The ProVIDe Study

Does better early nutrition in preterm babies improve development?

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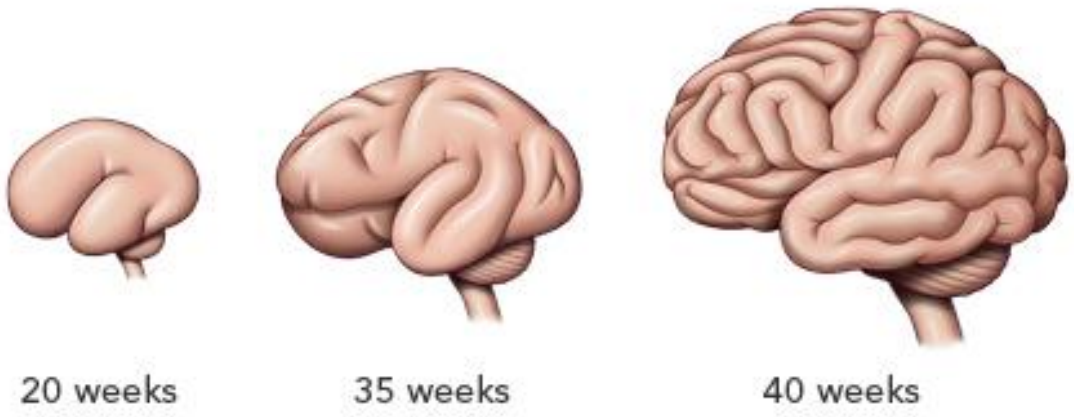
Background

- Preterm birth and being born very small have long term effects on growth and neurodevelopment
- Up to 50% of ELBW babies experience neurodevelopmental or learning impairment in childhood

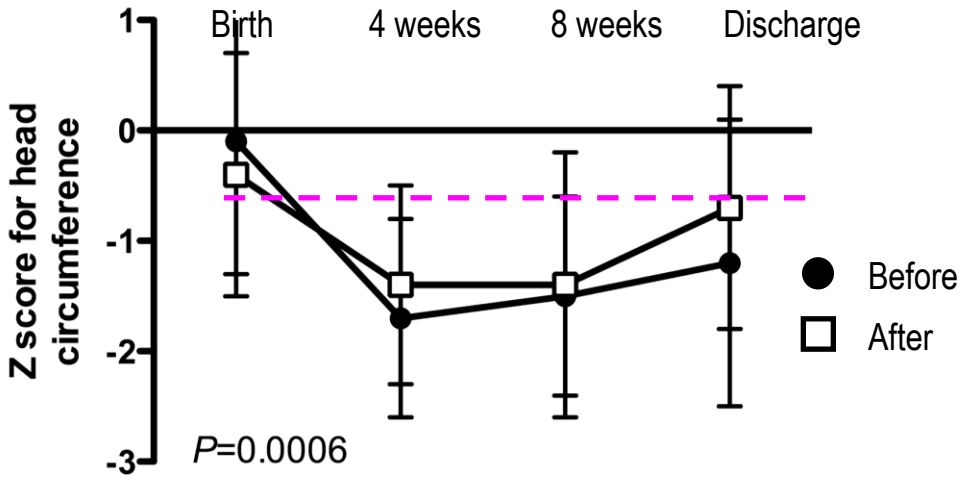
Brain growth 29 to 41weeks gestation



- Extremely rapid growth *in utero* - 29 to 41weeks gestation
- Total brain tissue volume increases by 22 mL each week (3 D MRI)[1]

