The Effect of Supplementation of Docosahexaenoic Acid and Arachidonic Acid on Visual Acuity and Neurodevelopment in Larger Preterm Infants

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Background: Preterm infants may be born with deficits of both docosahexaenoic acid (DHA) and arachidonic acid (AA), but studies on supplementation of DHA and AA for preterm infants are limited.

Methods: Preterm infants with a gestational age between 30 and 37 weeks who met all the inclusion criteria were enrolled in this double blind, randomized, comparative study. Infants over 2000 g body weight, over 32 weeks of gestation and in full feeding status would enter into the active intervention period of 6 months. Sixteen infants received Neoangelac Plus with AA and DHA supplementation. Eleven infants received Neoangelac without AA and DHA supplementation. The babies had scheduled physical examinations and their cognitive development, visual acuity, and vital signs to be checked. Adverse events were also recorded.

Results: The mean Mental Development Index (MDI) scores for the supplementation and non-supplementation groups were 96.1 $\pm$ 8.6 and 91.7 $\pm$ 10.4 respectively at 6 months and 98.7 $\pm$ 8.0 and 90.5 $\pm$ 6.9 respectively at 1 year. The mean Physical Development Index (PDI) scores of these two groups were 102.2 $\pm$ 10.5 and 95.4 $\pm$ 13.2 respectively at 6 months and 98.0 $\pm$ 5.8 and 86.7 $\pm$ 11.1 respectively at 1 year. By repeated measures ANOVA, significant differences existed between groups for MDI and PDI (p = 0.020 and 0.008). However, there were no differences in visual acuity, physical examination variables or vital signs between these two groups. No obvious adverse effects were observed during the study period.

Conclusion: These results showed possible benefits in the neurodevelopment of larger preterm infants given formula supplemented with DHA and AA.

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Key words: docosahexaenoic acid, arachidonic acid, cognitive development, visual acuity.

Interest in factors that effect early infant development of visual acuity and mental development has led investigators to focus on long-chain polyunsaturated fatty acids (LCPUFAs). LCPUFAs are important components of the cell membranes in the human brain and retina. Docosahexaenoic acids (22:6ω3; DHA) and arachidonic acid (20:4ω6; AA) are major ω3 and ω6 LCPUFAs deposited in the membranes of

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the developing brain and retinal photoreceptor cells during the perinatal period.[1,2] Some studies showed improvement in visual and cognitive function in term babies fed formula supplemented with DHA and AA.[3-6]

In utero, the placenta selectively and substantially extracts DHA and AA from the mother and enriches the fetal circulation. Eighty percent of intrauterine DHA and AA accumulation occurs during the last trimester of pregnancy.[2] The physiologic requirements for DHA and AA are highest during the perinatal period. Preterm infants may be born with deficits of both DHA and AA due to early interruption of placental transport. Whether endogenous synthesis of DHA and AA is enough to meet the physiologic requirements of preterm infants is still unknown. After birth, feeding the usual enteral and parenteral formulas without DHA and AA to preterm infants results in a rapid decline of the plasma proportions of DHA and AA to one-quarter to one-third of the intra-uterine expectation.[7-11] Therefore, preterm infants may require a dietary source of DHA and AA. Clinical trials have been designed to examine whether LCPUFA enrichment of infant formula has beneficial effects on maturational events in the visual system and on the development of cognitive function in preterm infants.[12-18] These trials have shown significant transient functional advantages of LCPUFA supplementation on visual acuity,[14,15] but there were too few neurodevelopmental results for interpretation.

This new study will observe the effects of 6 months postnatal intervention with infant formula supplemented with AA and DHA on visual acuity and cognitive development in larger preterm infants in southern Taiwan.

METHODS

The primary objective of this study was to evaluate the effects of infant formula supplemented with DHA and AA on the cognitive development and visual acuity of larger preterm infants, whose gestational age was between 30 and 37 weeks, after 6 months intervention. In addition, this study also evaluated the safety of supplementation with DHA and AA in larger preterm infants.

