensormedics, Carefusion, Yorba Linda, California) ventilation. In general, high frequency oscillatory ventilation was utilized as rescue treatment for refractive hypercarbia, pulmonary interstitial emphysema, or pulmonary hemorrhage. The timing of extubation was determined by the attending physician, however, all infants had to be given a trial of extubation once weaned and stable on minimal ventilator support (mean airway pressure ≤6 cm H_2O, FiO_2<30%). Infants were treated with caffeine prior to elective extubation and were initially extubated to nasopharyngeal continuous positive airway pressure of 6 cm H_2O. During the study period, bronchodilator therapy was allowed as an adjunctive treatment and used at the discretion of the attending physician. Routine diuretic therapy was not employed. Open label steroid use, either systemic or inhaled, was prohibited during the study period.

All infants received parenteral nutrition beginning on day 1 of life, and all infants received 7 days of trophic (12 mL/kg/day) breastmilk feeds beginning on day 7 of life. Feeds were then advanced by 15 mL/kg/day, as tolerated, to 180 mL/kg/day. Donor breast milk from our preterm milk bank was provided to infants if no maternal breastmilk was available. Parenteral nutrition was discontinued when enteral feedings reached 100 mL/kg/day.

Red cell transfusions were used to maintain hematocrit thresholds defined by the severity of respiratory illness. Neonates with moderate to marked respiratory requirements and/or sepsis were transfused for hematocrits below 35%. A transfusion threshold of 30% was used for those with modest respiratory requirements. More stable infants were transfused for hematocrits <20% and postmenstrual age of <32 weeks.

Infants were assessed continuously with transcutaneous carbon dioxide monitoring and pulse oximetry. The range of ventilator and supplemental oxygen support was recorded daily, as were blood pressures, blood glucoses, feeding tolerance, transfusions, and episodes of sepsis. Sepsis was defined as clinical signs of infection with a positive blood culture. Hypertension was defined as sustained mean blood pressure ≥65 mm Hg. Refractive hyperglycemia was defined as sustained serum glucose >150 mg/dL with a minimum glucose infusion rate of 3.5 mg/kg/minute. Infants had cranial ultrasounds performed on day of life 4 and 14 and at 35 weeks of postmenstrual age. Indirect ophthalmoscopy was performed by a pediatric ophthalmologist when the infants were 6-7 weeks of age, with the findings dictating the timing of subsequent assessments. Hearing evaluations were performed by auditory brainstem response prior to hospital discharge.

Follow-up evaluations were initially performed at 6 and 24 months of age, using age corrected for prematurity.[19] School age follow-up was then performed at 7 years of age. Evaluations included an interval health history, anthropometric measures, neuromotor assessment, and developmental testing.[20-22] At 7 years of age, cognitive testing was performed using the Wechsler Intelligence Scale for Children, 5th edition (WISC V).[23] School performance was evaluated by parent and teacher reports to determine whether children were in a regular classroom without supplemental support or whether education was provided as part of an individualized education program (IEP). All developmental testing was carried out by examiners blinded to infant treatment group.

Deafness was defined as the need for bilateral hearing aids. Blindness was defined as no vision in both eyes. An abnormal neurologic examination was defined as blindness, deafness, or cerebral palsy. At 7 years of age, cerebral palsy was classified using the Gross Motor Function Classification System for Cerebral Palsy.[22] Neurodevelopmental impairment was defined as an abnormal neurologic examination and/or WISC V IQ score <70.

Outcome Measures

The primary outcome measure of the study was intact survival, defined as survival to 7 years of age without severe neurologic, cognitive, or academic handicap (normal neurologic examination, IQ >70, and receiving education in a regular classroom without an IEP). Secondary outcomes included duration of mechanical ventilation, supplemental oxygen requirement at 36 weeks of corrected age (BPD), feeding tolerance, transfusion exposure, sepsis, length of initial hospitalization, rates of re-hospitalization, and growth at 7 years of age.