1. Huppi PS et al, Annals of Neurology 1998;43:224-35
2. Cheong JL et al, Pediatrics 2008;121:e1534-40

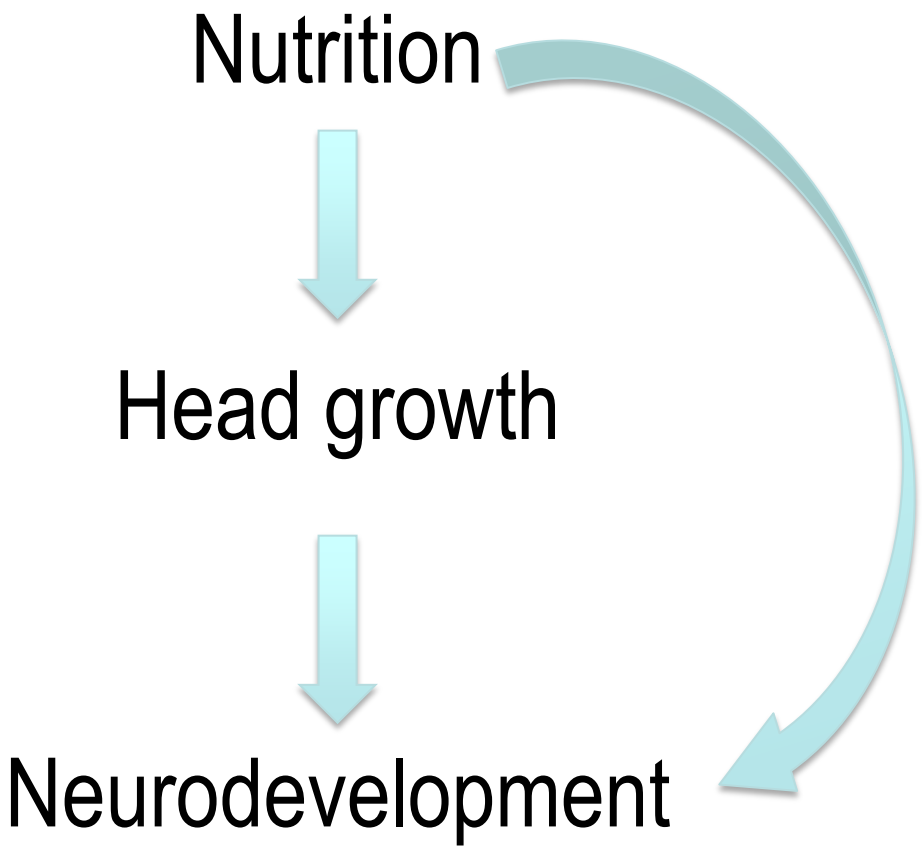
Head circumference



- Prospective study
- 100 ELBW babies - ACH
- 50 before and 50 after a change in nutrition policy to ↑protein to meet RNIs
- z scores for head circumference – birth to discharge