This was a double-blind, randomized, comparative study which was approved by Institutional Review Board of Chang Gung Memorial Hospital. After a screening period, infants who met all the following criteria were eligible for the entry into the study: (1) A gestational age at birth between 30 and 37 weeks; (2) Normal fundus oculi; (3) Recruitment prior to commencement of feeding and after obtaining written informed parental consent. Babies with any of the following conditions or treatments were excluded: (1) Breast feeding; (2) A maternal history of infection, diabetes mellitus, gestational diabetes mellitus, cocaine or alcohol abuse, systemic diseases or if intrauterine growth retardation had been diagnosed during pregnancy; (3) Major congenital abnormality; (4) Severe intraventricular hemorrhage > grade 2; (5) Cystic periventricular leukomalacia; (6) Retinopathy of prematurity ≧ stage 2; (7) Bronchopulmonary dysplasia on radiographs or O_2 usage ≧ 28 days; (8) Body weight less than the third percentile; (9) Surgical intervention for necrotizing enterocolitis (10) Mechanical ventilation after achieving enteral intake > 110 kcal/kg per day; (11) A 5-min Apgar score < 7; (12) Administration of blood transfusion, blood products, or parenteral lipids with DHA or AA. Infants over 2000 g body weight, over 32 weeks of gestation and in full feeding status would enter the active intervention period. Infants were randomly assigned by drawing lots to receive either “Neoangelac Plus” or “Neoangelac” for 6 months. Except for the formula manufacturer, no member of the research team knew which babies received the supplemented and unsupplemented formula. “Neoangelac” was provided by “Multipower Enterprise Corporation”. It is an infant formula that is based on the composition of human milk. This product provides an adequate ratio of linoleic acid: α-linolenic acid (10 : 1). “Neoangelac Plus” is also an infant formula which is “Neoangelac” supplemented with an adequate amount of DHA (0.05%) and AA (0.10%). Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months. The total duration of this study was 25 weeks, including 1 week of screening and 24 weeks of intervention.

Infants’ data, physical examinations, vital signs, inclusion criteria, exclusion criteria, and medical and disease history were assessed at study entry. Height, weight, head circumference and vital signs were assessed monthly. At 4 months and 6 months after study entry, a visual acuity analysis was performed

using steady-state visual evoked potentials (VEP) and preferential looking tests with Lea grating acuity cards and Hiding Heidi low contrast "FACE" cards. The steady-state VEP was recorded with a UTAS-E3000 system from LKC Technologies (MD, USA). The stimulus was a checkerboard pattern with 80% contrast. The checks alternated at 10 reversals per second. Five check sizes were used and 40 sweeps were averaged in every step. The amplitude of every step was calculated with Fourier transform analysis. The VEP acuity was calculated after extrapolating the regression line to zero amplitude. Grating acuity was measured with Lea grating cards from Precision Vision (IL, USA). Contrast sensitivity was also measured with Hiding Heidi low contrast "FACE" cards from Precision Vision. A cognitive examination was done using Bayley MDI and PDI at 6 months and 1 year after entering the study. Adverse events including vomitus, diarrhea, abdominal distension, skin rash, and allergy, either spontaneously reported or observed by the research team or ward personnel during hospitalization, were recorded. Adverse events were recorded in response to an open, standardized question during hospitalization.

The statistical analyses for cognitive development, steady-state VEP, height, weight, head circumference and vital signs were done by repeated measures ANOVA. The visual acuities measured by Lea grating acuity cards and Hiding Heidi were analyzed by general equation estimator. The infants' data and infants' characteristics were summarized for each group and also compared between groups by using Fisher's exact test for quantitative variables and the T-test for continuous variables. Adverse events were listed.

