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Long-Term Effects of Caffeine Therapy for Apnea of Prematurity

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ABSTRACT

BACKGROUND

Methylxanthine therapy is commonly used for apnea of prematurity but in the absence of adequate data on its efficacy and safety. It is uncertain whether methylxanthines have long-term effects on neurodevelopment and growth.

METHODS

We randomly assigned 2006 infants with birth weights of 500 to 1250 g to receive either caffeine or placebo until therapy for apnea of prematurity was no longer needed. The primary outcome was a composite of death, cerebral palsy, cognitive delay (defined as a Mental Development Index score of <85 on the Bayley Scales of Infant Development), deafness, or blindness at a corrected age of 18 to 21 months.

RESULTS

Of the 937 infants assigned to caffeine for whom adequate data on the primary outcome were available, 377 (40.2%) died or survived with a neurodevelopmental disability, as compared with 431 of the 932 infants (46.2%) assigned to placebo for whom adequate data on the primary outcome were available (odds ratio adjusted for center, 0.77; 95% confidence interval [CI], 0.64 to 0.93; P=0.008). Treatment with caffeine as compared with placebo reduced the incidence of cerebral palsy (4.4% vs. 7.3%; adjusted odds ratio, 0.58; 95% CI, 0.39 to 0.87; P=0.009) and of cognitive delay (33.8% vs. 38.3%; adjusted odds ratio, 0.81; 95% CI, 0.66 to 0.99; P=0.04). The rates of death, deafness, and blindness and the mean percentiles for height, weight, and head circumference at follow-up did not differ significantly between the two groups.

CONCLUSIONS

Caffeine therapy for apnea of prematurity improves the rate of survival without neurodevelopmental disability at 18 to 21 months in infants with very low birth weight. (ClinicalTrials.gov number, NCT00182312.)

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*Members of the Caffeine for Apnea of Prematurity Trial Group are listed in the Appendix.

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Apnea of prematurity is one of the most common reasons for the initiation of drug therapy in neonatal medicine.[1] The methylxanthines — aminophylline, theophylline, and caffeine — have been administered to preterm infants as respiratory stimulants for more than 30 years.[2] Caffeine is presently one of the 10 most frequently prescribed medications in neonatal intensive care.[1] Despite their widespread use, caffeine and the other methylxanthines have been evaluated in only a few small, short-term studies.[3-5] It has been uncertain whether these drugs might adversely affect the development of the preterm brain and of other organs. Methylxanthines are inhibitors of adenosine receptors,[6] and adenosine has been shown to protect the brain from energy failure and cell death during experimental hypoxia and ischemia in various animal models.[7,8]

We conducted this large, international, randomized, placebo-controlled trial of caffeine to study the short- and long-term efficacy and safety of methylxanthine therapy for apnea of prematurity in infants with very low birth weight. We previously examined the short-term outcomes of the study participants before their first discharge home and found that caffeine reduced the rate of bronchopulmonary dysplasia.[9] However, information on short-term outcomes is insufficient to assess the overall benefits and risks of common neonatal interventions.[10-12] The primary goal of this study was to determine whether caffeine therapy for apnea of prematurity alters the rate of survival without neurodevelopmental disability at a corrected age of 18 to 21 months.

Methods

Initial Study Period

Infants with a birth weight of 500 to 1250 g were eligible for this study if their clinicians considered them to be candidates for methylxanthine therapy during the first 10 days of life. The indications for the use of methylxanthines included the prevention or treatment of apnea and the facilitation of the removal of an endotracheal tube. The exclusion criteria, randomization procedures, use of study drug, and short-term outcomes have been reported previously.[9] In summary, 2006 infants were enrolled between October 1999 and October 2004 and randomly assigned to receive caffeine citrate or normal saline placebo. Randomization was stratified according to the study center. Caffeine citrate for injection was supplied by Sabex. In the single study site in the United States, Cafcit (Roxane Laboratories) was used. Neither Sabex nor Roxane Laboratories had any role in the design of the study.

A loading dose of 20 mg of caffeine citrate per kilogram of body weight was followed by a daily maintenance dose of 5 mg per kilogram. If apneas persisted, the daily maintenance dose could be increased to a maximum of 10 mg of caffeine citrate per kilogram. The drug was monitored according to its clinical effect only.[13] Infants received their first dose of study drug at a median age of 3 days and were weaned off the study drug before reaching a median postmenstrual age of 35 weeks. One hundred ninety (9.5%) of the study participants received one or more doses of open-label methylxanthines.[9]

The research ethics boards of all clinical centers approved the protocol. Written informed consent was obtained from a parent or guardian of each infant. An investigational new drug application was filed with Health Canada. Clinical trial notification applications were filed in Australia. Appropriate regulatory approvals were obtained elsewhere.

