Vitamin A Supplementation for Extremely Low Birth Weight Infants: Outcome at 18 to 22 Months

Namasivayam Ambalavanan, MD*; Jon E. Tyson, MD, MPH‡; Kathleen A. Kennedy, MD, MPH‡; Nellie I. Hansen, MPH§; Betty R. Vohr, MD‖; Linda L. Wright, MD¶; Waldemar A. Carlo*; and National Institute of Child Health and Human Development Neonatal Research Network

ABSTRACT. *Background.* **A National Institute of Child Health and Human Development Neonatal Research Network randomized trial showed that vitamin A supplementation reduced bronchopulmonary dysplasia (O_2 at 36 weeks' postmenstrual age) or death in extremely low birth weight (ELBW) neonates (relative risk [RR]: 0.89). As with postnatal steroids or other interventions, it is important to ensure that there are no longer-term adverse effects that outweigh neonatal benefits.**

Primary Objective. **To determine if vitamin A supplementation in ELBW infants during the first month after birth affects survival without neurodevelopmental impairment at a corrected age of 18 to 22 months.**

Design/Methods. **Infants enrolled in the National Institute of Child Health and Human Development vitamin A trial were evaluated at 18 to 22 months by carefully standardized assessments: Bayley Mental Index (MDI) and Psychomotor Index (PDI), visual and hearing screens, and physical examination for cerebral palsy (CP). The medical history was also obtained. Neurodevelopmental impairment (NDI) was predefined as ≥1 of MDI <70, PDI <70, CP, blind in both eyes, or hearing aids in both ears.**

Results. **Of 807 enrolled infants, 133 died before and 16 died after discharge. Five hundred seventy-nine (88%) of the 658 remaining infants were followed up. The primary outcome of NDI or death could be determined for 687 of 807 randomized infants (85%). Baseline characteristics and predischarge and postdischarge mortality were comparable in both study groups. NDI or death by 18 to 22 months occurred in 190 of 345 (55%) infants in the vitamin A group and in 204 of 342 (60%) of the control group (RR: 0.94; 95% confidence interval: 0.80-1.07). RRs for low MDI, low PDI, and CP were also <1.0. We found no evidence that neonatal vitamin A supplementation reduces hospitalizations or pulmonary problems after discharge.**

Conclusion. **Vitamin A supplementation for ELBW infants reduces bronchopulmonary dysplasia without increasing mortality or neurodevelopmental impairment at 18 to 22 months. However, this study was not powered to evaluate small magnitudes of change in long-term outcomes.** *Pediatrics* **2005;115:e249–e254. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1812;** ***vitamin A, retinol, follow-up studies, premature infant, outcomes assessment, bronchopulmonary dysplasia.***

ABBREVIATIONS. ELBW, extremely low birth weight; BPD, bronchopulmonary dysplasia; NDI, neurodevelopmental impairment; NICHD, National Institute of Child Health and Human Development; RR, relative risk; CI, confidence interval; CP, cerebral palsy; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index.

Extremely low birth weight (ELBW; birth weight ≤ 1000 g) infants are at high risk for mortality, bronchopulmonary dysplasia (BPD, neonatal chronic lung disease), and long-term neurodevelopmental impairment (NDI). ELBW infants are often deficient in vitamin A (retinol),[1] which may increase the risk for BPD.[2] Randomized, controlled trials and a recent systematic review demonstrate that vitamin A supplementation decreases BPD or death.[3–5] In a large trial conducted by the multicenter Neonatal Research Network of the National Institute of Child Health and Human Development (NICHD), 807 ELBW infants receiving respiratory support 24 hours after birth were randomized to sham injections (controls) or vitamin A at a dose of 5000 IU administered intramuscularly 3 times per week for 4 weeks.[4] Death or BPD at 36 weeks' postmenstrual age occurred in significantly fewer infants in the vitamin A group than in the controls (55% vs 62%; relative risk [RR]: 0.89; 95% confidence interval [CI]: 0.80-0.99) due to a decrease in the rate of BPD.[4]