Statistical Analyses

The sample size necessary for sufficient statistical power was calculated based on a retrospective evaluation of neurodevelopmental impairment in infants born at 24-27 weeks of gestation treated with a 42-day course of dexamethasone for evolving BPD. We considered that a 30% reduction in steroid exposure without a negative impact on outcomes would be meaningful. For a type I error of <5% and a statistical power of >80%, we calculated a minimum sample size of 36 in each group. Study recruitment was terminated after 59 infants were enrolled because differences in outcomes were identified in preliminary 6 month data presented at the 2011 Pediatric Academic Societies meeting.[19] Clinical data were summarized as mean ± SD, median ± IQR, or percentage and were analyzed with the student t test, the Mann-Whitney U test, or $\chi 2$ test as appropriate. A P value of < .05 was considered to indicate statistical significance.

Results

Infants were enrolled between October 1, 2006 and December 31, 2010. During the enrollment period, 59 of 73 eligible infants (80%) were entered into the study. Lack of enrollment was due to refusal of consent in all cases. Those infants who were eligible but not enrolled had demographic and clinical characteristics comparable with the study population.

Infants in the 42-day and 9-day groups had similar social and perinatal characteristics (Table I). Infants in both groups had a mean gestational age of 25 weeks and mean birthweight of <800 g. Approximately 80% of infants were inborn, and

Table I. Sociodemographic and prerandomization characteristics of study infants

Characteristics	42-d group	9-d group
Perinatal	n = 30	n = 29
Gestational age (wk)	25.2 ± 1.2	25.2 ± 1.1
Birthweight (g)	769 ± 149	785 ± 167
Male sex	14 (47)	17 (59)
Maternal betamethasone	19 (63)	18 (62)
Inborn	24 (80)	23 (79)
Multiple gestation	12 (40)	7 (24)
Vaginal delivery	12 (40)	6 (21)
Apgar score at 5 min	7 ± 2	7 ± 2
Respiratory distress syndrome	29 (97)	25 (86)
HFOV	20 (67)	17 (59)
Day 4 cranial ultrasound		
No IVH	22 (73)	24 (83)
Grade I/II IVH	8 (27)	3 (10)
Grade III IVH	0	2 (7)
Social characteristics of survivors evaluated at school age	n = 28	n = 26
Maternal age (y)	27 ± 7	27 ± 7
Married mother	13 (46)	14 (54)
White race	18 (64)	21 (81)
Maternal education (y)		
<12	8 (29)	1 (4)
12-15	14 (50)	19 (73)
≥16	6 (21)	6 (23)

HFOV, high frequency oscillatory ventilation; *IVH*, intraventricular hemorrhage. HFOV, high frequency oscillatory ventilation
There were no significant differences between groups.
Data are mean ± SD or n (%).

greater than 60% delivered after the completion of a maternal betamethasone series. The majority received exogenous surfactant for the diagnosis of respiratory distress syndrome, and high frequency oscillatory ventilation was used in more than one-half of the infants in each group. Complicating air-leak occurred in 5 infants in each group, and no infants had pulmonary hemorrhage. Two infants in each group received hydrocortisone for the treatment of refractory hypotension prior to study enrollment. Thirty percent of infants underwent patent ductus arteriosus ligation after contraindicated or failed indomethacin treatment. Nosocomial infection prior to study entry occurred in 3 infants (10%) in the 42-day group and none in the 9-day group. All infants received indomethacin for the prevention of intraventricular hemorrhage and approximately 75% of study infants had normal cranial ultrasounds.

The mean age at randomization was similar for infants in the 42-day and the 9-day groups (14 ± 4 and 13 ± 3 days, respectively). The groups also were similar at study entry for respiratory requirements, including mean FiO_2 (72 ± 13 and $77 \pm 16\%$, respectively) and mean airway pressure (10.3 ± 2.0 and 10.4 ± 1.7 cm H_2O).

All 30 infants in the 42-day group survived to hospital discharge, and all were alive at 7 years of age. Two infants in the 9-day group died in the neonatal intensive care unit (at ages 32 and 111 days), and 1 infant died 1 month following neonatal intensive care unit discharge. All 3 deaths in the 9-day group were the result of respiratory failure.

The steroid protocols were followed without modification in 58 of the 59 infants. One infant in the 42-day group developed hypertension and required a single dexamethasone dose reduction. No infants had refractive hyperglycemia, and none required insulin.