An external safety monitoring committee reviewed the study data every 4 to 6 months during the enrollment phase. Only this committee and the selected study pharmacists had access to the prespecified and randomly generated sequence of treatment-group assignments. After a recommendation by the safety monitoring committee, the steering committee agreed to analyze the protocol-specified short-term neonatal outcomes after the completion of the initial hospitalization of the study infants. We previously reported these short-term results, including the finding that caffeine decreased the rate of bronchopulmonary dysplasia and also temporarily reduced weight gain.[9]

Primary Outcome

The primary outcome was death before a corrected age of 18 months or survival with one or more of the following: cerebral palsy, cognitive delay, hearing loss requiring amplification, and bilateral blindness. Cerebral palsy was diagnosed if the child had a nonprogressive motor impairment characterized by abnormal muscle tone and decreased range or control of movements. The level of gross motor function was determined with the use of the Gross Motor Function Classification

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System.[14] A normal level of 0 is assigned if the child is able to walk 10 steps independently at 18 months. Levels between 3 and 5 (the highest possible score) indicate progressively more serious limitations of gross motor function. Cognitive delay was defined as a Mental Development Index score of less than 85 (1 SD below the mean of 100) on the Bayley Scales of Infant Development II.[15] The score was assumed to be less than 85 if the child could not be tested because of severe developmental delay. Audiometry was performed to determine the presence or absence of hearing loss. Blindness was defined as a corrected visual acuity less than 20/200. Follow-up was targeted for a corrected age of 18 months, but the protocol allowed a window of 18 to 21 months (12 to 21 months for audiologic testing). Efforts to conduct assessments continued beyond a corrected age of 21 months when necessary.

Documentation of the presence of the composite primary outcome required confirmation that the infant had died or had survived with one or more of the four types of disability. Documentation of the absence of the composite primary outcome required confirmation that the infant had survived without any disability. Since a single missing component of the follow-up assessment could result in a designation of "missing" for the primary outcome, we developed a priori criteria to determine what constituted "adequate evidence" for the presence or absence of each component of the primary outcome. These criteria required an in-person assessment by an appropriate health professional and the successful determination of the Mental Development Index score. In cases in which it was difficult to perform audiometry, deafness requiring amplification of hearing was assumed to be absent if there was no indication of hearing loss during the clinical examination and the psychometric test.

OTHER OUTCOMES

Height, weight, and head circumference were measured and individual percentiles were computed in the data center according to the corrected age at the time of the follow-up assessment.[16] Data on retinopathy of prematurity were incomplete at the end of the initial hospitalization because the results of retinal examinations that were performed after transfer from the initial study center to another hospital were collected only during the 18-month follow-up visit.[9] Infants were screened for retinopathy according to local nursery protocols. All stages of retinopathy were recorded according to the international classification.[17,18]

STATISTICAL ANALYSIS

On the assumption of an incidence of 20% for the primary outcome, we needed 1000 infants in each group for the study to have a statistical power of 80% to detect a 25% relative reduction in the risk of death or disability. Since randomization was stratified according to study center, the analyses of the primary outcome and of all other dichotomous outcomes were adjusted with the use of a logistic-regression model that included terms for treatment and center (results from smaller centers were combined). The regression coefficient associated with treatment in the fitted model yielded a point estimate and a 95% confidence interval for the treatment effect expressed as an odds ratio. The quotient of the estimated coefficient and its standard error was used as a z-test statistic for the null hypothesis of no treatment effect. The mean differences between the two groups for quantitative outcomes were adjusted according to center with the use of multiple linear regression. All P values are two-sided and have not been adjusted for multiple testing.

RESULTS

STUDY PARTICIPANTS

The numbers of infants who were screened for the study, the numbers randomly assigned to receive caffeine citrate or placebo, and the numbers assessed at a corrected age of 18 to 21 months are shown in Figure 1. Follow-up assessments began on August 8, 2001, and ended on January 18, 2007. Adequate data for an analysis of the primary composite outcome were available for 1869 (93.2%) of the infants who were enrolled in the study.

