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Low-Dose Dexamethasone Facilitates Extubation Among Chronically Ventilator-Dependent Infants: A Multicenter, International, Randomized, Controlled Trial

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ABSTRACT

OBJECTIVE. Postnatal corticosteroid therapy is controversial. The aim of this study was to determine the short-term effects of low-dose dexamethasone treatment among chronically ventilator-dependent neonates.

METHODS. Very preterm (gestational age: <28 weeks) or extremely low birth weight (birth weight: <1000 g) infants who were ventilator dependent after the first 1 week of life were eligible and were assigned randomly to receive masked dexamethasone (0.89 mg/kg over 10 days) or saline placebo. Data on ventilator and oxygen requirements and deaths were recorded.

RESULTS. Seventy infants were recruited from 11 centers, at a median age of 23 days. More infants were extubated successfully by 10 days of treatment in the dexamethasone group (60%, 21 of 35 patients) than in the control group (12%, 4 of 34 patients) (odds ratio [OR]: 11.2; 95% confidence interval [CI]: 3.2–39.0). Ventilator and oxygen requirements improved substantially, and the duration of intubation was shorter. There was little evidence for a reduction in either the mortality rate (dexamethasone group: 11%; control group: 20%; OR: 0.52; 95% CI: 0.14–1.95) or the rate of oxygen dependence at 36 weeks (dexamethasone group: 85%; control group: 91%; OR: 0.58; 95% CI: 0.13–2.66). There were no obvious effects of low-dose dexamethasone on blood glucose concentrations, blood pressure, or other complications. No infant experienced intestinal perforation.

CONCLUSIONS. Low-dose dexamethasone treatment after the first 1 week of life clearly facilitates extubation and shortens the duration of intubation among ventilator-dependent, very preterm/extremely low birth weight infants, without any obvious short-term complications. Combined with recent evidence that infants at very high risk of bronchopulmonary dysplasia may benefit in the long term, our study

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Key Words
infant, preterm, low birth weight, low-dose dexamethasone, extubation, bronchopulmonary dysplasia

Abbreviations
OR— odds ratio
CI— confidence interval
ELBW— extremely low birth weight
DART—Dexamethasone: A Randomized Trial
IQR—interquartile range
F_{IO_2}—inspired oxygen concentration
BPD— bronchopulmonary dysplasia
RCT—randomized, controlled trial

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reopens debate regarding the role of low-dose, late postnatal, corticosteroid therapy.

CORTICOSTEROIDS FOR VENTILATOR-DEPENDENT infants facilitate extubation and reduce the rate of bronchopulmonary dysplasia (BPD), whether they are given early,[1] moderately early,[2] or later[3] in the newborn period. However, recent controversy about adverse long-term effects of corticosteroids on the brain has led to a decrease in the use of corticosteroids. This might mean that infants who could benefit are being deprived of corticosteroids or that lower doses are being prescribed than those demonstrated to be effective in randomized, controlled trials (RCTs).[1–3] The Dexamethasone: A Randomized Trial (DART) study was an international, multicenter RCT that had as its main aim assessment of the effects of low-dose dexamethasone on long-term rates of survival free of major neurologic disability. However, enrollment had to stop when recruitment fell to a rate that was too low for completion of the study. The aim of this report, and a secondary aim of the DART study, was to examine the short-term effects, especially respiratory effects, of low-dose dexamethasone given after the first 1 week of life for ventilator-dependent, very preterm/extremely low birth weight (ELBW) infants.

METHODS

At participating centers, very preterm (gestational age: <28 weeks) or ELBW (birth weight: <1000 g) infants who were ventilator dependent after the first 1 week of life (>168 hours of age) and for whom clinicians considered corticosteroids a treatment option were eligible for the study. There were no baseline values for oxygen or ventilator requirements, because there was no consensus regarding what these requirements should be. Infants with acquired cranial ultrasound abnormalities, such as intraventricular hemorrhage, that were detected before eligibility were included in this study, as were infants who had received low-dose, short-course, steroid therapy for blood pressure control in the early days after birth. The only infants excluded were those with congenital neurologic defects or other disorders, such as chromosomal anomalies, that were likely to cause substantial long-term neurologic deficits.

Random allocation was computer-generated centrally, independent of all investigators except for the statistician (J.B.C.), and was stratified according to participating center, with randomly permuted blocks of 2 to 8 infants. After written informed consent was obtained, infants were allocated randomly to receive twice-daily doses of either a 10-day tapering course of dexamethasone sodium phosphate (0.15 mg/kg per day for 3 days, 0.10 mg/kg per day for 3 days, 0.05 mg/kg per day for 2 days, and 0.02 mg/kg per day for 2 days; total of 0.89 mg/kg over 10 days) or an equivalent volume of 0.9% saline placebo. A repeat course of the same blinded drug was a therapeutic option for the attending clinicians. The dexamethasone preparation did not contain bisulfite preservative. Syringes were labeled identically within the pharmacy department of the center, concealing treatment allocation from the study site's investigators and the infant's caregivers. Use of open-label corticosteroids after randomization was discouraged but not prohibited; some infants might have received both a second course of treatment and open-label corticosteroids. Open-label corticosteroids were allowed after an initial survey of prospective collaborators during the design period (1998–1999) indicated that the study would not have been possible at all if open-label corticosteroids were banned.