Nineteen of 29 infants (66%) in the 9-day group qualified for only 1 course of dexamethasone, 5 infants (17%) received 2 courses, and the remaining 5 infants (17%) received all 3 courses. Therefore, the mean total steroid dose received by infants in the 42-day group (7.96 mg/kg) was significantly greater than that received by those in the 9-day group (4.04 ± 0.07 mg/kg), ($P < .001$). Nine of the 10 infants who received more than one 9-day course of dexamethasone were born at <25 weeks of gestational age. Infants in the 42-day group were extubated significantly earlier than those in the 9-day group (median 23 vs 35 days, respectively, $P < .01$), had less frequent need for reintubation (7 vs 25%, $P < .001$), and had a shorter total duration of ventilation (median 25 vs 37 days, $P < .005$) (Table II). The percentages of successfully extubated infants in each group are presented as a function of study day in Figure 1. After 1 week, 15 of 30 (50%) infants in the 42-day group were successfully extubated compared with only 4 of 29 (15%) in the 9-day group ($P < .005$). Successful extubation continued to be significantly higher for infants in the 42-day group at weeks 2, 3, and 4, $P < .005$ (Figure 1).

More than 90% of infants had BPD, and over one-half of infants in each group were discharged on supplemental oxygen. Open use of systemic steroids after completion of the

Table II. **Respiratory outcomes**

Outcome variables	42-d group (n = 30)	9-d group (n = 29)
Age at first extubation (d)*	23 (19,31)	35 (18,54)
Requirement for reintubation[†]	2 (7)	7 (25)
Total duration of ventilation (d)[‡]	25 (21,34)	37 (24,54)
BPD[§]	28 (93)	25/28 (89)
Home supplemental oxygen	17 (57)	15/27 (56)
Total duration of supplemental oxygen (d)	148 (89,205)	159 (82,229)

Data are median (IQR) or n (%).
*$P < .01$
[†]$P < .001$
[‡]$P < .005$
§Supplemental oxygen requirement at 36 weeks of corrected age.

42-day study period was similar for infants in the 42-day and the 9-day groups (20% and 34%, respectively).

Infants in the 42-day group reached full enteral feeds (120 kcal/kg/day) significantly earlier than those in the 9-day group (40 ± 10 vs 46 ± 11 days, respectively, $P < .05$) and received significantly fewer red blood cell transfusions (2.0 ± 1.6 vs 3.5 ± 1.7, $P < .01$). There were no differences between the groups in rates of nosocomial sepsis (27% vs 31%), or retinopathy of prematurity requiring laser treatment (10% in both groups). One infant in each group developed periventricular leukomalacia. No infants developed necrotizing enterocolitis or had spontaneous intestinal perforation. There was no difference in length of hospital stay between groups (104 ± 19 vs 103 ± 28 days).

7 Year Outcomes

At 7 years, 54 of the 56 survivors (96%) were evaluated (Table III). The mean age at evaluation was 7.4 ± 0.6 years for those in the 42-day group and 7.5 ± 0.6 years for those in the 9-day group. There were no differences between the 42-day and the 9-day groups for height (122 ± 7 vs 122 ± 8 cm, respectively), weight (22.9 ± 5.8 vs 22.5 ± 5.3 kg) or head circumference (51 ± 2 vs 51 ± 2 cm). The rates of re-hospitalization for respiratory
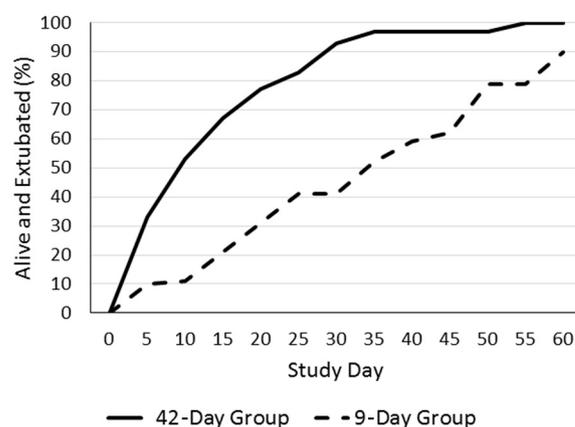

Figure 1. Percent of study infants alive and extubated over the course of the study. Differences in rates of extubation were significant at weeks 1, 2, 3, and 4, $P < .005$.