The characteristics of these 1869 children were similar in the two groups at birth and at the time of randomization (Table 1). The frequency of bronchopulmonary dysplasia was reduced by caffeine therapy. The children's ages at follow-up and the characteristics of their maternal caregivers were similar in the two groups (Table 1).

PRIMARY OUTCOME

The results for the primary composite outcome and for its components are shown in Table 2. Caffeine significantly improved the rate of survival without neurodevelopmental disability at a corrected age of 18 to 21 months. Of the 937 in-

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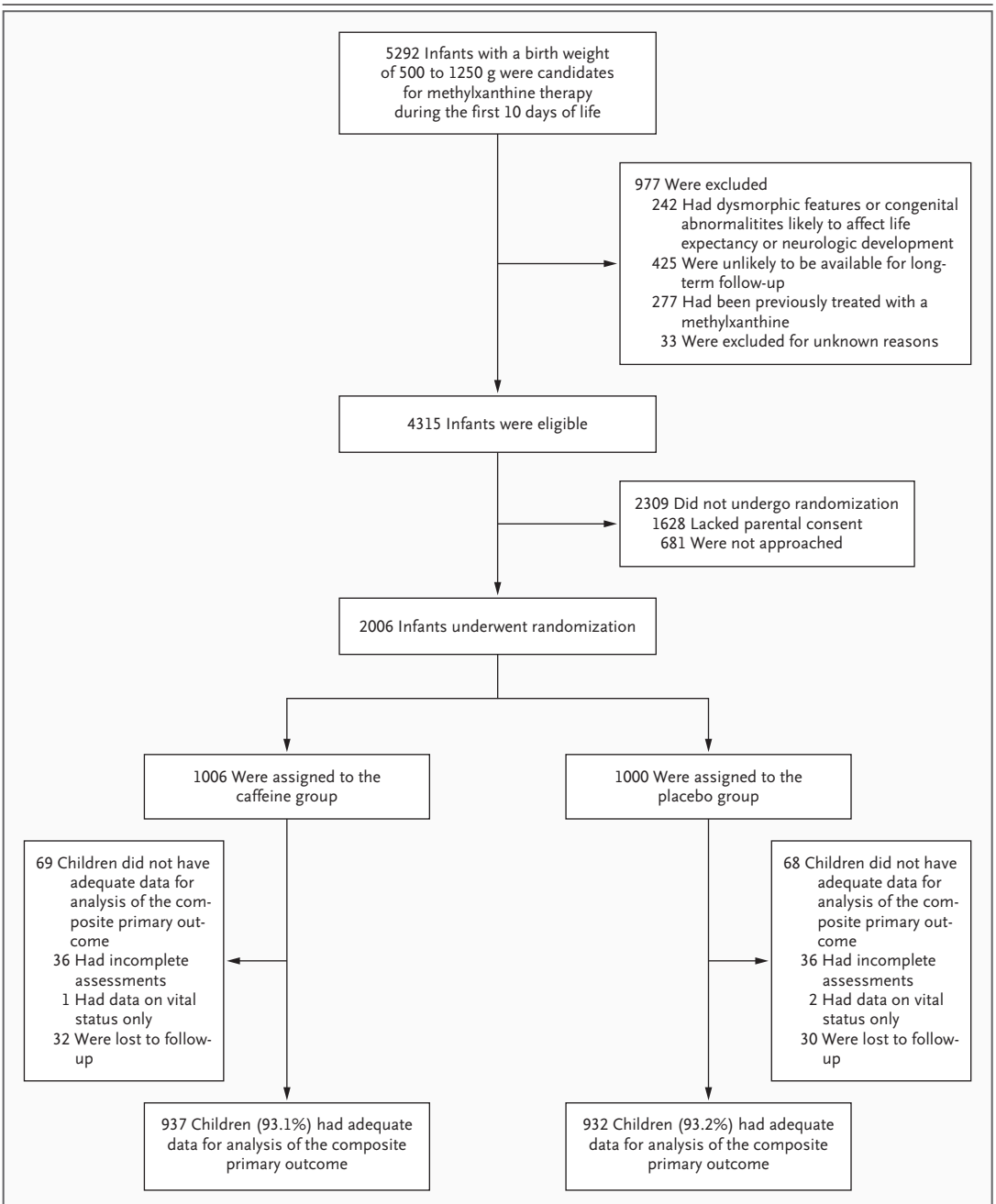

Figure 1. Numbers of Infants Who Were Eligible for the Study, Randomly Assigned to Receive Caffeine Citrate or Placebo, and Followed to a Corrected Age of 18 to 21 Months.