However, as emphasized by the experience with postnatal steroids and other interventions, it is important to ensure that the benefit of a neonatal intervention is not outweighed by longer-term adverse effects.[6,7] It is also essential to identify longer-term benefits of a neonatal intervention. The objective of this study was to evaluate rates of death, NDI, and other adverse outcomes such as pulmonary problems and rehospitalizations before 18 to 22 months' adjusted age among infants who were enrolled in the NICHD vitamin A trial.[4] Our primary question was whether vitamin A administration had discernible

From the *Department of Pediatrics, University of Alabama, Birmingham, Alabama; ‡Department of Pediatrics, University of Texas Medical School, Houston, Texas; §Research Triangle Institute, Research Triangle Park, North Carolina; ‖Department of Pediatrics, Women and Infants Hospital, Providence, Rhode Island; and ¶National Institute of Child Health and Human Development Neonatal Research Network, Bethesda, Maryland.

Accepted for publication Nov 8, 2004.
doi:10.1542/peds.2004-1812
This work was presented in part at the Pediatric Academic Societies Meeting; May 1-4, 2004; San Francisco, CA.
No conflict of interest declared.

Address correspondence to Namasivayam Ambalavanan, MD, 525 New Hillman Building, 619 S 20th St, University of Alabama, Birmingham, AL 35249. E-mail: ambal@uab.edu

effects on the likelihood of survival without impairment at 18 to 22 months' corrected age.

METHODS

The population was drawn from the cohort of ELBW infants who participated in the vitamin A trial[4] and were followed up at 18 to 22 months' adjusted age. Participation in the vitamin A trial[4] and in the follow-up program required informed consent from parents or caregivers and was approved by the Institutional Review Board of each center. During the follow-up visit, a comprehensive history, physical examination, and neurodevelopmental assessment were performed by trained and certified personnel[8] who were masked with respect to the infant's group assignment in the vitamin A trial. Neurologic assessments were done by the Amiel-Tison method.[9] Cerebral palsy (CP) was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture. The developmental assessment consisted of the Bayley Scales of Infant Development II.[10] A Mental Developmental Index (MDI) or a Psychomotor Developmental Index (PDI) of <70 (>2 SDs below the mean for normal infants) was considered abnormal. Infants with very severe developmental delay were assigned MDI and PDI scores of 49. Blindness was defined as blindness in both eyes, and hearing impairment was defined as having hearing aids in both ears. NDI was defined as ≥1 of the following: MDI <70, PDI <70, CP, blind in both eyes, or hearing aids in both ears.

The primary outcome, NDI or death, was assigned using data from all participants in the vitamin A trial. Infants who died before the follow-up evaluation and surviving children who had NDI at the follow-up evaluation were assigned as having the outcome; surviving children without NDI were assigned as not having the outcome. Children who survived but were lost to follow-up or followed but not evaluated completely for NDI were assigned as missing this outcome. Six neurodevelopmental binary outcomes were assigned for the children who completed the follow-up evaluation: (1) MDI score <70 vs MDI ≥70; (2) PDI score <70 vs PDI ≥70; (3) CP present or absent; (4) blindness present or absent; (5) hearing impairment: present or absent; and (6) NDI present or absent. Additionally, MDI and PDI scores were studied as continuous variables. Other outcomes were also assessed based on review of medical history as reported at the 18- to 22- month visit by the mother or the caregiver, including number of rehospitalizations between initial discharge to home and follow-up, current, regular, or intermittent use of diuretics or bronchodilators as of the follow-up evaluation, oxygen prescribed for home use or use in a chronic care facility, and oxygen still prescribed at follow-up.

Infants in the vitamin A and control groups were compared on baseline characteristics determined at study randomization, MDI and PDI scores, and each binary and ordinal outcome. Statistical significance for unadjusted comparisons of continuous variables, including MDI and PDI scores, was determined by Wilcoxon tests, and for categorical variables by Fisher's exact and χ^2 tests. RRs and 95% CIs were estimated for binary outcomes. For binary outcomes with at least 40 events, logistic regression models were used to make comparisons between the treatment groups adjusted for study center and birth weight strata (401–750 or 751–1000 g). Statistical significance was determined by Wald χ^2 tests, and adjusted RRs were estimated by correcting the odds ratios.[11] For binary outcomes with <40 events, RRs were adjusted for birth weight strata only, and statistical significance was determined using the Mantel-Haenszel method.