Data were recorded on demographic variables and on ventilator settings and oxygen requirements at baseline and daily through the 10 days of treatment, with values recorded at the start of each 24-hour period, as were daily data on variables that could be affected by corticosteroids (such as blood glucose levels and blood pressure). Weight, length, and head circumference were measured, where possible, at the beginning and at the end of the 10-day treatment course. Weight, length, and head circumference measurements at the time of discharge were converted to z scores.[4] Oxygen and ventilator requirements at postmenstrual age of 36 weeks were recorded. BPD was defined as an oxygen requirement at 36 weeks and severe BPD as a requirement for >30% oxygen at 36 weeks. Target ranges for oximeters were not specified, because no uniform ranges were known to be superior. Infants were considered to have failed extubation over the 10-day period of treatment if they remained intubated throughout, died, or were withdrawn from the study. Mortality rates were determined to the last age known for each child, including after discharge home. The major cause of each death was determined from medical reports or autopsy findings, if available. Other complications that occurred at any time after randomization were documented and included infections, necrotizing enterocolitis, patent ductus arteriosus, retinopathy of prematurity, gastrointestinal hemorrhage or perforation, cardiac hypertrophy, and cranial ultrasound abnormalities.

The sample size calculation for the original trial was based on detecting an improvement in rates of survival free of major neurosensory disability from 50% to 60%, with a 2-sided, type I, error rate of 5% and 80% power, and required 814 infants to be recruited. Because the study was stopped early at 70 patients, we had 80% power to detect differences in proportions from 90% to 58%, anticipating that 90% of the placebo group would not be extubated successfully after 10 days.

Analysis was on an intention-to-treat basis and followed standard principles for RCTs. We present descrip-

tive comparisons of groups regarding baseline measures. Outcome comparisons were based on dichotomous end points and were assessed with χ^2 tests. Secondary analyses were adjusted for potential confounding attributable to baseline imbalance with logistic regression. Rates of change over 10 days of treatment were compared between groups with linear models fitted with generalized estimating equations, to allow for nonindependence of outcomes among patients. Data were analyzed with Stata, version 8.[5] The study was approved first by the Research and Ethics Committee at the Royal Women's Hospital (Melbourne, Australia) and then by the equivalent committees at each participating center.

RESULTS

The first infant was recruited into the DART study in March 2000. Recruitment ceased in October 2002, after 70 infants had been recruited from 11 centers in 3 countries. The number of infants recruited per center ranged from 2 to 19. A minority of potentially eligible infants were recruited into the study (Fig 1). In addition to the centers that actually recruited patients into the study, several other centers sought consent but failed to recruit. The study was stopped not only because <10% of the initial sample had been recruited after 2.5 years, making it unlikely that the total sample size of 814 would be achieved within a reasonable time, but also because the rate of recruitment had decreased, not increased, although more centers had entered the study since its inception.

The infants recruited into the study were at very high risk; they were quite immature (median gestational age: 25 completed weeks; interquartile range [IQR]: 24–26 weeks) and tiny at birth (median birth weight: 680 g; IQR: 605–782 g). Most had been intubated in the delivery room and had been receiving assisted ventilation since birth. Their mothers were mostly white and had been given steroids prenatally, and just over 50% of the infants had been delivered through cesarean section. The baseline characteristics were similar between the 35 infants allocated to the dexamethasone group and the 35 control infants (Table 1). A small proportion of infants in each group had been exposed to short-course, low-dose corticosteroids before trial entry, for purposes of blood pressure control. The prior corticosteroid was hydrocortisone for 9 of 11 infants; there was little difference in the doses of hydrocortisone between the groups ($P = .75$; median dose of hydrocortisone: dexamethasone group, 13.8 mg; placebo group, 15.3 mg). One infant was exposed to prednisolone eye drops and the other was given a total of 1.4 mg of prednisolone.

The median age at entry into the study was in the 4th week of life for both groups, but 2 children were entered on the 7th day of life, just before 168 hours of age, which was a protocol violation. One child was receiving nasal intermittent positive pressure ventilation in addition to nasal continuous positive airway pressure ventilation at entry, which was also a protocol violation. These infants were included in all outcome analyses, except for extubation for the child who was not intubated at the time of entry into the study. The age at entry, the type and duration of assisted ventilation, and the mean airway pressure and inspired oxygen concentration (F_{IO_2}) at the time of trial entry were similar for the 2 groups (Table 2).