Table III. Neurodevelopmental outcomes at 7 years

Outcome characteristics	42-d group	9-d group
Survival	30/30 (100)	26/29 (90)
Evaluated at 7 y	28/30 (93)	26/26 (100)
Abnormal neurologic examination	1 (4)	5 (19)
Wechsler Intelligence Scale for Children, 5th edition IQ	89 ± 12	82 ± 19
IQ <70	2 (7)	5 (19)
IQ <50	0	4 (15)
Survival without neurodevelopmental impairment*	26 (93)	19 (66)
Regular classroom without IEP†	21 (75)	10 (38)

Data are mean ± SD or n (%).
*Survival with normal neurologic examination and IQ>70, P < .05.
†Education in a regular classroom without an IEP, P < .01.

illness were also similar for children in the 42-day (14%) and the 9-day groups (19%).

Results of neurodevelopmental evaluation are presented in **Table III**. One child in the 42-day group had cerebral palsy. Five children (19%) in the 9-day group had an abnormal neurologic examination, including 1 child who was blind and 4 children with cerebral palsy. The mean IQ for children in the 42-day group was 89 ± 12, with 2 children scoring <70. The mean IQ for children in the 9-day group was 82 ± 19, with 5 children scoring <70 and 4 of those children scoring <50. As a result, significantly more children in the 42-day group were alive and without neurodevelopmental impairment (93%) compared with those in the 9-day group (66%), P < .02 (**Table III**). These outcomes at 7 years are consistent with the study's findings in the first 2 years of life, which were published previously.[19]

School performance was significantly better in the 42-day group compared with the 9-day group. In the 42-day group, 21 of 28 children (75%) were receiving education in a regular classroom without an IEP. In contrast, only 10 of the 26 survivors (38%) in the 9-day group were functioning in school without an IEP (P < .01). Therefore, at 7 years of age, intact survival (alive, normal neurologic examination, IQ >70, and functioning in the classroom without supplemental educational support) was significantly greater for children in the 42-day group than in the 9-day group (75% vs 35%, respectively, P < .005) (**Figure 2**).

Discussion

An American Academy of Pediatrics policy statement on the use of postnatal corticosteroids was published in 2010 and acknowledged that available data were not sufficient to provide definitive recommendations.[13] Since that statement, there remain many unanswered questions, including the optimal timing and the ideal form, dosage, and duration of corticosteroid treatment.[24] As a result, there continues to be significant variation among providers in the clinical application of a therapy to which approximately 9% of very low birth weight infants are exposed.[25] Attempts to lessen morbidity by limiting dose exposure have been recommended and remain common in practice.[26-28]

The results of our randomized trial suggest that minimizing corticosteroid exposure in extremely preterm infants at very high risk for BPD results in greater short-term respiratory morbidity. Although linking steroid exposure to the
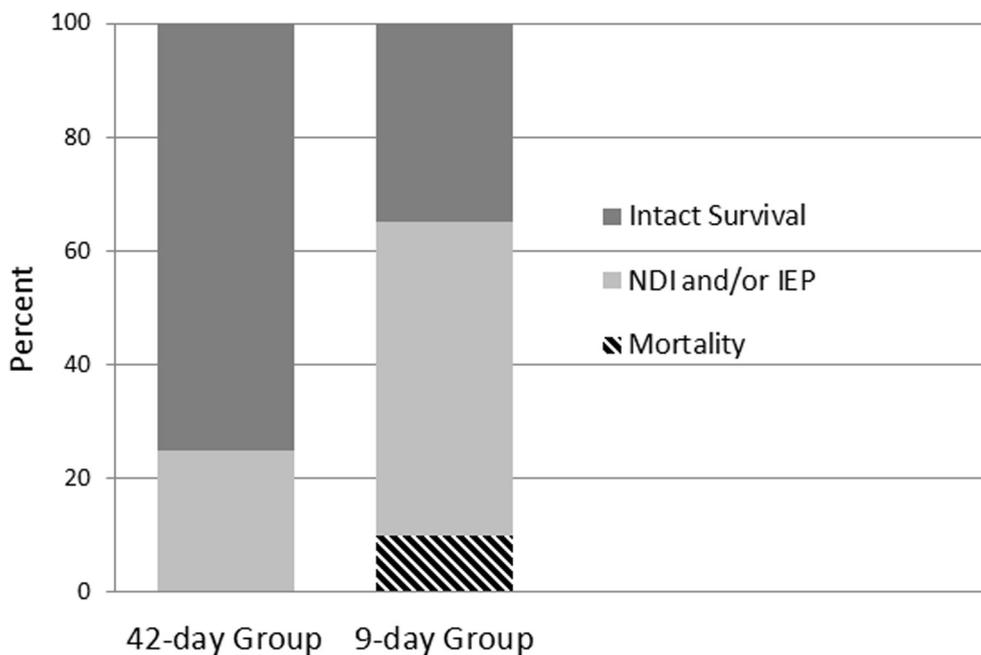