fants assigned to caffeine for whom adequate data on the primary outcome were available, 377 (40.2%) died or survived with a neurodevelopmental disability, as compared with 431 of the 932 infants (46.2%) assigned to placebo for whom adequate data on the primary outcome were available (odds ratio adjusted for center, 0.77; 95% confidence interval [CI], 0.64 to 0.93; P=0.008). The number of infants who would need to be treated with caffeine to prevent one adverse outcome was 16 (95% CI, 9 to 56). There was no significant difference between the two groups in the rate of death before the age of 18 months. The rates of deafness and bilateral blindness were low and likewise not significantly different between the two groups. However, treatment with caffeine as compared

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Table 1. Characteristics of the Children and Their Families.*

Characteristic	Caffeine Group (N=937)	Placebo Group (N=932)	P Value
Infants			
Birth weight — g	961±186	952±181	0.29
Gestational age — wk	27.4±1.8	27.3±1.8	0.45
Female sex — no. (%)	468 (49.9)	435 (46.7)	0.17
Birth weight <10th percentile for gestational age — no. (%)†	149 (15.9)	148 (15.9)	1.00
Exposure to antenatal corticosteroids — no. (%)	829 (88.5)	817 (87.7)	0.62
Singleton birth — no. (%)	672 (71.7)	668 (71.7)	1.00
Age at randomization — days			0.09
Median	3	3	
Interquartile range	2–5	1–5	
Outcome before first discharge home — no. (%)			
Death	52 (5.5)	55 (5.9)	0.77
Bronchopulmonary dysplasia‡	326 (36.4)	428 (48.3)	<0.001
Brain injury§	116 (12.8)	126 (14.0)	0.49
Corrected age of surviving children at follow-up — mo¶			0.11
Median	18.8	18.7	
Interquartile range	18.3–19.9	18.2–19.7	
Maternal caregivers at follow-up‖			
Relationship to child — no. (%)			0.43
Biologic mother	847 (96.8)	845 (97.2)	
Adoptive mother	5 (0.6)	1 (0.1)	
Foster mother	10 (1.1)	11 (1.3)	
Other or unknown	13 (1.5)	12 (1.4)	
Race or ethnic group — no. (%)			0.63
White	703 (80.3)	687 (79.1)	
Black	60 (6.9)	55 (6.3)	
Asian	68 (7.8)	72 (8.3)	
Other or unknown	44 (5.0)	55 (6.3)	
Level of education — no. (%)			0.51
Did not finish high school	194 (22.2)	188 (21.6)	
Completed high school or equivalent	222 (25.4)	233 (26.8)	
Some college or university	454 (51.9)	438 (50.4)	
Unknown	5 (0.6)	10 (1.2)	
Single parent — no. (%)	86 (9.8)	77 (8.9)	0.56
Employed person in the household — no. (%)	766 (87.5)	761 (87.6)	0.94

* These data are for the 1869 children with adequate information for the ascertainment of the composite primary outcome at a corrected age of 18 to 21 months. Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding.

† The 10th percentile for gestational age in a normal population was reported by Kramer et al.[19]

‡ Bronchopulmonary dysplasia was defined by the use of supplemental oxygen at a postmenstrual age of 36 weeks. This outcome was for infants who were alive at a postmenstrual age of 36 weeks (895 in the caffeine group and 887 in the placebo group).

§ Brain injury was defined as the finding of any of the following during cranial ultrasound examinations: intraparenchymal echodense lesions, cystic periventricular leukomalacia, porencephalic cysts, and ventriculomegaly with or without intraventricular hemorrhage. This outcome is for infants who underwent cranial ultrasonography at least once after randomization (903 in the caffeine group and 899 in the placebo group).

¶ These data exclude 62 children in the caffeine group and 63 children in the placebo group who died before a corrected age of 18 months.

‖ These data exclude the maternal caregivers of 62 children in the caffeine group and 63 children in the placebo group who died before a corrected age of 18 months. Race or ethnic group was self-reported.

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Table 2. Primary Outcome of Death or Neurodevelopmental Disability.