RESULTS

A total of 807 infants born between November 1995 and July 1997 participated in the vitamin A trial: 405 in the vitamin A group and 402 in the control group. Of these infants, 133 died before discharge and 16 died after discharge, leaving 658 surviving infants, 579 (88%) of whom were assessed at 18 to 22 months' corrected age. The follow-up rate (vitamin A: 87%; controls: 89%; $P = .6$) and mortality (vitamin A: 18%; controls: 19%; RR: 0.95; 95% CI: 0.69–1.28, $P = .7$) were similar in the vitamin A and control groups. NDI could not be assessed for 41 surviving infants. Therefore, the primary outcome, death or impairment, at 18 to 22 months was determined for 687 of 807 infants (85% in both vitamin A and control groups).

Baseline characteristics of the vitamin A and control group infants at randomization were comparable for the infants who were followed up or who died before follow-up (Table 1). Baseline characteristics were also comparable between the groups for the subset of infants who were followed-up (data not shown). Among those seen at the follow-up visit, 40 of 579 infants (7%) were not evaluated for MDI and 45 (8%) were not evaluated for PDI, mostly for reasons of mild/moderate sensory impairment, behavior problems, non–English-speaking family with no interpreter available, and intercurrent illness. Infants with severe developmental delay were assigned a score of 49, as described in "Methods."

In comparisons of all measured neurodevelopmental outcomes, no significant differences between the treatment groups were found (Tables 2 and 3). Moderate/severe CP was 10% in both groups (RR: 0.99; 95% CI: 0.60-1.61; $P = 1.0$). The incidence of blindness and hearing impairment was low in both groups and did not differ between the groups.

We found no evidence of benefit from vitamin A supplementation on pulmonary morbidity after discharge (Table 4). The point estimates for the RR were 1.86 and 2.80 for ongoing oxygen use and diuretics. CIs associated with these estimates were very broad because of the small numbers of infants in either study group with these adverse outcomes (Table 4), and differences between the groups were not significant. Although no differences were found between the groups in the percent of children prescribed oxygen for home use or in the duration of oxygen supplementation, it is necessary to note that therapies being received at the time of follow-up at 18 to 22 months may be more likely to be reliably recorded than therapies initiated or discontinued soon after discharge home.

The presence of NDI at follow-up was associated with the diagnosis of BPD at 36 weeks' postmenstrual age: 54% of infants who had BPD developed NDI compared with only 37% of infants who did not have BPD (RR: 1.48; CI: 1.22-1.80; $P < .001$).

DISCUSSION

This study demonstrated comparable neurodevelopmental outcomes at 18 to 22 months in vitamin A–treated infants relative to controls (RR: 0.94 [0.80–1.07] for NDI or death; RR: 0.90 [0.73–1.08] for NDI; and RR: 0.86 [0.58–1.24] for CP). The strengths of our study include evaluation of a multicenter cohort of ELBW infants, with the primary outcome at 18 to 22 months determined for 85% of randomized infants, and the use of masked, certified examiners and reliable standardized assessment tools for multiple neurodevelopmental outcomes. The current study is important because it demonstrates that vitamin A is unlike postnatal steroids and other interventions that have been used for the prevention of BPD or other

TABLE 1. Baseline Characteristics at Randomization of Vitamin A Trial Participants Who Died or Attended Follow-up

Characteristic	Vitamin A Group (N = 363)	Control Group (N = 365)	P Value*
Gestational age, wk			
Mean ± SD	26.7 ± 1.9	26.7 ± 1.7	.7
Birth weight, g			
Mean ± SD	769 ± 135	766 ± 139	.7
SGA, *n* (%)	86 (24)	105 (29)	.1
Male, *n* (%)	180 (50)	173 (47)	.6
Race, *n* (%)			
Black	180 (50)	174 (48)	.9
White	112 (31)	118 (32)	
Hispanic	62 (17)	61 (17)	
Other	9 (2)	12 (3)	
Antenatal steroids, *n* (%)	273 (75)	266 (73)	.4
Apgar ≤3, *n* (%)			
At 1 min	157 (44)	137 (38)	.1
At 5 min	37 (10)	26 (7)	.1
Delivery room care, *n* (%)			
Intubation	326 (90)	331 (91)	.7
Drugs for resuscitation	37 (10)	38 (10)	1.0
Surfactant use, *n* (%)	296 (82)	297 (81)	1.0
Respiratory status at 24 h			
Mechanical ventilation, *n* (%)	329 (91)	330 (90)	1.0
Mean airway pressure			
Mean ± SD	6.9 ± 2.5	7.0 ± 2.5	.6
Fraction of inspired oxygen			
Mean ± SD	0.41 ± 0.19	0.41 ± 0.19	.9

* P values for comparisons between the vitamin A and control groups by Fisher's exact, χ^2, or Wilcoxon tests.