Substantially more infants were extubated successfully by 10 days in the dexamethasone group than in the control group (odds ratio [OR]: 11.2; 95% confidence interval [CI]: 3.2–39.0; $P < .001$) and at other time points during the 10-day treatment course (Table 3 and Fig 2). The rate of extubation remained substantially higher after adjustment for mean airway pressure at randomization, gestational age, and gender with logistic regression (adjusted OR: 11.6; 95% CI: 3.2–42.7; $P < .001$). Age at randomization was not related substantially to the outcome of extubation ($P = .24$), and its inclusion in the logistic regression analyses did not alter the conclusions. Twelve of 21 dexamethasone-treated infants were reintubated after the initial extubation, compared with 1 of 4 placebo-treated infants. However, there was an important reduction in the duration of intubation after randomization in the dexamethasone group among those who survived to discharge home

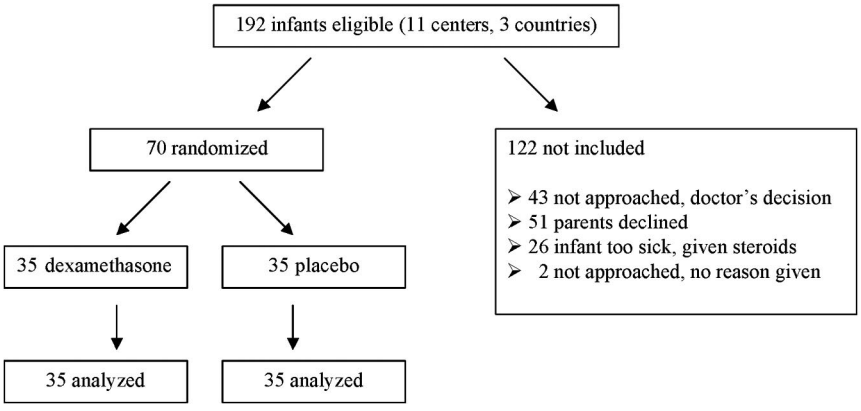

FIGURE 1
Diagram of patient flow.

TABLE 1 **Demographic Data Compared Between Groups**

Variable	Dexamethasone ($n = 35$)	Placebo ($n = 35$)
Mother		
Age at delivery, median (IQR), y	29 (22–34)	28 (25–34)
White, no. (%)	27 (77.1)	26 (74.3)
Smoking in pregnancy, no. (%)	13 (37.1)	7 (20.0)
Infertility treatment, no. (%)	7 (20.0)	4 (11.4)
Preeclampsia, no. (%)	5 (14.3)	5 (14.3)
Prenatal steroids, no. (%)	31 (88.6)	31 (88.6)
Chorioamnionitis requiring antibiotics, no. (%)	13 (37.1)	11 (31.4)
Cesarean delivery, no. (%)	16 (45.7)	22 (62.9)
Infant		
Born in level III center, no. (%)	33 (94.3)	31 (88.6)
Gestational age, median (IQR), completed wk	24 (24–25)	25 (24–26)
Birth weight, median (IQR), g	652 (590–730)	700 (612–790)
Male, no. (%)	16 (45.7)	21 (60.0)
Multiple birth, no. (%)	10 (28.6)	13 (37.1)
Apgar score at 1 min, median (IQR)	5 (4–6)	5 (3, 6)
Apgar score at 5 min, median (IQR)	7 (7–8)	7 (6, 9)
Intubated in delivery room, no. (%)	33 (94.3)	32 (91.4)
Maximal appropriate pressure in first 1 wk of life, median (IQR), cm H_2O	20 (18–23)	20 (19–24)
Maximal appropriate F_{IO_2} in first 1 wk of life, median (IQR), %	50 (35–70)	50 (33–61)
Surfactant, no. (%)	33 (94.3)	34 (97.1)
Before randomization		
Any corticosteroids received, no. (%)	6 (17.1)	5 (14.3)
PDA, no. (%)	26 (74.3)	26 (74.3)
PDA requiring surgery, no. (%)	5 (14.3)	3 (8.6)
Air leak, no. (%)	5 (14.3)	6 (17.1)

Data are number (percentage) unless otherwise specified. PDA indicates patent ductus arteriosus.

TABLE 2 **Infant Characteristics at the Time of Randomization**

Variable	Dexamethasone ($n = 35$)	Placebo ($n = 35$)
Age, median (IQR), d[a]	23 (20–34)	22 (13–28)
Type of ventilation[b]		
HFV, no. (%)	5 (14.3)	8 (22.9)
IPPV, no. (%)	30 (85.7)	26 (74.3)
Duration of IPPV, median (IQR), d	19 (10–24)	14 (6–24)
Duration of HFV, median (IQR), d	1 (0–11)	2 (0–11)
Mean airway pressure, median (IQR), cm H_2O	10.0 (8.4–11.5)	10.0 (9.0–11.4)
F_{IO_2}, median (IQR), %	47 (40–55)	45 (33–60)

Data are number (percentage) unless otherwise specified. IPPV indicates intermittent positive pressure ventilation; HFV, high-frequency ventilation.

[a] Two children were 6 days of age when entered into the study (1 in each group), which was a protocol violation.

