Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand).

This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognise the author's right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author's permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage. [http://researchspace.auckland.ac.nz/feedback](http://researchspace.auckland.ac.nz/feedback)

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library Thesis Consent Form and Deposit Licence.

Note : Masters Theses

The digital copy of a masters thesis is as submitted for examination and contains no corrections. The print copy, usually available in the University Library, may contain corrections made by hand, which have been requested by the supervisor.
Neonatal Hypoglycaemia

Deborah Louise Harris

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Nursing, The University of Auckland, 2013
Abstract

Aim

Neonatal hypoglycaemia is common and a preventable cause of neurological impairment, but the best way to detect and manage it remains unclear. The aim of the studies in this thesis was to provide the basis for a more rational approach to the clinical management of neonatal hypoglycaemia.

Method

To determine the relationship between neurological function, blood glucose concentrations and alternative cerebral fuels, we induced hypoglycaemia in newborn lambs and conducted an observational study in at-risk babies (the BABIES study). Neurological function was measured using continuous amplitude integrated electroencephalography (aEEG) and glucose concentrations were measured using standard blood glucose measurements (glucose oxidase) and continuous interstitial glucose monitoring.

We assessed current management of neonatal hypoglycaemia by a survey of the Australian and New Zealand Neonatal Network. We then undertook a randomised trial (The Sugar Babies) to determine whether 40% dextrose gel was more effective than feeding alone to treat neonatal hypoglycaemia.

Findings

We did not find changes in the aEEG related to glucose concentrations. Continuous glucose monitoring showed moderate agreement with blood glucose concentrations in lambs and better agreement in babies. However, 81% of episodes of low interstitial glucose concentrations were not detected by blood glucose measurement.

Most survey respondents would treat babies with a blood glucose concentration of \(<2.6\) mmol/L. However, respondents reported a wide variation in treatment thresholds and interventions.

In the Sugar Babies Study, half of babies in all at risk groups became hypoglycaemic, in a timeframe that did not correspond to current screening guidelines. Babies who received dextrose gel were less likely to remain hypoglycaemic or be admitted to the Newborn
Intensive Care Unit for hypoglycaemia, received fewer formula feeds and were less likely to be formula fed at two weeks of age.

Conclusion
The aEEG is not clinically useful in monitoring neonatal hypoglycaemia. Continuous interstitial glucose monitoring is safe and reliable, but not yet appropriate for widespread clinical use. Dextrose gel should be considered for first line treatment of hypoglycaemia in late-preterm and term babies. These studies have substantially increased the understanding of neonatal hypoglycaemia, and are likely to alter clinical management.
Dedication

This thesis is dedicated to those babies who made the BABIES and Sugar Babies studies possible.
Acknowledgements

The decision to start doctoral studies was carefully made. There were three factors which were essential prior to taking those first steps six years ago. The first was the support of my husband, Kevin. The second was the topic had to be clinically focused and have the potential to make it better for the babies. Finally, my primary supervisor had to be Jane Harding. Without any of these foundations I would not have started the journey. I remain grateful every day for the privileged opportunity and for those who have shared and guided the journey.

The studies which make up this thesis were performed at the University of Auckland within the Liggins Institute and the Ngapouri Farm Laboratory. The clinical studies – BABIES and Sugar Babies, were performed at Waikato Women’s Hospital. I have been generously supported by; Waikato Hospital, Auckland Medical Research Foundation, Waikato Medical Research Foundation, the Maurice and Phyllis Paykel Trust, the New Zealand Nursing Education and Research Foundation, and the Rebecca Roberts Scholarship.

Our first study was the Lamb Study. Every part of this study was a vertical learning curve. Mark Oliver and the team at Ngapouri willingly shared their knowledge, skills and experience. As a result, I hope one day to return to the animal laboratory. After the experiments were completed, Eric Thorstensen from the Liggins laboratory taught me the skills required to analyse the blood samples taken from the lambs.