TABLE 2. NDI or Death Among Vitamin A Trial Participants by Treatment Group

Outcome*	Vitamin A Group	Control Group	Adjusted RR Vitamin A Versus Control (95% CI)†	P Value‡
Death, n/N (%)	73/405 (18)	76/402 (19)	0.95 (0.69–1.28)	.8
NDI in survivors, n/N (%)	117/272 (43)	128/266 (48)	0.90 (0.73–1.08)	.3
NDI/death, n/N (%)	190/345 (55)	204/342 (60)	0.94 (0.80–1.07)	.3

* Deaths are reported among 807 children enrolled in the vitamin A trial. NDI is reported among children who completed follow-up and could be assessed for NDI, N = 538. NDI could not be determined for 41 of 579 children who completed follow-up. NDI/death is reported among children who died prior to follow-up and those who survived and were evaluated for NDI at follow-up (see "Methods").
† RRs were adjusted for study center and birth weight strata (401–750 or 751–1000 g).
‡ P values from Wald χ^2 tests.

TABLE 3. Other Neurodevelopmental Outcomes Among Vitamin A Trial Participants who Attended Follow-up by Treatment Group

Outcome*	Vitamin A Group (N = 290)	Control Group (N = 289)	Adjusted RR Vitamin A Versus Control (95% CI)†	P Value‡
MDI (mean ± SD)	77 ± 17	77 ± 18	—	.5
Median	79	78		
MDI <70, n/N (%)	87/271 (32)	104/268 (39)	0.83 (0.64–1.05)	.1
PDI (mean ± SD)	81 ± 18	79 ± 19	—	.5
Median	83	83		
PDI <70, n/N (%)	66/268 (25)	79/266 (30)	0.84 (0.62–1.12)	.3
CP§, n/N (%)	43/287 (15)	51/283 (18)	0.86 (0.58–1.24)	.4
Blind in both eyes, n/N (%)	2/289 (0.7)	0/288 (0)	—	.5
Hearing impairment, n/N (%)	5/290 (1.7)	4/288 (1.4)	1.26 (0.34–4.64)	1.0

* Total N is shown in each group when outcomes are missing for some children who attended the follow-up visit.
† RRs were adjusted for study center and birth weight strata (401–750 or 751–1000 g), except for RR for hearing impairment, which was adjusted for birth weight strata only.
‡ P values from Fisher's exact, χ^2, or Wilcoxon tests.
§ Includes mild, moderate, and severe CP.

adverse outcomes but were later shown to possibly have harmful long-term effects on neurodevelopmental outcome.[6,7]

The major limitation of our study is that the original trial was not designed to have high power to assess findings at follow-up. To confirm with 80% power that a reduction in the proportion of children with NDI of the magnitude observed in the vitamin A–treated group (5%) was statistically significant, we would have needed >1500 children in each group. Although our results are not statistically conclusive, it is reassuring that the RRs for NDI and

TABLE 4. Other Outcomes Among Vitamin A Trial Participants as Reported by the Mother (or Other Responsible Caregiver) at the 18 to 22 Month Follow-Up Visit

Outcome*	Vitamin A Group (N = 288)†	Control Group (N = 289)	Adjusted RR Vitamin A Versus Control (95% CI)‡	P Value§
Rehospitalized, %	50	49	1.03 (0.87–1.20)	.7
Respiratory rehospitalization, %	30	29	1.03 (0.79–1.31)	.8
Diuretics at 18- to 22-mo follow-up, %	4	1	2.80 (0.91–8.64)	.06
Bronchodilators at 18- to 22-mo follow-up (%)	39	37	1.06 (0.84–1.29)	.6
O_2 prescribed for home use, n/N (%)	104/287 (36)	93/288 (32)	1.18 (0.92–1.47)	.2
Duration of O_2 use, n (%)‖				
1–3 mo	7 (7)	10 (11)	—	.1
4–6 mo	24 (23)	25 (27)		
>6 mo	73 (70)	57 (62)		
O_2 still prescribed at follow-up, n/N (%)	18/287 (6)	10/288 (3)	1.86 (0.88–3.93)	.1
Ventilator/CPAP still prescribed at follow-up, n/N (%)	1/287 (0.4)	0/287 (0)	—	1.0