[b] One child in the placebo group was receiving nasal intermittent positive pressure ventilation at the time of randomization, which was a protocol violation.

(dexamethasone group: median: 14 days; IQR: 5.5–21.5 days; placebo group: median: 21 days; IQR: 9–35 days; $P = .03$). The durations of hospitalization after randomization among those who survived to discharge home were similar between groups (dexamethasone group: median: 112 days; IQR: 104–128 days; placebo group: median: 116 days; IQR: 105–129 days; $P = .88$).

There was no clear-cut difference in the mortality rates between the groups (OR: 0.52; 95% CI: 0.14–1.95; $P = .33$) (Table 3), and there was little change after adjustment for confounding with logistic regression (adjusted OR: 0.54; 95% CI: 0.13–2.26; $P = .40$). Of the 11 infants who died, 3 died during the first 10-day course of the DART study, 5 died after the 10-day course but before discharge, and 3 died after discharge home. In the dexamethasone group, there was 1 death resulting from BPD, 2 deaths resulting from sepsis, and 1 sudden unexplained death after discharge home. In the placebo group, there were 4 deaths resulting from BPD, 2 deaths resulting from sepsis, and 1 death resulting from acute respiratory failure 5 days after initiation of therapy.

There was little difference in the rates of BPD among infants who survived to a corrected age of 36 weeks (OR: 0.58; 95% CI: 0.08–3.32; $P = .71$; adjusted OR: 0.69; 95% CI: 0.13–3.54) (Table 3), in the rates of severe BPD, or in the proportions of infants who went home with oxygen (Table 3). The combined rates of death or BPD, death or severe BPD, or death or home oxygen were not substantially different between the 2 groups (Table 3).

Over the 10 days of the first treatment course, the mean airway pressure, the peak inspired pressure, and the F_{IO_2} all decreased significantly in the dexamethasone group, compared with the placebo group (Fig 3). There were no substantial differences between the groups in rates of change or levels of blood glucose concentrations or in any blood pressure measurements during the 10 days of treatment ($P > .23$) (Fig 4).

The rates of requiring a second course of treatment within the DART study, open-label use of corticoste-

TABLE 3 **Major Infant Outcomes**

Variable	No. (%)		*P*
	Dexamethasone ($n = 35$)	Placebo ($n = 35$)	
Failure to extubate			
By day 3[a]	23 (65.7)	33/34 (97.1)	<.01
By day 7[b]	17 (48.6)	30/34 (88.2)	<.01
By day 10[c]	14 (40.0)	30/34 (88.2)	<.01
Death			
To discharge	3 (8.6)	5 (14.3)	.45
After discharge	1 (2.9)	2 (5.7)	.56
Any time before follow-up evaluation	4 (11.4)	7 (20.0)	.32
BPD at 36 wk[d]	28/33 (84.9)	29/32 (90.6)	.48
Severe BPD (>30% oxygen) at 36 wk[d]	10/33 (30.3)	13/32 (40.6)	.38
Home with oxygen	15 (42.9)	16 (45.7)	.81
Death or BPD at 36 wk	30 (85.7)	32 (91.4)	.45
Death or severe BPD at 36 wk	12 (34.3)	16 (45.7)	.33
Death or home with oxygen	18 (51.4)	21 (60.0)	.46

[a] Includes 1 death in the placebo group, 1 death in the dexamethasone group, and 1 withdrawal from the study in the placebo group.
[b] Includes 1 additional death in the placebo group and 5 additional withdrawals in the placebo group.
[c] Includes 1 additional withdrawal in the placebo group.
[d] Among those who survived to 36 weeks.

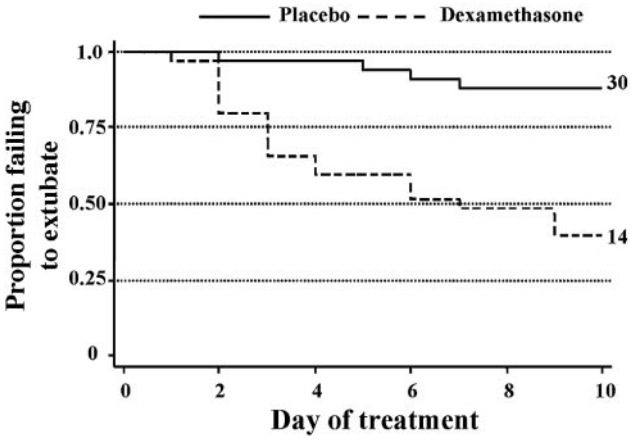

FIGURE 2
Kaplan-Meier survival curve for proportion failing to extubate over the 10 days of treatment.

roids, infections of various types, necrotizing enterocolitis, patent ductus arteriosus, or severe retinopathy of prematurity were similar for the 2 groups (Table 4). No infant had gut perforation or gastrointestinal hemorrhage in either group. One child in the placebo group, but none in the dexamethasone group, had cardiac hypertrophy. Few infants in either group had major cranial ultrasound abnormalities after study entry (Table 4).

