SAFETY AND EFFICACY OF HIGH DOSE DOCOSAHEXAENOIC ACID FOR THE PRETERM INFANT

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SUMMARY

There has been substantial research demonstrating improvements in visual and cognitive performance of preterm infants after feeding formulas containing n-3 long chain polyunsaturated fatty acid (LCPUFA). The amount of docosahexaenoic acid (DHA) estimated to be accrued by the fetus in the last trimester of gestation is greater than that supplied in current preterm formulas and breast milk of average DHA content (~0.3% of total fat in Western women). Yet many trials have compared infants fed formula containing concentrations near 0.3% DHA with infants fed formula containing no LCPUFA. No research has addressed whether the average breast milk DHA milk results in optimal development of preterm infants. The focus of this thesis was to compare the efficacy and safety of supplementing preterm infants with milk containing docosahexaenoic acid (DHA) at concentrations that meet the estimated *in utero* accretion rate (~1%) compared with current clinical practices (~0.3%).

In a double-blind, randomised controlled trial (RCT), infants born <33 weeks gestation were assigned to receive milk containing one of two doses of DHA. Treatment group infants received milk containing high dose DHA (1%) and infants in the control group infants received milk containing standard levels DHA (0.2 - 0.35%). Lactating mothers consumed capsules containing either tuna oil (900mg DHA) or soy oil (no DHA) that resulted in breast milk with either a high or typical concentration of DHA. Standard preterm formula milk with a corresponding DHA composition was fed to infants if formula feeds were required. The intervention period was from five days of commencing enteral feeds through to the infants estimated due date (EDD). Primary efficacy assessment was sweep visual evoked potential (VEP) acuity at 4 months corrected age (CA). Secondary efficacy outcomes included VEP acuity at 2 months CA and VEP latency at 2 and 4 months CA. Infant anthropometry was assessed regularly throughout the trial and the primary safety outcome was weight at 4 months CA. Other clinical safety

data including incidence and severity of diseases commonly associated with prematurity were also assessed.

The success of the intervention was demonstrated with infants in the treatment group having a significantly higher level of erythrocyte membrane DHA at EDD compared with the control group (% total erythrocyte phospholipids (mean ± SD), treatment group 6.8 ±1.2, control group 5.2 ± 0.7, $p<0.0005$). The primary efficacy outcome of acuity at 4 months CA was significantly higher in the treatment compared with the control group infants (mean ± SD acuity (in cpd) treatment group 9.6 ± 3.7, control group 8.2 ± 1.8, $p = 0.025$). No significant differences were found in acuity at 2 months CA or latency at 2 or 4 months CA between infants in the control and treatment groups.

No significant differences in weight, length or head circumference were found between treatment compared with control infants at EDD or at 4 months CA. Nor were any differences found in other clinical outcomes commonly associated with prematurity including, tolerance, necrotising enterocolitis, sepsis, retinopathy of prematurity, bronchopulmonary dysplasia or intraventricular haemorrhage.

Increasing milk DHA to 1% of total fat suggests that the DHA requirement of preterm infants may be higher than the level available in preterm formula or breast milk of Australian women. Addressing both breast and formula milks demonstrates wide generalisability of these findings to common feeding practices in neonatal nurseries. Further studies are needed to determine whether this feeding strategy and dose of DHA is capable of improving other aspects of infant development.

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying.

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'Fight through ignorance, want, and care
Through the griefs that crush the spirit;
Push your way to a fortune fair,
And the smiles of the world, you'll merit.

Long, as a boy, for the chance to learn
For the chance that Fate denies you;
Win degrees where the Life-lights burn,
And the scores will teach and advise you.'

Henry Lawson

LIST OF ABBREVIATIONS

AA	Arachidonic acid
AC	alternating current
AFT	adaptive filter technique
AGA	appropriate for gestational age
ALA	Alpha linolenic acid
ANZNN	Australia and New Zealand Neonatal Network
AR	analytical reagent
BF	Breast fed
BPD	Bronchopulmonary dysplasia
BSID	Bayley Scales of Infant Development
CA	Corrected age
CDC	Centre for Disease Control
CDI	Communicative development inventory
CI	confidence interval
cm	centimetre
CNRC	Child Nutrition Research Centre
CPAP	continuous positive airway pressure
cpd	cycles per degree
CLD	Chronic lung disease
df	degrees of freedom
DHA	Docosahexaenoic acid
DPA	docosapentaenoic acid
EDD	estimated due date
EEG	electroencephalogram
EFA	essential fatty acid
EI	enteral intake
EPA	Eicosapentaenoic acid
ERG	Electroretinogram
Exc	Exclusive or exclusively
FAME	fatty acid methyl ester
FF	Formula fed
FFA	Free fatty acids
FT	full term
FTII	Fagan test of infant intelligence
GA	gestational age
GC	gas chromatograph
GI	gastrointestinal
HC	Head circumference
HDL	high density lipoprotein
HMD	Hyalin membrane disease
Hz	hertz
IQ	intelligence quotient
ITT	intention-to-treat
IV	intravenous
IVH	Intraventricular haemorrhage
kJ	kilojoule
kg	kilogram

L	litre
LA	Linoleic acid
LBW	low birth weight
LCPUFA	Long chain polyunsaturated fatty acid
LDL	low density lipoprotein
LED	Light emitting diode
LOS	length of stay
LPL	Lipoprotein lipase
MDI	motor development index
mL	millilitres
mo	months
MRI	Magnetic Resonance Imaging
msec	milliseconds
MUAC	mid upper arm circumference
ND	no difference
NEC	necrotising enterocolitis
NH&MRC	National Health and Medical Research Council
NICU	neonatal intensive care unit
NR	reported
NS	not significant
PC	Phosphatidyl choline
PCA	post conceptual age
PDA	patent ductus arteriosus
PDI	psychomotor development index
PE	Phosphatidyl ethanolamine
PET	Positron emission tomography
PI	Phosphatidyl inositol
PL	phospholipid
PMA	Post menstrual age
PS	Phosphatidyl serine
PUFA	polyunsaturated fatty acid
PVL	periventricular leukomalacia
RBC	red blood cell
RCT	Randomised Controlled Trial
RDS	Respiratory distress syndrome
REC	Research Ethics Committee
ROP	Retinopathy of prematurity
RR	Relative Risk
SD	Standard deviation
SES	socioeconomic status
SGA	Small for gestational age
SNR	signal to noise ratio
TLC	Thin layer chromatography
UV	ultraviolet
VEP	Visual evoked potential
VLBW	very low birth weight
yr	year