* CPAP indicates continuous positive airway pressure. Total N is shown in each group when outcomes are missing for some children with medical history information.
† Medical history information was unavailable for 2 of 290 children in the vitamin A group who attended follow-up.
‡ RR adjusted for study center and birth weight strata (401–750 or 751–1000 g) except RR for use of diuretics and O_2 still prescribed at follow-up adjusted for birth weight strata only.
§ P values from χ^2 tests except ventilator/CPAP by Fisher's exact test.
‖ Among the subset of children who were prescribed oxygen for home use. Duration was missing for 1 child in the control group.

other neurodevelopmental outcomes among vitamin A–treated infants compared with controls were all <1.0. A higher percentage of black children than white children was included in our study population. It is unclear whether this may affect the generalizability of our results to ELBW populations with different racial distributions.

The efficacy of vitamin A supplementation in reducing BPD before nursery discharge has been well established. Vitamin A supplementation has been identified as a "potentially better practice" for the prevention of chronic lung disease based on level 1 evidence (strong evidence from at least 1 systematic review of multiple well-designed randomized, controlled trials).[12] The number needed to treat to benefit 1 infant (by preventing BPD) is 14, a smaller number than for many therapies such as diuretics and bronchodilators commonly used for premature and term newborns, older children, and adults.[13–15] A recent survey showed that most neonatologists in the United States do not supplement vitamin A to ELBW infants because they consider the benefit to be small or they do not appreciate the quality of the evidence supporting the benefit.[16] BPD and long-term neurodevelopmental morbidity are complex disorders, and it is unlikely that any 1 intervention would have a major impact on their incidence. It may not be reasonable to expect improvements in survival or morbidity of a magnitude such as those seen with antenatal steroids[17] or postnatal surfactants[18] for these disorders. In complex disorders such as BPD, it may be more reasonable to expect improvements in outcome to occur gradually, in small increments with treatment advances. The RR of 0.87 and the number needed to treat of 14, identified in the systematic review of all relevant trials,[5] indicates that vitamin A supplementation is an incremental advance in our progress in reducing BPD in preterm infants. Nevertheless, our findings and those of other studies[5,16,19] indicate a need to optimize the duration, route, and dose of vitamin A supplementation and better assess the effects during the neonatal period and at follow-up.

It is difficult to determine if the effects of vitamin A supplementation on neurodevelopment are independent of its effects on respiratory status in the neonatal period. NDI is of many causes. Similar to other investigators,[20,21] we found that BPD was significantly associated with NDI at follow-up in this trial. Vitamin A supplementation may influence NDI indirectly through respiratory effects, perhaps by attenuating lung inflammation or cytokine release. Vitamin A may also have direct effects on neurodevelopment. Retinoic acid, the active metabolite of vitamin A, is essential for postnatal maturation of the cerebral cortex in animal models[22] and for development of the hindbrain and the visual and auditory systems.[23] Even in the mature brain, retinoic acid signaling has been localized to sites of functional or structural plasticity in the central nervous system.[24] Vitamin A deficiency, which is common in ELBW infants, may therefore contribute to neurologic sequelae. Additional follow-up of the infants, although not currently planned, may yield additional information on the neurologic sequelae of vitamin A deficiency and the effects of supplementation in ELBW infants. Vitamin A is also required for innate and adaptive immunity,[25,26] and it is possible that vitamin A deficiency may increase the risk of sepsis or lead to lung and brain injury by accentuation of inflammatory processes and consequent cytokine release.

It is of interest that 20% and 25% of infants followed in the control and vitamin A groups, respectively, were on home oxygen for >6 months. More than 1 in 3 ELBW infants was also receiving bronchodilators at the time of the 18- to 22-month visit. It is difficult to arrive at valid conclusions from these observations in the absence of a common standard of practice or established guidelines on the use of home oxygen or respiratory medications; however, it may be justifiable to state that no marked improvements

in postdischarge pulmonary outcome were noted after vitamin A supplementation in the neonatal period.