Outcome	Caffeine Group	Placebo Group	Unadjusted Odds Ratio	Odds Ratio Adjusted for Center (95% CI)	P Value	Odds Ratio Adjusted for Center and Patient Characteristics (95% CI)*
	no./total no. (%)					
Composite						
Death or disability	377/937 (40.2)	431/932 (46.2)	0.78	0.77 (0.64–0.93)	0.008	0.79 (0.65–0.96)
Components						
Death before 18 mo†	62/974 (6.4)	63/970 (6.5)	0.98	0.97 (0.67–1.40)	0.87	0.99 (0.65–1.50)
Cerebral palsy‡	40/909 (4.4)	66/901 (7.3)	0.58	0.58 (0.39–0.87)	0.009	0.59 (0.39–0.89)
Cognitive delay‡§	293/867 (33.8)	329/858 (38.3)	0.82	0.81 (0.66–0.99)	0.04	0.83 (0.67–1.02)
Severe hearing loss‡¶	17/909 (1.9)	22/905 (2.4)	0.77	0.77 (0.40–1.45)‖	0.41	0.81 (0.43–1.55)‖
Bilateral blindness‡	6/911 (0.7)	8/905 (0.9)	0.74	0.74 (0.26–2.15)‖	0.58	0.79 (0.27–2.31)‖

* The odds ratio has been adjusted for the gestational age and sex of the infant, the mother's education at the time of the assessment, antenatal administration of corticosteroids, and multiple birth.
† This outcome is for children whose vital status was known at a corrected age of 18 months.
‡ Data for this outcome exclude children who died before the scheduled tests and those who were alive but were not tested.
§ Cognitive delay was defined as a Mental Development Index score of less than 85.
¶ These data are for children who underwent audiometry (810 in the caffeine group and 805 in the placebo group) and for those who did not undergo audiometry but who had no indication of severe hearing loss during the clinical examination and the Bayley Test (99 in the caffeine group and 100 in the placebo group).
‖ The odds ratio for this outcome was not adjusted for center because there were too few events.

with placebo significantly reduced the incidence of cerebral palsy (4.4% vs. 7.3%; odds ratio adjusted for center, 0.58; 95% CI, 0.39 to 0.87; P=0.009) and of cognitive delay (33.8% vs. 38.3%; odds ratio adjusted for center, 0.81; 95% CI, 0.66 to 0.99; P=0.04).

We conducted a post hoc stepwise logistic-regression analysis to explore possible mechanisms for the effect of caffeine on the rate of survival without neurodevelopmental disability. Six explanatory variables were examined: the postmenstrual ages at which each of three levels of respiratory support — positive airway pressure through an endotracheal tube, any positive airway pressure, and oxygen therapy — were last administered, the use of postnatal corticosteroids and of surgery to close a patent ductus arteriosus, and the rate of bronchopulmonary dysplasia. Treatment with caffeine led to reductions in all six variables.[9]

With the exception of surgery for closure of a patent ductus arteriosus, each of the individual variables explained between approximately 20% and 50% of the effect of caffeine — in terms of the log odds ratio — on death or disability at 18 to 21 months. However, because of intercorrelation, their explanatory effects overlapped. The strongest intermediate variable was the postmenstrual age at last use of any positive airway pressure (P<0.001). Earlier discontinuation of any positive airway pressure in the caffeine group alone explained 49% of the beneficial long-term drug effect. The second most important intermediate variable was the postmenstrual age at last use of supplemental oxygen; individually, it explained 32% of the long-term caffeine effect. However, once the postmenstrual age at last use of positive airway pressure had entered the stepwise regression model, only the use of postnatal corticosteroids added a statistically significant (P=0.02) but small (4%) amount of explanatory power. All six intermediate variables together explained 55% of the observed benefit of caffeine therapy on the primary composite outcome at 18 months.

OTHER OUTCOMES

The overall frequency of retinopathy of prematurity did not differ significantly between the two groups, but a post hoc analysis showed that severe eye disease was less common in infants assigned to caffeine (Table 3).

Most cases of cerebral palsy were mild. Only 31 children (1.7%) — 12 in the caffeine group and 19 in the placebo group — had cerebral palsy with gross motor function levels of 3 to 5 (Table 3).

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Table 3. Other Outcomes.