The weight change over the 10 days of treatment was lower in the dexamethasone group (mean increase over 10 days: dexamethasone group: 76 g; SD: 16 g; $n = 30$; placebo group: 152 g; SD: 22 g; $n = 23$; mean difference: −76 g; 95% CI: −129 to −23 g; $P = .006$). There were similar trends in length and head circumference that were relatively imprecise (mean increase in length over 10 days: dexamethasone group: 1.14 cm; SD: 0.28 cm; $n = 25$; placebo group: 1.75 cm; SD: 0.31 cm; $n = 21$; mean difference: −0.61 cm; 95% CI: −1.45 to 0.22 cm; $P = .15$; mean increase in head circumference over 10 days: dexamethasone group: 0.76 cm; SD: 0.15 cm; $n = 25$; placebo group: 1.27 cm; SD: 0.21 cm; $n = 21$; mean difference: −0.50 cm; 95% CI: −1.01 to 0.01 cm; $P = .054$). By the time of discharge, the *z* scores for weight, length, and head circumference were not substantially different between the groups (mean difference in *z* scores: weight: −0.02; 95% CI: −0.67 to 0.62; length: −0.50; 95% CI: −1.43 to 0.42; head circumference: −0.13; 95% CI: −0.89 to 0.62).

The volumes of study medication given during the first course of treatment were similar in the 2 groups (dexamethasone group: median: 8.8 mL/kg; IQR: 8.4–9.1 mL/kg; placebo group: median: 8.8 mL/kg; IQR: 7.7–9.1 mL/kg). The median dose of dexamethasone given during the first course was 0.88 mg/kg (IQR: 0.84–0.91 mg/kg). Among the few infants treated with a second course, the volumes were similar in the 2 groups (dexamethasone group: median: 8.7 mL/kg; IQR: 8.0–9.1 mL/kg; $n = 10$; placebo group: median: 8.9 mL/kg; IQR: 8.7–9.4 mL/kg; $n = 11$). The doses of open-label corticosteroids, in dexamethasone-equivalent doses, were similar between the 2 groups among those so treated (dexamethasone group: median: 3.9 mg/kg; IQR: 2.0–8.4 mg/kg; $n = 8$; placebo group: median: 2.3 mg/kg; IQR: 1.5–6.4 mg/kg; $n = 13$; $P = .51$). For 1 infant in each group, dosages of open-label corticosteroids were not recorded. Among those so treated, the doses of open-label dexamethasone were much higher than the doses received by those in the dexamethasone group during the first or second course of treatment.

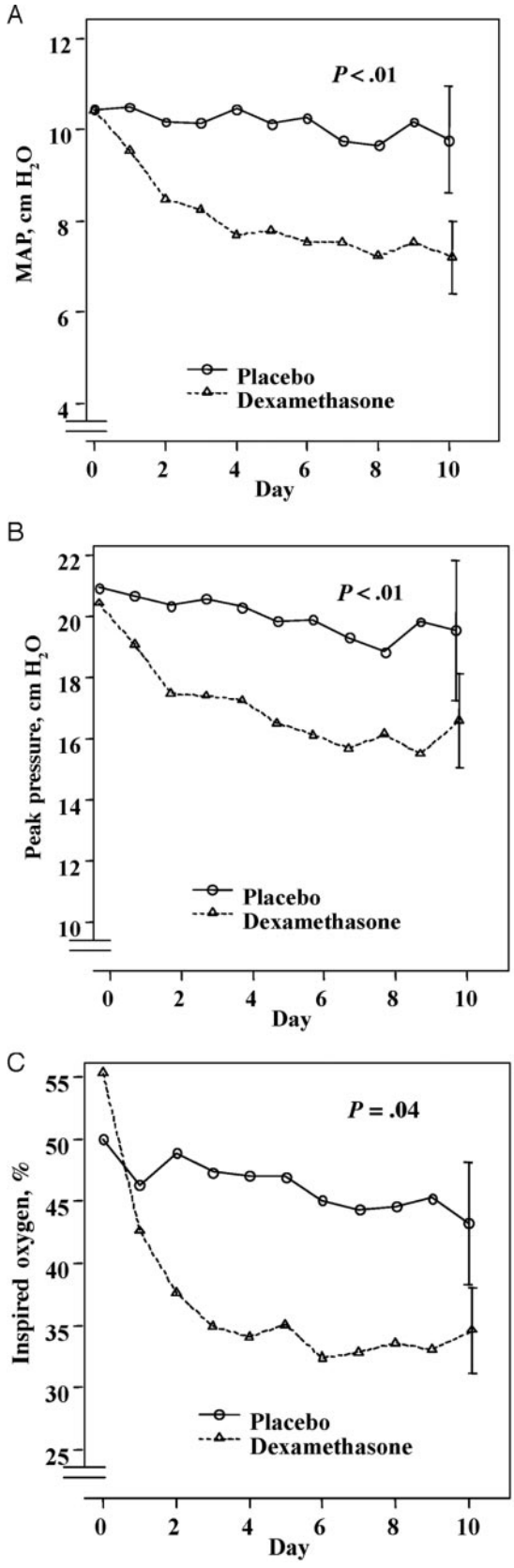

FIGURE 3
Changes over time in mean values for mean airway pressure (MAP) (A), peak pressure (B), and F_{IO_2} (C), with 95% CIs at day 10. *P* values are shown for differences between groups in rate of linear change over 10 days of treatment.