CONCLUSIONS

Vitamin A supplementation for ELBW neonates, an intervention shown to safely reduce BPD in the neonatal period, does not seem to adversely affect neurodevelopmental outcomes at 18 to 22 months. The overall findings of our trial and others indicate that vitamin A supplementation constitutes an advance in treating ELBW infants. It may, therefore, be considered reasonable to implement routine supplementation of vitamin A in ELBW neonates. Additional study is needed to optimize the duration, route, and dose of vitamin A supplementation and to better define its short- and long-term effects.

ACKNOWLEDGMENTS

This study was funded by cooperative agreements with the National Institute of Child Health and Human Development grants U10 HD21373, U10 HD27904, U10 HD19897, U10 HD27871, U10 HD27851, U10 HD27856, U10 HD27880, U10 HD21397, U10 HD21415, U10 HD21364, U10 HD27853, U10 HD34216, U10 HD21385, U10 HD34167, U10 HD27881, and U01 HD36790 and by General Clinical Research Center grants # M01 RR 06022, M01 RR 00750, M01 RR 00070, M01 RR 08084, and M01 RR 00997. Appendix lists NICHD Neonatal Research Network Centers.

REFERENCES

1. Shenai JP, Chytil F, Jhaveri A, Stahlman MT. Plasma vitamin A and retinol-binding protein in premature and term neonates. *J Pediatr.* 1981; 99:302–305
2. Shenai JP, Chytil F, Stahlman MT. Vitamin A status of neonates with bronchopulmonary dysplasia. *Pediatr Res.* 1985;19:185–188
3. Shenai JP, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. *J Pediatr.* 1987;111:269–277
4. Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely-low-birth-weight infants. *N Engl J Med.* 1999;340:1962–1968
5. Darlow BA, Graham PJ. Vitamin A supplementation for preventing morbidity and mortality in very low birthweight infants. *Cochrane Database Syst Rev.* 2002;(4):CD000501
6. 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
7. Silverman WA. A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics.* 2004;113:394–396
8. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994. *Pediatrics.* 2000;105:1216–1226
9. Amiel-Tison C. Neuromotor status. In: Taeusch HW, Yogman MW, eds. *Follow-up Management of the High-Risk Infant*. Boston, MA: Little Brown and Company; 1987:115–126
10. Bayley N. *Bayley Scales of Infant Development-II.* San Antonio, TX: Psychological Corporation; 1993
11. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA.* 1998;280: 1690–1691
12. Sharek PJ, Baker R, Litman F, et al. Evaluation and development of potentially better practices to prevent chronic lung disease and reduce lung injury in neonates. *Pediatrics.* 2003;111(4). Available at: www.pediatrics.org/cgi/content/full/111/4/e426
13. Brion LP, Primhak RA, Ambrosio-Perez I. Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease. *Cochrane Database Syst Rev.* 2002;(1):CD001817
14. Ng GY, da S, Ohlsson A. Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants. *Cochrane Database Syst Rev.* 2001;(3):CD003214
15. Ambalavanan N, Whyte RK. Mismatch between evidence and practice: common therapies in search of evidence. *Clin Perinatol.* 2003;30:305–331
16. Ambalavanan N, Kennedy K, Tyson J, Carlo WA. Survey of vitamin A supplementation for extremely-low-birth-weight infants: is clinical practice consistent with the evidence? *J Pediatr.* 2004;145:304–307
17. Crowley P. Prophylactic corticosteroids for preterm birth. *Cochrane Database Syst Rev.* 2000;(2):CD000065
18. Soll RF, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev.* 2001;(2):CD000144
19. Ambalavanan N, Wu TJ, Tyson JE, Kennedy KA, Roane C, Carlo WA. Comparison of three vitamin A dosing regimens in extremely-low-birth-weight infants. *J Pediatr.* 2003;142:656–661
20. Schmidt B, Asztalos EV, Roberts RS, et al. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA.* 2003;289:1124–1129
21. Hack M, Wilson-Costello D, Friedman H, Taylor GH, Schluchter M, Fanaroff AA. Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000 g: 1992–1995. *Arch Pediatr Adolesc Med.* 2000;154:725–731
22. Wagner E, Luo T, Drager UC. Retinoic acid synthesis in the postnatal mouse brain marks distinct developmental stages and functional systems. *Cereb Cortex.* 2002;12:1244–1253
23. Zile MH. Function of vitamin A in vertebrate embryonic development. *J Nutr.* 2001;131:705–708
24. Thompson Haskell G, Maynard TM, Shatzmiller RA, Lamantia AS. Retinoic acid signaling at sites of plasticity in the mature central nervous system. *J Comp Neurol.* 2002;452:228–241
25. Stephensen CB. Vitamin A, infection, and immune function. *Annu Rev Nutr.* 2001;21:167–192
26. Stephensen CB, Rasooly R, Jiang X, et al. Vitamin A enhances in vitro Th2 development via retinoid X receptor pathway. *J Immunol.* 2002;168: 4495–4503