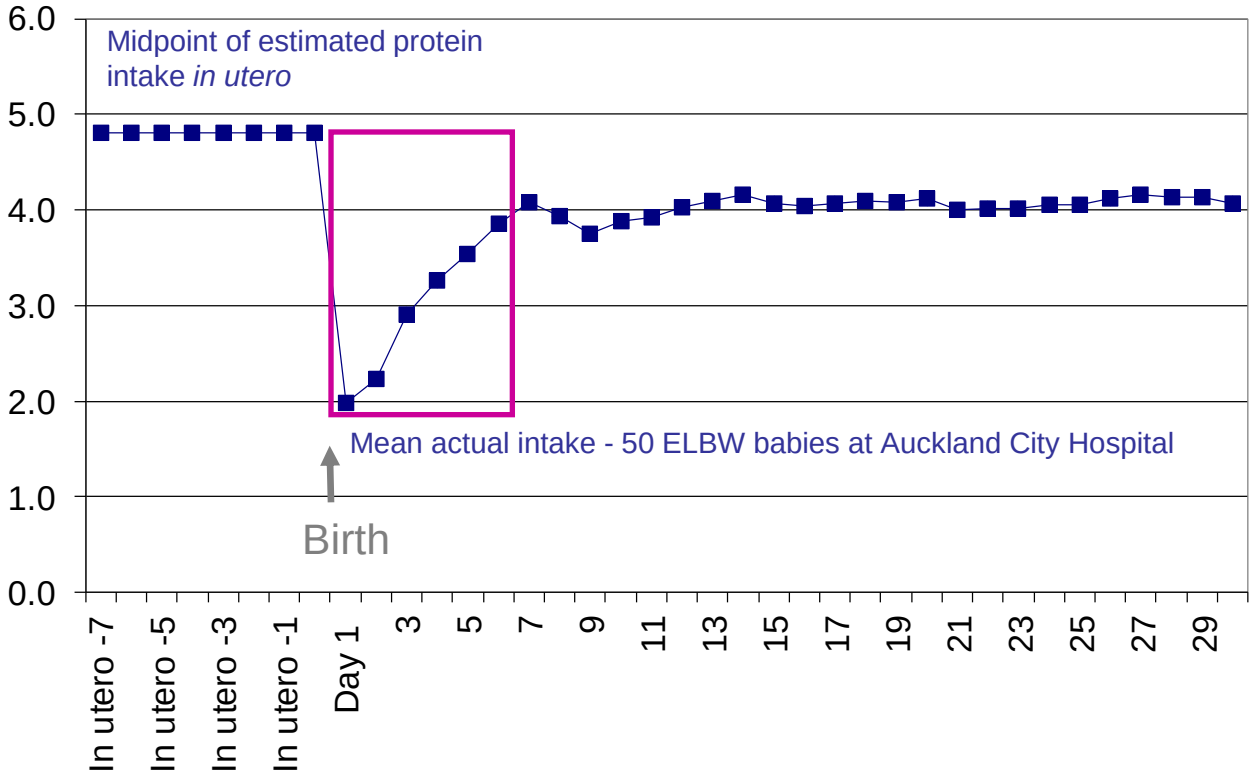
- Intrauterine growth = z score change of zero - - - - - -
- Not the classic faltering growth of poorly nourished term infants
- ELBW babies - head growth affected much more quickly
- Falling up to 2 z scores in the 1st month[1, 2]

1. Cole TJ et al, Archives of Disease in Childhood 2011; 96(Suppl 1); A3-A4.
2. Cormack BE, Bloomfield FH. Archives of Disease in Childhood Fetal and Neonatal Edition 2013. doi:10.1136/archdischild-2012-302868



- Increased protein intake in the neonatal period improves growth and neurodevelopment
- Optimal amount of protein required is unknown

Nutrition *in utero* vs. postnatal



A serious nutritional insult at a time of very rapid growth

Week 1 nutrition - a key modifiable factor for improving growth

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Protein IVN: Impact on Development

Hypothesis

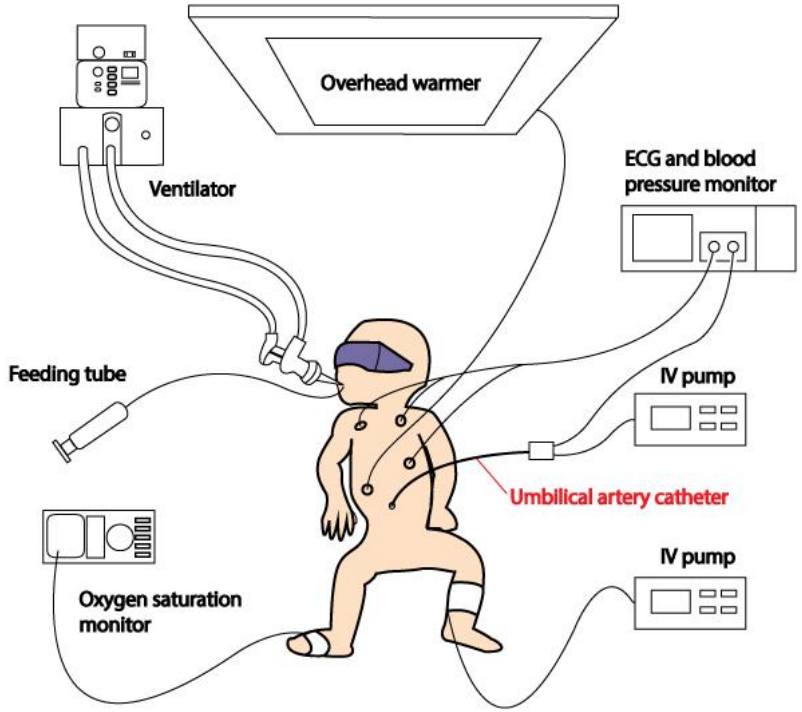
For ELBW babies, increased protein intake in the first week after birth will improve survival free from any neurodevelopmental impairment at 2 years corrected age