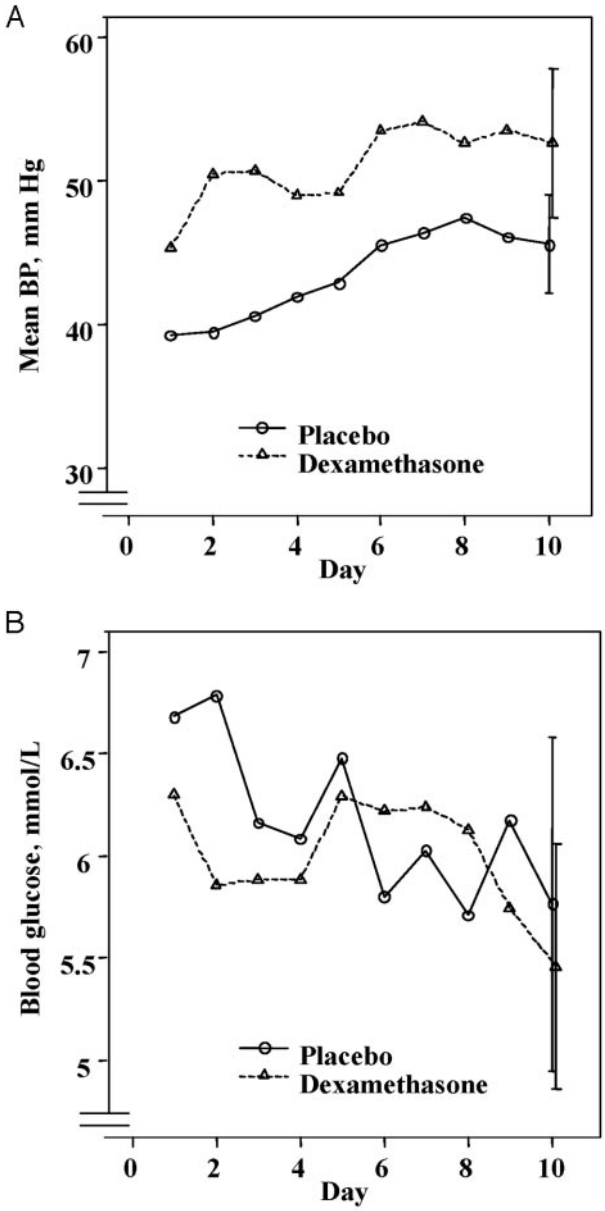

FIGURE 4
Changes over time in mean values for mean blood pressure (BP) (A) and blood glucose concentration (B), with 95% CIs at day 10.

DISCUSSION

Low-dose dexamethasone after the first 1 week of life clearly facilitated extubation among ventilator-dependent very preterm or ELBW infants, was accompanied by acute improvements in ventilation and oxygen requirements, and resulted in a shorter duration of intubation. There was no increase in any of the short-term complications associated with higher doses or earlier courses of dexamethasone, such as gastrointestinal hemorrhage or intestinal perforation, and there were no obvious effects on blood glucose concentrations or blood pressure. There were no substantial effects on rates of death or BPD. There was a small reduction in the dexa-

TABLE 4 **Rates of Other Complications After Randomization**

	No. (%)		*P*
	Dexamethasone Group ($n = 35$)	Placebo Group ($n = 35$)	
Treatment with second course within DART study	10 (28.6)	11 (31.4)	.79
Late rescue with systemic corticosteroid therapy	9 (25.7)	14 (40.0)	.20
Any infection	27 (77.1)	28 (80.0)	.77
Blood culture-proven sepsis	15/34 (44.1)	18 (51.4)	.54
Definite bacterial infection	18/34 (52.9)	21 (60.0)	.55
Fungal infections	3/30 (10.0)	0/32 (0)	.07
Viral infections	3 (8.6)	3/34 (8.8)	.97
NEC	2 (5.7)	2 (5.7)	1.00
PDA	12 (34.3)	15 (42.9)	.46
Treated with indomethacin	12	15	
Treated with surgery	5	2	
Severe ROP	16/32 (50.0)	9/30 (30.0)	.11
ROP requiring treatment[a]	8/31 (25.8)	3/30 (10.0)	.11
Major cranial ultrasound abnormalities			
Intraparenchymal hemorrhage	0/30 (0.0)	1/29 (3.5)	.30
Cystic PVL	1/30 (3.3)	2/29 (6.9)	.53

NEC indicates necrotizing enterocolitis; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; PVL, periventricular leukomalacia.
[a] Laser photocoagulation or cryotherapy.

methasone group in the change in weight over the 10 days of treatment, of marginal clinical importance.