APPENDIX. NICHD Neonatal Research Network, 1996–2006

Center	Principal Investigator	Follow-up Principal Investigator	Network Coordinator	Follow-up Coordinator
Brown University	William Oh, MD	Betty Vohr, MD	Angelita Hensman, RNC	Lucey Noel, RNC
Case Western Reserve University	Avroy A. Fanaroff, MB, BCh	Dee Wilson, MD	Nancy Newman, RN	Bonnie Siner, RN
Duke University	Ronald N. Goldberg, MD	Ricki Goldstein, MD	Kathy Auten, RN	Melody Lohmeyer, RN
Emory University	Barbara J. Stoll, MD	Barbara J. Stoll, MD	Ellen Hale, RNC, BS	Ellen Hale, RNC, BS
Harvard University	Ann R. Stark, MD	Ann R. Stark, MD	Kerri Fournier, RN	
Indiana University	James A. Lemons, MD	Anna Dusick, MD	DeeDee Appel, RN	Leslie Richards, RN
Stanford University	David K. Stevenson, MD	Susan Hintz, MD	Bethany Ball, RN	Bethany Ball, RN
University of Alabama	Waldemar A. Carlo, MD	Myriam Peralta, MD	Monica Collins, RN	Vivien Phillips
University of California–San Diego	Neil N. Finer, MD	Yvonne Vaucher, MD	Wade Rich, RN	Martha Fuller, RN
University of Cincinnati	Edward F. Donovan, MD	Jean Steichen, MD	Cathy Grisby, RN	Tari Gratton, RN
University of Miami	Shahnaz Duara, MD	Charles Bauer, MD	Ruth Everett, RN	Mary Allison, RN
University of New Mexico	Lu-Ann Papile, MD	Lu-Ann Papile, MD	Conra Backstrom, RN	
University of Rochester	Dale L. Phelps, MD	Gary Myers, MD	Linda Reubens, RN	Diane Hust, RN
University of Tennessee	Sheldon B. Korones, MD	Kimberly Yolton, PhD	Tina Hudson, RN	
University of Texas–Dallas	Abbot R. Laptook, MD	Roy Heyne, MD	Susie Madison, RN	Jackie Hickman, RN
University of Texas–Houston	Jon E. Tyson, MD, MPH	Pamela Bradt, MD	Georgia McDavid, RN	Shannon Rossi
Wake Forest University	T. Michael O'Shea, MD	Robert Dillard, MD	Nancy Peters, RN	Barbara Jackson, RN
Wayne State University	Seetha Shankaran, MD	Yvette Johnson, MD	Gerry Muran, BSN	Debbie Kennedy, RN
Yale University	Richard A. Ehrenkranz, MD	Richard A. Ehrenkranz, MD	Pat Gettner, RN	Elaine Romano, MSN
NICHD	Linda L. Wright, MD	Beth B. McClure, MS	Rose Higgins, MD	Carolyn Petrie, MS
Research Triangle Institute	W. Kenneth Poole, PhD	W. Kenneth Poole, PhD	Betty Hastings	Beth B. McClure, MS

The biostatistics center for the vitamin A trial was the George Washington University Biostatistics Center in Rockville, MD. Investigators were Joel Verter, PhD, and L. Mele, ScM.

* Steering Committee Chairman: Alan H. Jobe, MD, PhD.