RESULTS

Initially we planned to enroll 30 infants in each group, but because of the strict criteria, an outbreak of severe acute respiratory syndrome (SARS), and an increase in breast feeding due to government policies, the number of subjects was lower. A total of twenty-eight preterm infants were enrolled in this study. One infant was excluded later because of retinopathy of prematurity grade III which was found at 7 weeks. Sixteen infants received Neoangelac Plus. Eleven infants received Neoangelac. There were no significant differences in infants' data or gender between these two groups. (Table 1). At 6 months, the Bayley PDI examination could not be completed in two infants, because of an acidental fracture in one and a neurodevelopmental delay in the other. The mean MDI scores of the Neoangelac Plus and Neoangelac groups at 6 months were 96.1 $\pm$ 8.6 and 91.7 $\pm$ 10.4, respectively (Table 2). The mean PDI scores of these two groups at 6 months were 102.2 $\pm$ 10.5 and 95.4 $\pm$ 13.2, respectively (Table 2). At 1 year, one infant could not return to the hospital to complete the Bayley scale examination because of an outbreak of SARS. One infant was lost to follow-up and another infant still could not complete the PDI examination because of neurodevelopmental delay. The mean MDI scores of these two groups at 1 year were 98.7 $\pm$ 8.0 and 90.5 $\pm$ 6.9, respectively (Table 2). The mean PDI scores of these two groups at 1 year were 98.0 $\pm$ 5.8 and 86.7 $\pm$ 11.1, respectively (Table 2). By repeated measures ANOVA, the MDI (p-value = 0.020) and PDI (p-value = 0.008) scores were significantly different between groups. Twenty-four infants and 23 infants completed the steady-state VEP examination at 4 months and 6 months, respectively. The others could not cooperate with the examination. The visual acuity performed by steady-state VEP was presented by LogMar. The mean values of the VEP of the Neoangelac Plus and Neoangelac groups at 4 months were 0.19 $\pm$ 0.27 and 0.36 $\pm$ 0.34, respectively

Table 1. Infants' Data Analysis (T-test)

	Group		
	Neoangelac Plus N = 16	Neoangelac N = 11	p-value
Gestation at birth (weeks)	33.3 $\pm$ 0.5	33.0 $\pm$ 0.5	0.712
Birth weight (kg)	1.98 $\pm$ 0.11	1.99 $\pm$ 0.12	0.979
Gestation at study entrance (weeks)	35.6 $\pm$ 0.2	35.5 $\pm$ 0.2	0.805
Height at study entrance (cm)	46.0 $\pm$ 2.2	44.6 $\pm$ 2.5	0.146
Weight at study entrance (kg)	2.50 $\pm$ 0.49	2.34 $\pm$ 0.32	0.439
Pulse Rate at study entrance (beats/min)	149.5 $\pm$ 7.4	148.8 $\pm$ 12.6	0.859
Gender* (Male:Female)	5:11	5:6	0.687

Data are presented as mean $\pm$ SD except gender.
* The variable was tested by Fisher's exact test.

Table 2. Cognitive Examination

	Group	
	Neoangelac Plus N = 16	Neoangelac N = 11
PDI*		
6 months	102.2 ± 10.5	95.4 ± 13.2‡
1 year	98.0 ± 5.8†	86.7 ± 11.1‡
MDI*		
6 months	96.1 ± 8.6	91.7 ± 10.4
1 year	98.7 ± 8.0†	90.5 ± 6.9II

Abbreviations: PDI: Psychomotor Development Index; MDI: Mental Development Index.
* significant difference exists between groups by repeated measures ANOVA.
† N = 15
‡ N = 9
II N = 10
Data are presented as mean ± SD

Table 3. Visual Acuity

	Group	
	Neoangelac Plus N = 16	Neoangelac N = 11
VEP (Log Mar)		
4 months	0.19 ± 0.27*	0.36 ± 0.34‡
6 months	0.10 ± 0.17†	0.13 ± 0.22‡
Lea grating acuity card		
Cycles Per Degree		
4 months		
0.25	0 (0%)	1 (9%)
0.50	0 (0%)	2 (18%)
1.00	14 (88%)	5 (45%)
2.00	2 (12%)	3 (27%)
6 months		
1.00	1 (6%)	3 (27%)
2.00	14 (88%)	7 (64%)
4.00	1 (6%)	1 (9%)
Hiding Heidi Analysis		
4 months		
25 %	5 (31%)	2 (18%)
100 %	11 (69%)	9 (82%)
6 months		
10 %	2 (12%)	1 (9%)
25 %	14 (88%)	9 (82%)
100 %	0 (0%)	1 (9%)