Outcome Variable	Caffeine Group	Placebo Group	Unadjusted Odds Ratio	Odds Ratio Adjusted for Center (95% CI)	P Value
Retinopathy of prematurity — no./total no. (%)					
All stages*	382/966 (39.5)	417/955 (43.7)	0.84	0.83 (0.69 to 1.01)	0.06
Severe retinopathy†	49/965 (5.1)	75/955 (7.9)	0.63	0.61 (0.42 to 0.89)	0.01
Cerebral palsy with a GMFCS level of 3 to 5 — no./total no. (%)‡§	12/905 (1.3)	19/898 (2.1)	0.62	0.62 (0.30 to 1.29)	0.20
Seizure disorder — no./total no. (%)‡	13/907 (1.4)	12/903 (1.3)	1.08	1.08 (0.49 to 2.38)	0.85
			Unadjusted Mean Difference	Mean Difference Adjusted for Center (95% CI)	
Height percentile¶					
Mean	40.7	40.5	0.19	0.21 (–2.48 to 2.90)	0.88
Median (interquartile range)	38.5 (14.5 to 64.9)	36.8 (14.6 to 64.0)			
Weight percentile‖					
Mean	27.9	28.5	–0.60	–0.59 (–3.22 to 2.05)	0.66
Median (interquartile range)	16.8 (3.9 to 46.1)	16.8 (3.7 to 48.5)			
Head circumference percentile**					
Mean	54.3	52.1	2.16	2.28 (–0.63 to 5.18)	0.12
Median (interquartile range)	56.4 (27.0 to 83.8)	51.1 (25.0 to 81.8)			

* This outcome is for infants who were alive at a postmenstrual age of 36 weeks. Data for infants who died before 36 weeks were included if retinopathy was documented on retinal examination before death (one infant in the caffeine group).
† This outcome is for infants who were alive at a postmenstrual age of 36 weeks. Severe retinopathy was defined as unilateral or bilateral disease of stage 4 or 5. Infants were also classified as having severe retinopathy if they received cryotherapy or laser therapy in at least one eye.
‡ This outcome excludes children who died before the scheduled tests and those who were alive but were not tested.
§ GMFCS denotes Gross Motor Function Classification System. The definitions of the levels are as follows. Level 3: sits with external support for lower trunk; rolls, creeps on stomach. Level 4: good head control in supported sitting; can roll to supine, may roll to prone position. Level 5: unable to maintain antigravity head and trunk postures in prone or sitting position; little or no voluntary movement.
¶ These data are for 886 infants in the caffeine group and 883 in the placebo group.
‖ These data are for 892 infants in the caffeine group and 892 in the placebo group.
** These data are for 890 infants in the caffeine group and 887 in the placebo group.

The mean Mental Development Index score on the Bayley test was significantly higher in the caffeine group than in the placebo group (90.1±16.6 vs. 87.5±17.2; mean difference adjusted for center, 2.54; 95% CI, 1.00 to 4.06; P=0.001). The mean Psychomotor Development Index score was also higher in infants assigned to caffeine than in infants assigned to placebo (90.1±14.6 vs. 88.4±15.9; mean difference adjusted for center, 1.66; 95% CI, 0.26 to 3.06; P=0.02). Distributional differences between the Psychomotor Development Index scores in the two groups were most apparent in the range of scores below 85 (Fig. 2).

The rate of seizure disorders and the average percentiles for height, weight, and head circumference were similar in the two groups (Table 3). A descriptive summary of adverse events after the first discharge home has been provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

DISCUSSION

We performed this international, randomized, placebo-controlled trial of caffeine to resolve the longstanding uncertainty about the efficacy and safety of methylxanthine therapy for apnea of prematurity.[3-5,11] We reported previously that caffeine reduced the rate of bronchopulmonary dysplasia in study participants.[9] The present report of the primary study outcome at a corrected age of 18 to 21 months shows that caffeine improved the rate of survival without neurodevelopmental disability.

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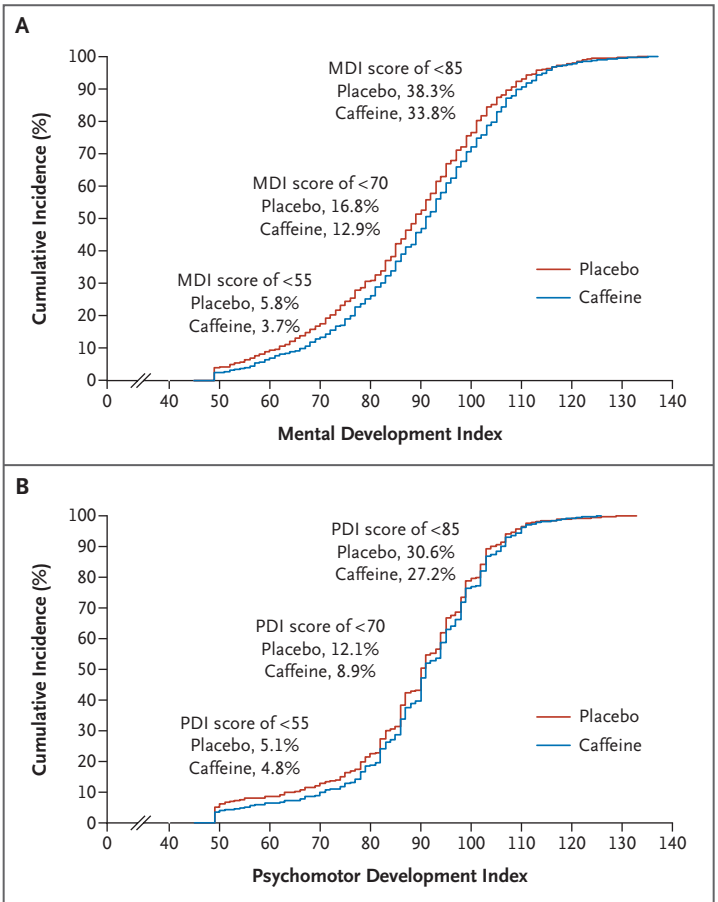