Methods

Multicentre, double-blind, placebo controlled RCT of an extra 1 to 2 g/Kg.d of intravenous protein commencing within 24 hours of birth and continuing for the first 5 days

Intervention

- Umbilical arterial catheter (UAC) placed shortly after birth
- 0.5 ml/hour saline given to keep the line patent - 12 ml/day



Treatment group:
UAC solution: amino acid solution providing 1 g/day protein

Control group:
UAC solution: saline

Standard intravenous nutrition will be prescribed daily according to current NICU practice

Study Design

Inclusion criteria

Babies with a birthweight of less than 1000 g with a UAC

Exclusion criteria

- Admission to NICU >24 hours after birth
- Multiple births >2
- Known chromosomal or genetic abnormality, or congenital disorder affecting growth, inborn error of metabolism
- In danger of imminent death

Reasons for withdrawal

- Diagnosis of an inborn error of metabolism
- Parents may withdraw their baby from the study at any time

Waiver of consent for 24 hours

Northern B Health and Disability Ethics Committee has given ethical approval (No 13/NTB/84)

- Optimum ELBW Day 1 protein intake is unknown
- Day 1 RNI of 1 - 2 g/kg.d is unsupported by evidence[1]
- 4 g/kg protein, initiated after delivery, is safe with no evidence of metabolic acidosis, hyperammonaemia or azotaemia[2]
- Standard practice in some NICUs to give 3.5 – 4.0 g/kg.d as soon as possible after birth[3]
- Such variation ranging from 0 to 4 g/kg.d protein on Day 1[4-6] that the intakes of both groups will be within this range

1. Tsang RC et al, Nutrition of the Preterm Infant 2ed 2005
2. Thureen PJ et al, Clinical Perinatology 2000
3. Blanco CL et al, Journal of Pediatric Gastroenterology and Nutrition 2012
4. Cormack B et al, Journal of Paediatrics and Child Health 2012
5. Hans DM et al, Pediatrics 2009
6. Kiefer AS et al, American Journal of Perinatology 2009

Blinding

- Subjects and their families, clinical staff, investigators and assessors at follow up appointments – all blinded to allocation
- UAC solution bags – plain packaged, only numerical identifier
- Unblinding should occur only in exceptional circumstances
- The actual allocation must not be disclosed to parents and/or other study personnel including project office staff
- Any code break will be reported to the principal investigator without identifying treatment allocation

Outcome Measures

Primary:

Survival free from neurodevelopmental impairment at 2 years corrected age (CA)

Secondary:

- Growth from birth to NICU discharge
- Body composition at 36 weeks CGA by air displacement plethysmography (PEA POD) and DXA at 2 years CA
- Neonatal morbidity, length of NICU stay

Sample size:

Sample size of 430 babies will allow detection of an absolute difference of 15% in survival free of impairment at 2 years CA, i.e. from 50% to 65% (at least 85% power at a 5% level of significance (two-sided))