Abbreviation: VEP: visual evoked potential.
* N = 14
† N = 13
‡ N = 10

(Table 3). The mean values of the VEP of these two groups at 6 months were 0.10 ± 0.17 and 0.13 ± 0.22, respectively (Table 3). By repeated measures ANOVA, only time within subjects was significant (p valve = 0.009). This indicated that the visual acuity improved in both groups, regardless of whether the babies received DHA and AA supplementation or not. All infants completed the Lea grating acuity card and Hiding Heidi low contrast "FACE" card examinations at 4 months and 6 months and the results of analysis by general equation estimator were the same as that for the VEP. The physical examination showed that height, weight and head circumference increased steadily during 12 months in both groups (Table 4), but no significant differences existed between groups by repeated measures ANOVA. There were no differences in vital signs including pulse rate and respiratory rate between groups. During the study period, there were no serious adverse effects in either group. According to the results, we found a possible effect of DHA and AA supplementation on cognitive performance.

DISCUSSION

Rapoport et al. calculated the incorporation rates of polyunsaturated fatty acids from the plasma into the brain in adult rats and showed that at least 3-5% of esterified brain AA and 2-8% esterified brain DHA are replaced daily by unesterified polyunsaturated fatty acids in the plasma.[19] In the human brain, the AA replacement rate is 0.3% per day. Transport of LCPUFAs from the plasma may play an important role because of the limited ability of the brain to synthesize LCPUFAs in the face of high demand during infancy. The placenta selectively transfers DHA and AA to the fetus. After preterm birth, placental transport of DHA and AA is interrupted, thereby reducing DHA and AA accretion. Dietary supplementation, by altering the concentrations of plasma unesterified polyunsaturated fatty acids, can regulate the polyunsaturated fatty acid content in the brain. DHA and AA are both present in breast milk but not in many formulas. Some studies found less DHA and AA in the brain and plasma of formula-fed infants.[20-23] The above findings have led many investigators to conclude that both DHA and AA are essential nutrients for preterm infants. In considering the essentiality of DHA and AA, it is important to evaluate the effect of

Table 4. Physical Examination

	Group	
	Neoangelac Plus N = 16	Neoangela N = 11
Height (cm)		
at study entry	46.0 ± 2.17	44.6 ± 2.46
1 month	50.7 ± 2.20	49.4 ± 2.84
2 months	55.0 ± 2.13	53.5 ± 2.32
3 months	58.2 ± 2.50	56.2 ± 2.71
4 months	61.0 ± 2.34	59.4 ± 3.11
5 months	63.8 ± 2.89	62.2 ± 2.60
6 months	65.6 ± 2.50	64.0 ± 2.72
1 year	74.4 ± 2.54*	72.3 ± 2.46†
Weight (kg)		
at study entry	2.5 ± 0.49	2.4 ± 0.31
1 month	3.6 ± 0.62	3.5 ± 0.68
2 months	4.7 ± 0.73	4.6 ± 0.65
3 months	5.7 ± 0.83	5.6 ± 0.92
4 months	6.4 ± 0.80	6.3 ± 1.03
5 months	6.7 ± 0.88	6.8 ± 1.13
6 months	7.3 ± 0.89	7.2 ± 1.12
1 year	9.0 ± 0.95*	9.2 ± 1.41†
Head Circumference (cm)		
at study entry	32.3 ± 1.47	32.1 ± 1.09
1 month	35.1 ± 1.14	34.7 ± 1.26
2 months	37.4 ± 1.01	37.0 ± 0.91
3 months	39.0 ± 1.17	38.7 ± 1.33
4 months	40.5 ± 1.09	40.1 ± 1.35
5 months	41.3 ± 1.29	41.1 ± 1.41
6 months	42.1 ± 1.23	42.0 ± 1.42
1 year	45.2 ± 1.25*	45.0 ± 0.89†