Figure 2. Intact survival (survival with normal neurologic examination, IQ >70, and education in the classroom without supplemental educational support) at 7 years of age was significantly greater in the 42-day group than in the 9-day group (P < .005).

severity of illness resulted in infants with the most severe lung disease receiving the most dexamethasone, it also produced overall greater and prolonged requirement for respiratory support. Infants in the 9-day group frequently experienced a moderate plateau of illness, which prevented successful extubation, but did not allow for more steroid therapy per the study design. In fact, the majority of infants in the 9-day group received only one 9-day course of dexamethasone. One-third of infants had more dramatic swings in their respiratory support and received more than 1 course of dexamethasone during the initial 42-day period. Not surprisingly, the infants in the 9-day group who qualified for more than 1 dexamethasone course were also the least mature and, therefore, at greatest risk. Despite those in the 9-day group having an apparent greater severity of respiratory illness, the rate of BPD was approximately 90% in both groups, which is consistent with the liberal definition of BPD used and the very high-risk population studied.

Efforts to minimize steroid exposure also resulted in infants receiving a greater number of transfusions and taking a longer time to reach full enteral nutrition, both observations, which likely stem from their more complicated and unstable respiratory courses. Most importantly, our results showed that attempting to minimize steroid exposure had a negative impact on survival and increased the risk of neurodevelopmental sequelae. Not only was there less combined mortality and major neurologic morbidity in children in the 42-day dexamethasone group, but 75% of those children were functioning without supplemental educational support in the classroom. In comparison, less than 40% of survivors in the 9-day group were functioning in school without added educational support.

The findings from the current study are consistent with the report by Cummings et al from our institution in 1989.[4] In that study, the same 42-day dexamethasone protocol was compared with a nonmodifiable 18-day dexamethasone protocol and placebo. Pulmonary and neurodevelopmental outcomes were evaluated in infants ≤1250 g, determined to be at high risk for BPD by requirement for ventilation and supplemental oxygen at 2 weeks of age. Developmental follow-up assessments were performed initially at 15 months of corrected age and at age 15 years. Infants in the 42-day group had improved short- and long-term pulmonary and neurodevelopmental outcomes.[4,18] At 15 years of age, intact survival (survival with normal neurologic examination, IQ >70, and education in the normal classroom) was significantly greater for children in the 42-day group than for those in either the 18-day or the placebo groups.[18] Children in the 18-day dexamethasone group received less steroids than those in the 42-day dexamethasone group (2.99 vs 7.98 mg/kg) and had both respiratory and long-term developmental outcomes that were not better than those for children in the placebo group. Even when the modification of steroid dose is linked to clinical respiratory measures, as in the current study, rather than being assigned randomly, as in our prior study, a significant reduction in total dose exposure had a negative impact on outcomes.