Relevance of the study

- First direct evidence of the effects of giving preterm babies an earlier higher intake of intravenous protein in the first week after birth on neurodevelopment, growth and body composition at discharge
- Uses a simple, inexpensive method of administering additional protein that could easily be implemented in other neonatal units

The ProVIDe Study

is supported by Gravida, an A+ Trust Project Grant and the Nurture Foundation

A+ Trust

nurture

Gravida
NATIONAL CENTRE FOR GROWTH AND DEVELOPMENT

6 NZ ProVIDe Study Centres

- Auckland City Hospital
- Middlemore Hospital
- Waikato Hospital
- Wellington Hospital
- Christchurch Hospital
- Dunedin Hospital

ProVIDe Study Co-investigators

Professor Frank Bloomfield - Liggins Institute
Professor Caroline Crowther - Liggins Institute
Professor Jane Harding - Liggins Institute
Dr Cathryn Conlon - Nutrition researcher, Massey University
Dr Yannan Jiang - Statistician, The University of Auckland

Investigators in other centres:
Mike Meyer - Middlemore Hospital
Arun Nair - Waikato Hospital
Michael Hewson - Wellington Hospital
Adrienne Lynn - Christchurch Hospital
Roland Broadbent – Dunedin Hospital
Australian centres to follow…

Practical Details

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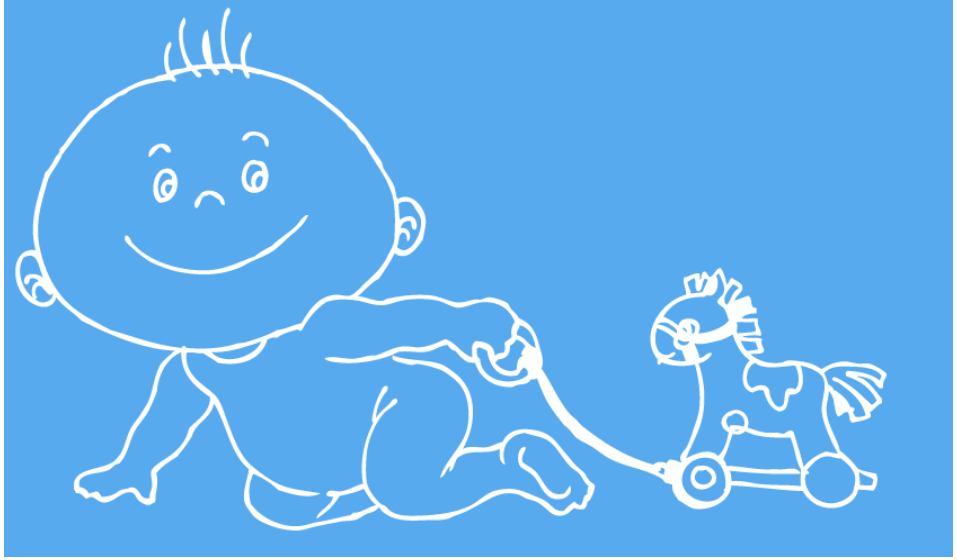
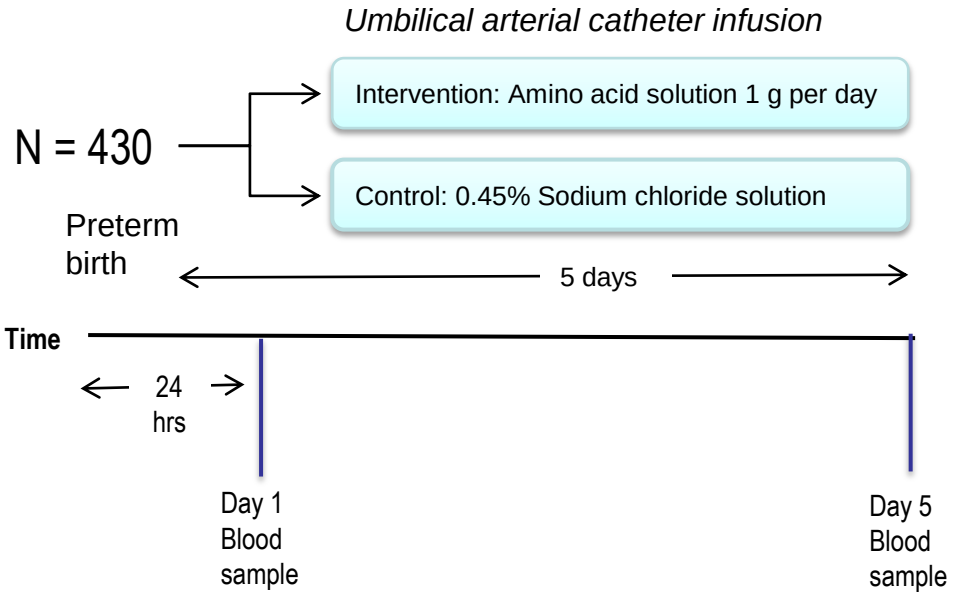