Figure 2. Bayley Test Results.

Panel A shows the cumulative incidence of individual Mental Development Index (MDI) scores for children who underwent a successful Bayley test and for those who were assigned a score of 49 because they were too cognitively impaired to be tested. Panel B shows the cumulative incidence of individual Psychomotor Development Index (PDI) scores for children who underwent a successful Bayley test. The cutoff score of less than 85 was prespecified. We included additional cutoff values in Panels A and B to assist in the interpretation of these graphs.

Caffeine reduced the incidences of cerebral palsy and cognitive delay but had no significant effects on the rates of death, severe hearing loss, or bilateral blindness (the other three components of the primary composite outcome). Our data indicate that approximately 16 infants would need to receive caffeine to prevent one adverse outcome at 18 months.[20]

What are the likely mechanisms for this neuroprotective effect of caffeine? Our post hoc analysis suggested that the earlier discontinuation of positive airway pressure in infants assigned to caffeine, as compared with placebo, was the most important intermediate variable. It explained almost half of the effect of caffeine on the composite 18-month outcome. Infants in the placebo group received positive airway pressure on average for one more week than did infants in the caffeine group.[9] Ventilator-induced lung injury in preterm infants promotes the development of bronchopulmonary dysplasia, which in turn is an important risk factor for neurodevelopmental disability in early childhood.[21,22] Even after further adjustments for five additional intermediate variables, however, 45% of the effect of caffeine on the 18-month outcome remained unexplained. Other potential mechanisms for the improved long-term outcome of the study participants assigned to caffeine warrant further study.

The clinicians in this study were instructed to use all necessary nonpharmacologic therapies to control apneas that did not respond to mild tactile stimulation.[9] Because there is no agreement about the change in oxygen saturation or the severity of bradycardia that represents prognostically important apnea,[11] it is conceivable that infants in the placebo group had more hypoxic–ischemic episodes due to apnea than did infants in the caffeine group. We did not collect data on the frequency and severity of apnea from the nurses' charts, because such records have been shown to be inaccurate.[23]

Although the present article focuses primarily on the outcomes at 18 months, we also observed that caffeine reduced the incidence of severe retinopathy of prematurity. We speculate that this reduced incidence of severe retinopathy among infants in the caffeine group was caused mainly by their shorter exposure to positive airway pressure and supplemental oxygen. Only 14 children — 6 in the caffeine group and 8 in the placebo group — were bilaterally blind at follow-up. However, impaired visual acuity after severe retinopathy may adversely affect child development in multiple domains.[24]

Outcomes at 18 to 21 months may not accurately predict function later in childhood.[25] Further follow-up of our study cohort to a corrected age of 5 years is in progress and includes detailed assessments of cognition, gross and fine motor function, vision, hearing, behavior, and general health. These additional outcome measurements will enable us to detect long-term consequences of methylxanthine therapy that may not become apparent until the study participants are old enough to enter school.[26]

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Aranda et al. first reported the use of caffeine for apnea of prematurity in 1977.[27] Four years earlier, Kuzemko and Paala had described the use of aminophylline to treat apneic attacks in preterm infants.[28] In a 1975 editorial, Lucey predicted that these observations might lead to important therapeutic advances but cautioned that the possible risks of therapy should be carefully balanced against the treatment gains.[29] The present results, showing that caffeine significantly improved survival without neurodevelopmental disability at a corrected age of 18 to 21 months, provide strong evidence that the overall benefits of methylxanthine therapy as used in this trial outweigh any potential risks up to 2 years after very preterm birth.