Data are presented as mean ± SD
* N = 15
† N = 10

these LCPUFAs on neurodevelopment and visual acuity. All studies on the effects of feeding unsupplemented formula vs. human milk, which contains DHA and AA, have shown the advantages of human milk.[24] However, infants cannot be assigned randomly breast-fed and formula-fed groups and the differences noted between these two groups can be ascribed to the effects of any of the myriad micro-components in human milk rather than the presence of LCPUFAs. In addition, the act of breast feeding provides a unique mother-infant interaction that may have important implications in infant growth and development.[25] For these reasons, studies on the effects of unsupplemented formulas vs. formulas supplemented with DHA and AA on visual acuity and neurodevelopment are more reasonable.

From previous studies,[12,26-27] we know that a short period of DHA supplementation, until term or until 2 months post term, is not sufficient to prevent a drop in DHA status during the ensuing months. By supplementing DHA in formula until 4 months post term, the normal erythrocyte phospholipid DHA content is maintained until 6 months post term. In our study, we supplemented DHA and AA in formula for 6 months in order to maintain normal erythrocyte phospholipid DHA and AA content over 6 months to meet the requirements of rapid brain and retinal development during this important period. After 6 months of age, infants frequently receive food containing fat, so it is impossible to control the intake of fatty acid and promptly evaluate the effect of supplementation of DHA and AA in formula.

The growth rates of preterm infants receiving formula supplemented with LCPUFAs from marine oil varied in different studies. Some studies observed slower growth in infants receiving supplemented formula than in those fed control formula.[28] Vanderhoof et al. demonstrated that addition of LCPUFAs from unicellular organisms to preterm formula provided acceptable growth through the first year of life.[29] Innis et al. indicated that inclusion of triglycerides enriched in AA and DHA in preterm formula was associated with an increase of in-hospital weight gain.[13] The effect of increased body weight and length appeared to continue for several weeks after discontinuation of the supplementation. Carlson et al. hypothesized that combined addition of AA and DHA to formulas offsets the observed negative impact of DHA on growth. Possibly, dietary AA has a clinically significant effect on growth in infants who are at a greater risk of low AA status, although a specific biological explanation is not available. In our study, we supplemented infant formula with AA and DHA extracted from unicellular organisms and found the supplemented infants had steady increases in body height, weight and head circumference through the first year of life, and no differences were found in comparison with the unsupplemented group.

Multiple reports have documented the essential roles of DHA and AA in retinal function maturation.[14,15] Carlson et al.[15] found preterm infants fed DHA had better visual acuity at 2 and 4 months of age, and Werkman et al.[14] also found a positive dif-

ference in preterm infants fed DHA and linoleic acid at ages up to 12 months after term. The meta-analysis for preterm infants showed an advantage of supplemented vs. unsupplemented formula of 0.47 ± 0.14 octaves at 2 months of age and 0.28 ± 0.08 octaves at 4 months of age as measured by preferential looking tests and an advantage of 0.83 ± 0.20 octaves at 4 months of age as measured by sweep VEP. No advantages were observed at other ages with either method.[30,31] Two studies of the visual acuity of supplemented vs. unsupplemented preterm infants have been reported since the meta analysis.[13,16] Innis et al. showed no increase in visual acuity in preterm infants fed formula containing DHA for less than 1 month when assessed at 2 or 4 months of corrected age, regardless of previous supplementation with DHA 4 to 5 months earlier.[13] O'Connor et al. showed no advantage from supplemented formula at any age with the preferential looking test but did find an advantage with supplemented formula at 6 months of age as measured by sweep VEP.[16] In our study, preterm infants fed supplemented formula seemed to have better visual acuity at 4 months on VEP and preferential looking tests but differences between these two groups were not significant. Delayed performance of these tests at 4 and 6 months or the small sample size with insufficient power may have led to a failure to find a difference.