Flowchart of the ProVIDe study



ProVIDe Study Protocol

Study day	Intervention/data collection
Day 0	Randomisation (consent within 24 hours)
(day of birth)	Guthrie test once UAC is placed before study infusion begins
Day 1	Blood sample (24 hours after UAC infusion is started)
Day 3	2nd ProVIDe study UAC fluid bag started (via website)
Day 5	Day 5 Blood sample and 2nd Guthrie Test (after UAC infusion stops) ProVIDe study UAC fluid finishes after 120 hours
Day 28	Weight, length and head circumference
Day 56	Weight, length and head circumference
36 weeks CGA	Weight, length and head circumference **Pea Pod Assessment (ACH only)**
NICU Discharge	Weight, length and head circumference
2 years CGA	Weight, length and head circumference **Dual-energy X-ray absorptiometry (DXA)** **Neurodevelopmental assessment** - BSID-III, gross motor function classification score and standard paediatric assessments

CGA = corrected gestational age

Biochemistry

Day	Blood test
Day 1 *(24 hours after UAC placed)*	Total protein, urea, albumin, pH, base excess, calcium, phosphate (0.5 ml)
Day 5 *(before UAC removed)*	Total protein, urea, albumin, pH, base excess, calcium, phosphate, (0.5 ml) Ammonia (0.5 ml)

See Bedside plan

Randomisation

https://www.ligginstrials.org

UAC Treatment Pack

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Important: Do not use this solution to flush the line.
Please use saline for all flushes. Do not add heparin.

Do not remove the black plastic bag.
Do not use the UAC to take Newborn Screening (Guthrie) blood samples.

Emergency contacts:
Barbara Cormack Mob 021 2529 469
Dr Frank Bloomfield
Mob 021 497598

UAC Treatment Pack No. PS005

For clinical trial use only via UAC as per protocol
100 ml ProVIDe Study UAC Infusion
(8.5% Trophamine or 0.45% Saline)
with 50 units heparin per 100 ml

Expiry date:
Store in the fridge (96 hour hang time)

Discard after _____on _____
Clinical Trials No. ACTRN12612001084875
Emergency contact Barbara Cormack Mob 021 2529 469
Dr Frank Bloomfield Mob 021 497598

Biomed Biomed Limited SU673/3
AUCKLAND

Five Nursing Care Differences

1. **Blinding** - black plastic bag, don't ask don't tell
2. **Heparin** - do not add more heparin
3. **UAC flushes** - don't flush UAC line with study fluid
4. **Newborn Metabolic Screening (Guthrie test)**
   Day 1 and Day 5 only 2 blood spots (not at 48 hours)
5. **UAC Hang time is 3 days**
   Visit the randomisation website again on day 3 to get 2nd UAC treatment pack number

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is supported by Gravida, an A+ Trust Project Grant, Cure Kids and the Nurture Foundation