Previous RCTs of steroid use among infants in which treatment was started after the first 1 week of life, for which data were incorporated into the existing Cochrane reviews,[2,3] used protocols with much higher doses of dexamethasone than those in our study, ranging from at least 1.5 mg/kg in pulses repeated every 10 days[6] up to 8.0 mg/kg,[7] although none of the studies reported the doses actually received by infants. The total dose for 1 course in our study was approximately one tenth that of the 42-day course in the study by Cummings et al,[7] ie, 8 mg/kg, the dose that was given most often to ventilator-dependent infants of similar birth weight, gestational age, and postnatal age in Victoria in the early 1990s.[8] We have reported not only the dose given during the study itself but also the dose of open-label steroids given outside the trial, which, when given to individuals, was usually much higher than the dose during the 10-day course of the study. However, only a minority of infants received open-label steroids.

Recently Walther et al[9] reported the results of a RCT of dexamethasone with a total dose of 1.9 mg/kg over 14 days. Although the main aim of their study was to describe endocrine effects of steroids, those authors also reported a higher rate of successful extubation by day 14 in the steroid group (13 of 17 dexamethasone-treated patients vs 8 of 19 placebo-treated patients). There are some major differences between the study by Walther et al[9] and our study. In addition to the total dose of dexamethasone being more than double that in our study, the infants in their study were much heavier (mean birth weight: 1012 g) and mature (mean gestational age: 28.5 weeks) at birth than were those in our study (mean birth weight: 701 g; gestational age: 24.9 weeks). In addition, the infants in their study were all between 7 and 14 days of age at enrollment, compared with only 23% of our infants (16 of 70 infants, with the rest being older). Also, the infants in their study had less severe lung disease at the time of entry into the study, with mean airway pressure of ~7 cm H_2O and mean F_{IO_2} of 41%, compared with mean airway pressure of 10.4 cm H_2O and mean F_{IO_2} of 47% in our study.

The observation that the duration of intubation was significantly shorter suggests a potential economic benefit of corticosteroids, because intubated time is more expensive than nonintubated time in the nursery.[10] The study was underpowered to detect important reductions in mortality or BPD rates. However, because open-label corticosteroids were allowed and were prescribed more often in the control group, any potential beneficial effects of corticosteroids in the initial treatment phase on mortality and BPD rates were likely diluted.

Some preparations of dexamethasone contain sulfite preservatives, which may have adverse neurologic effects.[11] We chose dexamethasone free of preservative, to avoid any confounding from sulfite preservatives.

Hyperglycemia and hypertension are reported to occur more frequently among infants treated with steroids after the first 1 week of life.[2,3] We compared blood glucose and blood pressure measurements as continuous variables, because this is a more-sensitive method of detecting any effects of low-dose dexamethasone therapy on these variables. We found no meaningful differences in the distributions of blood glucose or blood pressure measurements between the groups, and we conclude that there is little likelihood that low-dose dexamethasone therapy causes more hyperglycemia or

hypertension among infants who are already very unwell and for whom these problems are more likely.

There are 2 major complications that caused neonatologists to reduce postnatal corticosteroid use, ie, gut perforation and cerebral palsy. Gut perforation was reported in RCTs of corticosteroids used predominantly in the first 1 week of life,[1] rather than later, and was responsible for early termination of several RCTs,[12,13] which has been considered unfortunate by some observers.[14] Interestingly, in one study[12] in which the rate of spontaneous gut perforation was significantly higher with dexamethasone in the first 2 weeks of life but not in the study overall, the dose of dexamethasone used was identical to that in our study. Indeed, we based our dose of dexamethasone on that study, but we found no cases of gut perforation in either group; possibly this reflects differences in gut maturity among our infants, who were of advanced postnatal age, compared with those in the study by Stark et al,[12] in which treatment started on day 1.

Cerebral palsy was also confined largely to RCTs in which treatment was started in the first 1 week of life.[15] However, cerebral palsy is just one long-term problem that confronts clinicians considering corticosteroid therapy for ventilator-dependent infants; death is also a possibility. The importance of considering both death and cerebral palsy as possible outcomes is best illustrated in the one study in which treatment was started after the first 1 week of life, in which the cerebral palsy rate was significantly higher with corticosteroids.[16] In that study, the increased rate of cerebral palsy was offset by a higher mortality rate in the control group, and thus the rates of the combined outcome of death or survival with cerebral palsy were almost identical in the 2 groups (corticosteroid group: 33.3%, 19 of 57 patients; control group: 32.8%, 20 of 61 patients). In addition, the corticosteroid effect on the rate of death or survival with cerebral palsy decreases with increasing risk of BPD; at risks of BPD of >65%, there is evidence from reported RCTs that corticosteroids reduce substantially the composite outcome of death or cerebral palsy.[15] The infants in our study, with very high rates of BPD, clearly were within the range of BPD rates where a net benefit from steroids in the rate of survival free of cerebral palsy would be expected. We need to ensure that the lack of acute side effects with low-dose dexamethasone is accompanied by a lack of adverse neurologic outcomes, which have accompanied higher doses. We will continue to monitor the surviving children and to assess their neurologic condition and other health status at ≥2 years of age. Unfortunately, because the study was stopped with <10% of the projected sample size recruited, the chance of detecting any clear-cut effect on long-term outcomes is small.