Multiple other trials have attempted to address optimal timing and dosing of corticosteroids to prevent BPD. These studies have generated conflicting results with some concerns for steroid related morbidities.[1-3,27] Only 1 other study in infants at high risk of BPD was a randomized placebo controlled trial with zero contamination (treatment with dexamethasone in infants in the control group) and long-term follow-up.[29,30] The results from that study are similar to, but do not totally mirror those of our original investigation. The 42-day tapering course of dexamethasone significantly reduced the duration of mechanical ventilation and the risk of BPD but also significantly increased the rate of cerebral palsy without cognitive impairment in the dexamethasone group (18%) vs placebo (2%). Because death attributable to progressive respiratory failure occurred in only 7% of those treated with dexamethasone compared with 20% of those who received placebo ($P < .06$), neurodevelopmental concerns were offset and the 42-day course of steroids was not found to increase the composite outcome of death or major neurodevelopmental disability at school age.[29,30]

The conflicting data from randomized trials are reflected in conclusions from different meta-analyses. The Cochrane Collaboration, based on a review of 19 randomized controlled trials, published a cautioning recommendation in 2009 stating that "it appears prudent to reserve the use of late (d >7 d) corticosteroids to infants who cannot be weaned from mechanical ventilation and to minimize the dose and duration of any course of treatment."[27] Contradicting this recommendation, results from a meta-analysis by Onland et al, also published in 2009, suggested (as our data support) that a higher cumulative dose improved the combined outcome of survival without cerebral palsy in those infants who received dexamethasone as part of moderately early trials.[15,16] A 2017 Cochrane Review by Onland et al concluded, however, that despite the fact some studies reported a modulating effect of treatment in favor of higher dosage regimens, current level of evidence prevents recommendations on optimal corticosteroid treatment.[24] Our study contributes directly to the issue of dose exposure and suggests that attempts to limit steroid exposure may actually be counterproductive to both survival and long-term outcome in those infants with the very highest risk of pulmonary and neurodevelopmental disabilities.

The strengths of our study include its high rate of long-term follow-up. Our study also did not allow contamination with open label steroid (either systemic or inhaled) use during the 42-day protocol period of dexamethasone dosing. Our study results are tempered by a relative small sample size and may not be generalizable given our exclusion of infants with independent risk factors for neurodevelopmental impairment.

A 2014 commentary by DeMauro et al points out the collective errors made by neonatologists that have contributed to the dramatic shifts over time in the application of postnatal corticosteroids as a therapy.[31] We believe that, although not placebo controlled and comparing only 1 regimen to the

traditional 42-day course, our study demonstrates negative effects of steroid limitation in a very high-risk population. Large well-designed clinical trials are the only way that this issue can be settled and are urgently needed. We acknowledge that alternate protocols limiting steroid exposure should be investigated as part of these larger trials.

A 42-day tapering course of dexamethasone in extremely premature infants at very high risk for BPD decreased the duration of mechanical ventilation, decreased transfusion exposure, shortened the time to full enteral nutrition, and increased the rate of intact survival at school age compared with a treatment protocol that attempted to minimize steroid exposure. ∎

