The Efficiency and Safety of a Higher Protein Human Milk Fortifier on Growth for Preterm Human Milk-fed Infants.

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Abbreviations

AGA	Appropriate for gestational age
ANZNN	Australian & New Zealand Neonatal Network
AOAC	Association of Official Analytical Chemists
BCAA	Branch chain amino acids
BUN	Blood urea nitrogen
BW	Birth weight
CHO	Carbohydrate
CI	Confidence interval
CLD	Chronic lung disease
CNRC	Child Nutrition Research Centre
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous positive airway pressure
CSUN	Corrected serum urea nitrogen
CV	Coefficient of variation
D/C	Discharge
DMAC	Data Management and Analysis Centre
EBM	Expressed breast milk
EDD	Estimated date of delivery
ELBW	Extremely low birth weight
FMC	Flinders Medical Centre
GA	Gestational age
GEE	Generalised estimating equations
GIT	Gastro-intestinal tract
HMF	Human milk fortifier
IQ	Intelligence quotient
IR	Infra-red
IUGR	Intra-uterine growth retardation
IV	Inverse variance
IVF	In-vitro fertilisation
IVH	Intraventricular haemorrhage

LBW	Low birth weight
MDI	Motor developmental indices
NATA	National Association of Testing Authorities
NEC	Necrotising enterocolitis
NED	Neonatal Early Discharge
NICU	Neonatal Intensive Care Unit
NMI	National Measurement Institute
NNT	Number needed to treat
NPN	Non-protein nitrogen
OHC	Occipital head circumference
PDA	Patent ductus arteriosis
PDI	Psychomotor developmental indices
PMA	Post menstrual age
PVL	Periventricular leukomalacia
QL	Quantitation limit
RCT	Randomised controlled trial
ROP	Retinopathy of prematurity
SCBU	Special Care Baby Unit
SD	Standard deviation *or* Study day
SE	Standard error
SES	Socio-economic status
SGA	Small for gestational age
SUN	Serum urea nitrogen
TEM	Technical error of measurement
TGA	Therapeutic Goods Administration
VLBW	Very low birth weight
WCH	Women's and Children's Hospital
WHO	World Health Organisation
WMD	Weighted mean difference

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Abstract

Preterm births represent approximately 8% of births in Australia, and this rate has been increasing over the last decade. Nutrition is a cornerstone of their medical management, yet very premature infants remain difficult to adequately nourish and growth failure is a common consequence of prematurity. Human milk is the preferred feed but has inadequate protein to meet their high requirements and must be fortified. Commercial fortifiers contain conservative amounts of protein and fail to compensate for the fall in the protein content of expressed breast milk over time. This thesis tested the hypothesis that preterm infants fed human milk with a higher protein fortifier (1.4 g/100 mL) would have greater length gain with no metabolic disturbances when compared to infants fed human milk fortified to standard levels (1.0 g protein/100 mL).

In a randomised controlled trial infants born <31 weeks gestation, whose mothers intended to provide breast milk for their infants, were randomly allocated to receive either the experimental fortifier containing 1.4 g protein or a fortifier equivalent to standard care, containing 1 g protein. The fortifiers were manufactured specifically for the study and were made isocaloric by adjusting the carbohydrate content. They were identical in appearance and mixing rates and all personnel involved in the trial were blinded to the allocation. Preterm formula was used if breast milk supply was inadequate. The intervention period was from the start of fortification to discharge or the infant's estimated due date, whichever came first. The primary outcome was length gain (cm/week) and secondary

outcomes included other growth measurements (weight and head circumference gain), biochemical markers (urea nitrogen, creatinine, albumin, pH, amino acids) and data describing their clinical course during the hospital admission.

There was a slight improvement in length gain in the higher protein group but this did not reach statistical significance (mean (95% CI) 1.15 (1.10-1.19) and 1.09 (1.05-1.13) cm/week in the higher and standard groups respectively, $p = 0.08$). However, fewer infants were classified as small for gestational age for length at discharge in the higher protein group (49% versus 63% in the higher and standard protein groups, respectively, $p = 0.04$). There were no differences in weight or head circumference gain between the groups. Serum urea nitrogen concentrations and whole blood amino acid levels were higher in the higher protein group but plasma albumin, creatinine and pH were not different between groups. There were no differences in clinical outcomes such as retinopathy of prematurity, sepsis, necrotising enterocolitis, number of infants requiring surgery or length of hospital stay.

A higher protein human milk fortifier appears to be well tolerated and safe to use in preterm human milk fed infants born <31 weeks gestation. The extra protein protects against a classification of small for gestational age for length at discharge and may improve length gain. Further studies directed toward comparisons between fortifiers with levels of protein >1 g/100 mL are required to determine the optimum protein concentration of fortifiers.

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 has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue, the Australasian Digital Theses Program (ADTP) and also through web search engines.

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