To date, four studies of the effects of LCPUFA supplemented vs. unsupplemented formula on the cognitive function of preterm infants have been reported.[12,16-18] The results of these studies differed. Carlson et al. reported a somewhat lower MDI and PDI in supplemented infants at 12 months of age but this difference was not statistically significant.[17] The second report of Carlson et al. showed higher MDI and PDI in supplemented infants at 12 months of age,[12] but only if infants with bronchopulmonary dysplasia were excluded. O'Connor et al. reported no difference in MDI between supplemented and unsupplemented preterm infants but a higher PDI at 12 months of age in supplemented infants whose birth weights were less than 1250 gm.[16] Clanindinin et al. also reported an advantage from DHA and AA supplementation on the Bayley scale examination at 12 months of age.[18] In our study, the scores of the PDI and MDI were better in supplemented preterm infants. This result suggests a possible positive effect of LCPUFA supplementation on neurodevelopment. However, the study period was short and the case number was small. It is necessary to follow up the neurocognitive development and visual acuity of these infants until they are teenagers to observe the long term effects. It is also necessary to study more cases. A recent meta-analysis of the studies of subsequent cognitive outcome of breastfed vs formula-fed infants showed an advantage of 3 IQ points for breastfeeding.[24] If 3 IQ points is considered the maximal advantage of supplementation of LCPUFAs on cognitive function, it would be necessary to recruit more than 400 infants in each study group to detect such a small difference. Unfortunately, as of this time, no available study has included so many infants.

We did not find any major adverse effects from supplementation in our study. Prompt supplementation of AA and DHA in formula for preterm infants appears to be safe. Although we can not make conclusions regarding the essentiality of DHA and AA in formula for preterm infants, the addition of these potentially important fatty acids to formula for preterms may be considered.

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添加二十二碳六烯酸 (Docosahexaenoic Acid) 及花生四烯酸 (Arachidonic Acid) 對較大早產兒視力及神經學發展的影響

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背 景： 早產兒出生可能伴隨二十二碳六烯酸及花生四烯酸的缺乏，但是針對早產兒於配方奶中添加二十二碳六烯酸及花生四烯酸的研究卻相當有限。

方 法： 妊娠週數介於 30 到 37 週且合乎研究條件的早產兒被囊括入此研究。嬰兒於體重大於 2000 公克，週數達 32 週，且達完全餵食狀態後進入正式研究 6 個月。其中 16 位早產兒接受有添加二十二碳六烯酸及花生四烯酸之配方奶，11 位早產兒接受未添加二十二碳六烯酸及花生四烯酸之配方奶。嬰兒於 6 個月大及 1 歲大時接受貝利氏神經發展測驗，於 4 個月大及 6 個月大時接受視覺誘發電位及偏好視覺測驗 (Preferential looking test)。嬰兒每次回診皆接受身體檢查，紀錄身高、體重、頭圍及生命徵象。所有不良反應皆有紀錄。

結 果： 兩組嬰兒的平均 MDI (Mental Development Index) 於 6 個月大時分別爲 96.1 ± 8.6 及 91.7 ± 10.4，於 1 歲大時分別爲 98.7 ± 8.0 及 90.5 ± 6.9。平均 PDI (Psychomotor Development Index) 於 6 個月大時分別爲 102.2 ± 10.5 及 95.4 ± 13.2，於 1 歲大時分別爲 98.6 ± 5.8 及 86.7 ± 11.1。兩組嬰兒的 MDI 及 PDI 於 repeated measures ANOVA 統計上皆有顯著差異 (p = 0.020, 0.008)。視覺誘發電位及偏好視覺影像測驗的視力及每次回診的身體檢查及生命徵象，兩組均無有意義之差異。此外亦沒有明顯之不良作用被發現。

結 論： 結果顯示，於配方奶粉中添加二十二碳六烯酸及花生四烯酸可能對較大早產兒的神經學發展有所幫助。

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關鍵字： 二十二碳六烯酸，花生四烯酸，認知發展，視力。

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