References

1. Halliday HL, Ehrenkranz RA, Doyle LW. Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database Syst Rev 2003;1:CD001146.
2. Halliday HL, Ehrenkranz RA, Doyle LW. Moderately early (7-14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database Syst Rev 2003;1:CD001144.
3. Halliday HL, Ehrenkranz RA, Doyle LW. Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants. Cochrane Database Syst Rev 2003;1:CD001145.
4. Cummings JJ, D'Eugenio DB, Gross SJ. A controlled trial of dexamethasone in preterm infants at high risk for bronchopulmonary dysplasia. N Engl J Med 1989;320:1505-10.
5. Yeh TF, Lin YJ, Huang CC, Chen YJ, Lin CH, Lin HC, et al. Early dexamethasone therapy for preterm infants: a follow-up study. Pediatrics 1998;101:E7.
6. Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. BMC Pediatr 2001;1:1.
7. Yeh TF, Lin YJ, Lin HC, Huang CC, Hsieh WS, Lin CH, et al. Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity. N Engl J Med 2004;350:1304-13.
8. American Academy of Pediatrics, Committee on Fetus and Newborn and Canadian Paediatric Society, Fetus and Newborn Committee. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. Pediatrics 2002;109:330-8.
9. Hintz SR, Kendrick DE, Wilson-Costello DE, Das A, Bell EF, Vohr BR, et al. Early-childhood neurodevelopmental outcomes are not improving for infants born at <25 weeks' gestational age. Pediatrics 2011;127:62-70.
10. Yoder BA, Harrison M, Clark RH. Time-related changes in steroid use and bronchopulmonary dysplasia in preterm infants. Pediatrics 2009;124:673-9.
11. Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC. Impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk for chronic lung disease. Pediatrics 2005;115:655-61.
12. Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC. An update on the impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk of bronchopulmonary dysplasia. J Pediatr 2014;165:1258-60.
13. American Academy of Pediatrics, Committee on Fetus and Newborn. Postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. Pediatrics 2010;126:800-8.
14. Onland W, De Jaegere AP, Offringa M, van Kaam AH. Effects of higher versus lower dexamethasone doses on pulmonary and neurodevelopmental sequelae in preterm infants at risk for chronic lung disease: a meta-analysis. Pediatrics 2008;122:92-101.
15. Onland W, Offringa M, De Jaegere AP, van Kaam AH. Finding the optimal postnatal dexamethasone regimen for preterm infants at risk of bronchopulmonary dysplasia: a systematic review of placebo-controlled trials. Pediatrics 2009;123:367-77.
16. Yates HL, Newell SJ. Postnatal intravenous steroids and long-term neurologic outcome: recommendations from meta-analyses. Arch Dis Child Fetal Neonatal Ed 2012;97:299-303.