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No potential conflict of interest relevant to this article was reported.

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APPENDIX

The following investigators, research-team members, and hospitals participated in the 18-month follow-up of the Caffeine for Apnea of Prematurity Trial. Study sites are listed according to the number of children they assessed: McMaster University Medical Centre, Hamilton, ON, Canada — J. Dix, B. Adams, J. D'Ilario; Sunnybrook Health Sciences Centre, Toronto — E. Asztalos, M. Lacy, D. Hohn; Royal Women's Hospital, Melbourne, Australia — K. Callanan, N. Davis, J. Duff, G. Ford; Women's and Children's Hospital, Adelaide, Australia — R. Haslam, L. Goodchild, R. Lontis; Mercy Hospital for Women, Melbourne, Australia — S. Fraser, K. Saunders, G. Opie, E. Kelly; Centre Hospitalier Universitaire de Québec, Quebec City, Canada — S. Bélanger, P. St.-Amand, S. Ferland, A. Bairam; B.C. Children's Hospital, Vancouver, BC, Canada — A. Synnes, M. Whitfield, M. Rogers, J. Tomlinson; Ottawa Hospital, Ottawa — B. Lemyre, M. Blayney, J. Frank; Mount Sinai Hospital, Toronto — K. O'Brien, A.M. Hamilton; Academic Medical Center, Amsterdam — J. Kok, D. Nuytemans, A. van Wassenaer, M. Offringa; Royal University Hospital, Saskatoon, SK, Canada — K. Sankaran, S. Morgan, P. Proctor; Meir General Hospital, Kfar-Saba, Israel — R. Regev, S. Arnon, I. Netter; Foothills Hospital, Calgary, AB, Canada — R. Sauve, H. Christianson, D. Anseeuw-Deeks; Canberra Hospital, Canberra, Australia — G. Reynolds, S. Meskell; Soroka University, Beer Sheva, Israel — A. Golan, E. Goldstein; Brooklyn Hospital Center, Brooklyn, NY — M. LaCorte, P. LeBlanc, A. Braithwaite; University Hospital Maastricht, Maastricht, the Netherlands — T. Mulder, A. Ghys, M. van der Hoeven; St. Boniface, Winnipeg, MB, Canada — D. Moddemann, N. Granke, K. Penner; Ludwig Maximilian University, Munich, Germany — A. Schulze, P. Pudenz, M. Muller; Astrid Lindgren Children's Hospital, Stockholm — H. Lagercrantz, E. Herlenius, L. Legnevall; Windsor Regional Hospital, Windsor, ON, Canada — C. Nwaesei, H. Ryan, C. Saunders; Victoria General Hospital, Victoria, BC, Canada — C. Tan-Dy, M. Turner, S. Tulsiani; James Cook University Hospital, Middlesbrough, United Kingdom — S. Sinha, W. Tin; University of Sherbrooke, Sherbrooke, QC, Canada — H. Walti, D. Royer; Kaplan Medical Center, Rehovot, Israel — A. Juster-Reicher, E. Shinwell; Royal Victoria Hospital, Montreal — M. Khairy, P. Grier, J. Vachon; Kingston General Hospital, Kingston, ON, Canada — M. Clarke, H. MacLean; Royal Maternity Hospital Belfast, Northern Ireland — H. Halliday, C. Mayes, C. Cummings; Basel Children's Hospital, Basel, Switzerland — H. Fahnenstich, B. Tillmann, P. Weber; Moncton Hospital, Moncton, NB, Canada — R. Canning; Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom — N. Embleton, U. Wariyar; University Hospital Zurich, Zurich, Switzerland — H.-U. Bucher, J.-C. Fauchere; Northern Neonatal Initiatives, Middlesbrough, United Kingdom — S. Fritz; University Hospitals of Geneva, Geneva — P. Huppi; University of Tübingen, Tübingen, Germany — C. Poets, P. Urschitz-Duprat. **Steering Committee:** B. Schmidt (chair), K. Barrington, P. Davis, L.W. Doyle, A. Ohlsson, R.S. Roberts, A. Solimano, W. Tin; External Safety Monitoring Committee: M. Gent (chair), W. Fraser, E. Hey, M. Perlman, K. Thorpe; Coordinating and Methods Center in Hamilton, ON, Canada: R.S. Roberts, C. Chambers, L. Costantini, E. McGean.

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