Since the controversy regarding adverse effects of corticosteroids, many experts have recommended lower doses on the basis of anecdotal evidence, rather than data from RCTs. Our study provides the first evidence that a low dose of dexamethasone facilitates extubation, reduces oxygen and ventilator requirements, and shortens the duration of intubation. Combined with evidence that the adverse effects of corticosteroids are confined largely to treatment in the first 1 week of life and to high doses,[15] our study helps reopen the debate on corticosteroids and supports future RCTs of low-dose dexamethasone designed to improve long-term rates of survival free of disability among infants beyond the first 1 week of life. We hope that such a definitive trial may still be possible, to provide a clear answer to guide the clinical care of chronically ventilator-dependent infants.

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REFERENCES

1. Halliday HL, Ehrenkranz RA, Doyle LW. Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants [Cochrane review]. In: *The Cochrane Library*. Issue 1. Chichester, United Kingdom: John Wiley and Sons; 2004
2. Halliday HL, Ehrenkranz RA, Doyle LW. Moderately early (7–14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants [Cochrane review]. In: *The*

Cochrane Library. Issue 1. Chichester, United Kingdom: John Wiley and Sons; 2004
3. Halliday HL, Ehrenkranz RA, Doyle LW. Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants [Cochrane review]. In: *The Cochrane Library*. Issue 1. Chichester, United Kingdom: John Wiley and Sons; 2004
4. Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Stat Med.* 1998;17:407–429
5. Stata Corp. *Intercooled Stata 8.0 for Windows*. College Station, TX: Stata Corp; 2003
6. Brozanski BS, Jones JG, Gilmour CH, et al. Effect of pulse dexamethasone therapy on the incidence and severity of chronic lung disease in the very low birth weight infant. *J Pediatr.* 1995;126:769–776
7. 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;320:1505–1510
8. Victorian Infant Collaborative Study Group. Postnatal corticosteroids and sensorineural outcome at 5 years of age. *J Paediatr Child Health.* 2000;36:256–261
9. Walther FJ, Findlay RD, Durand M. Adrenal suppression and extubation rate after moderately early low-dose dexamethasone therapy in very preterm infants. *Early Hum Dev.* 2003;74:37–45
10. Kitchen WH, Bowman E, Callanan C, et al. The cost of improving the outcome for infants of birthweight 500–999 g in Victoria: the Victorian Infant Collaborative Study Group. *J Paediatr Child Health.* 1993;29:56–62
11. Baud O, Laudenbach V, Evrard P, Gressens P. Neurotoxic effects of fluorinated glucocorticoid preparations on the developing mouse brain: role of preservatives. *Pediatr Res.* 2001;50:706–711
12. Stark AR, Carlo WA, Tyson JE, et al. Adverse effects of early dexamethasone in extremely-low-birth-weight infants: National Institute of Child Health and Human Development Neonatal Research Network. *N Engl J Med.* 2001;344:95–101
13. Watterberg KL, Gerdes JS, Cole CH, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. *Pediatrics.* 2004;114:1649–1657
14. Roberts RS. Early closure of the Watterberg trial. *Pediatrics.* 2004;114:1670–1671
15. 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 of chronic lung disease. *Pediatrics.* 2005;115:655–661
16. O'Shea TM, Kothadia JM, Klinepeter KL, et al. 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: outcome of study participants at 1-year adjusted age. *Pediatrics.* 1999;104:15–21

GANGSTA, IN FRENCH

"One of the striking things about the scenes from France is how thoroughly the rioters have assimilated hip-hop and rap culture. It's not only that they use the same hand gestures as American rappers, wear the same clothes and necklaces, play the same video games and sit with the same sorts of car stereos at full blast. It's that they seem to have adopted the same poses of exaggerated manhood, the same attitudes about women, money and the police. They seem to have replicated the same sort of gang culture, the same romantic visions of gunslinging drug dealers. In a globalized age it's perhaps inevitable that the culture of resistance gets globalized, too. What we are seeing is what Mark Lilla of the University of Chicago calls a universal culture of the wretched of the earth. The images, modes and attitudes of hip-hop and gangsta rap are so powerful they are having a hegemonic effect across the globe. American ghetto life, at least as portrayed in rap videos, now defines for the young, poor and disaffected what it means to be oppressed. Gangsta resistance is the most compelling model for how to rebel against that oppression."

Brooks D. *New York Times*. November 10, 2005
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