17. Wilson-Costello D, Walsh MC, Langer JC, Guillet R, Laptook AR, Stoll BJ, et al. Impact of postnatal corticosteroid use on neurodevelopment at 18 to 22 months' adjusted age: effects of dose, timing, and risk of bronchopulmonary dysplasia in extremely low birth weight infants. Pediatrics 2009;123:e430-7.
18. Gross SJ, Anbar RD, Mettelman BB. Follow-up at 15 years of preterm infants from a controlled trial of moderately early dexamethasone for the prevention of chronic lung disease. Pediatrics 2005;115:681-7.
19. Marr BL, Bode MM, Gross SJ. Trial of 42 day vs. 9 day courses of dexamethasone for the treatment of evolving bronchopulmonary dysplasia in extremely preterm infants; Proceedings of the Pediatric Academic Societies; April 30-May 3; Denver, CO; 2011.
20. Bayley N. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio, TX: The Psychological Corporation; 2005.
21. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.
22. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214-23.
23. Wechsler D. Wechsler Intelligence Scale for Children. 5th ed. Bloomington, MN: NCS Pearson, Inc; 2014.
24. Onland W, DeJaegere AP, Offringa M, van Kaam AH. Systemic corticosteroid regimens for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev 2017;1:CD010941.
25. Virkud YV, Hornik CP, Benjamin DK, Laughon MM, Clark RH, Greenberg RG, et al. Respiratory support for very low birth weight infants receiving dexamethasone. J Pediatr 2017;183:30.e3.
26. Walsh MC, Yao Q, Horbar JD, Carpenter JH, Lee SK, Ohlsson A. Changes in the use of postnatal steroids for bronchopulmonary dysplasia in 3 large neonatal networks. Pediatrics 2006;118:1328-35.
27. Halliday HL, Ehrenkranz RA, Doyle LW. Late (>7days) postnatal corticosteroids for chronic lung disease in preterm infants. Cochrane Database Syst Rev 2009;1:CD001145.
28. Halliday HL. Update on postnatal steroids. Neonatology 2017;111:415-22.
29. Kothadia JM, O'Shea TM, Roberts D, Auringer ST, Weaver RG, Dillard RG. Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants. Pediatrics 1999;104:22-7.
30. O'Shea TM, Washburn LK, Nixon PA, Goldstein DJ. Follow-up of a randomized, placebo- controlled trial of dexamethasone to decrease the duration of ventilator dependency in very low birthweight infants: neurodevelopmental outcomes at 4 to 11 years of age. Pediatrics 2007;120:594-602.
31. DeMauro SB, Dysart K, Kirpalani H. Stopping the swinging pendulum of postnatal corticosteroid use. J Pediatr 2014;164:9-11.
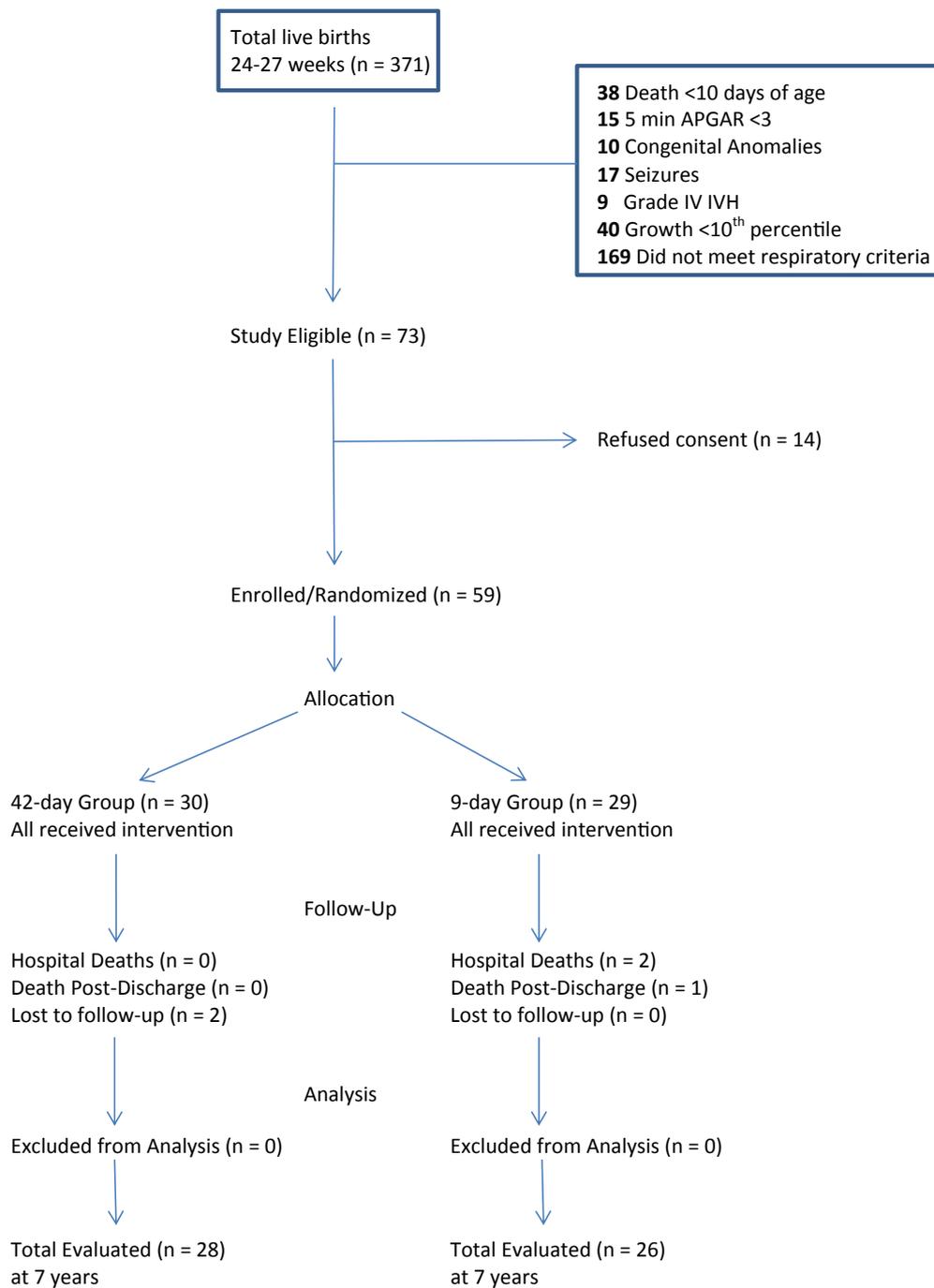
Figure 3. CONSORT Flowchart.

Randomized Trial of 42-Day Compared with 9-Day Courses of Dexamethasone for the Treatment of Evolving
Bronchopulmonary Dysplasia in Extremely Preterm Infants

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