The BABIES and Sugar Babies studies would not have been possible without the consent of families who believed that our studies were safe and worthwhile. I am indebted to these families and remain mindful of my on-going responsibility to care for such a special gift.

I am also indebted to the staff in the Newborn Intensive Care Unit, Delivery Suite, and Ward 52 who supported our clinical studies. In particular, Research Nurses Cathy McBride, Paula Middlemiss, and Susanne Butler who many times went above and beyond the call of duty.

I have been fortunate to work with and be supervised by Malcolm Battin who helped design the studies and read manuscripts. Malcolm also provided wise counsel, encouraging words, and much needed coffee from time to time. David Bourchier has also been an advisor, he has always been interested in the studies and my progress. In addition, David has had the
unfortunate task of being responsible for my clinical roster over the past six years. I am grateful for the flexibility he permitted which gave me time to spend on my research.

Phil Weston has been my clinical supervisor and friend. He has shared every part of this journey; from the animal laboratory, to working together on the clinical studies then entering, cleaning and discussing data, and finally presenting our findings at international meetings. Phil has been enabling, he has believed in my ability and shared my passion to make it better for the babies. I am grateful for his support, insight, strength, and care.

Jane Harding has been my inspiration, supervisor, mentor, teacher, and friend. Jane has patiently guided my stumbling, read countless draft manuscripts, suggested directions to investigate, and always encouraged my thinking. Thank you Jane, for the opportunity and for placing me so firmly under your wing.

I would also like to acknowledge my parents – David Allan and Stephanie Chapman. Both taught me among many things, the importance of a sound work ethic, resilience, and compassion. Without these skills, the studies that make up this thesis would not have been possible.

Jasmine Plimmer – my oldest friend. Thank you for your constant encouragement and understanding.

Alex Wallace – thank you for being my PhD buddy. Thank you for the endless chats about how to juggle PhD life, family life, and clinical practice. You are the only person I know who understands that a regular movie date means once every 18 months.

Finally, and most importantly, I would like to thank and acknowledge the love, support, and patience of Kevin, Sebastian, Oliver, and Elliott.

You are and always will be my North, South, East, and West.

Per aspera ad astrum
# Table of Contents

Abstract........................................................................................................................................ ii

Dedication....................................................................................................................................... iv

Acknowledgements........................................................................................................................ v

List of Figures ................................................................................................................................ x

List of Tables .................................................................................................................................. xi

List of Abbreviations and Symbols................................................................................................xii

Co-Authorship Forms .................................................................................................................... xiii

Chapter 1: Literature review........................................................................................................1

1.1 History ................................................................................................................................. 1

1.2 Definition of Neonatal Hypoglycaemia ........................................................................... 7

1.2.1 The clinical approach ...................................................................................................... 7

1.2.2 The epidemiological approach ..................................................................................... 7

1.2.3 Neurophysiological and metabolic-endocrine function ............................................. 9

1.2.4 The neurodevelopmental approach ............................................................................ 10

1.2.5 Variation in the definition ........................................................................................... 10

1.2.6 Current recommendations ........................................................................................... 11

1.3 Measurement of blood glucose concentrations .............................................................. 12

1.3.1 Intermittent blood glucose sampling .......................................................................... 13

1.3.2 Continuous glucose monitoring .................................................................................. 13

1.4 Metabolic adaptation .......................................................................................................... 13

1.4.1 Before birth .................................................................................................................. 13

1.4.2 At birth.......................................................................................................................... 14

1.4.3 Normal metabolic adaptation ...................................................................................... 15

1.4.4 Impaired metabolic adaptation ................................................................................... 17

1.5 Other factors causing neonatal hypoglycaemia ............................................................... 20

1.5.1 Normal substrate availability with increased metabolic demands .......................... 20

1.5.2 Normal metabolic demands with decreased substrate availability ....................... 21

1.6 Neonatal hypoglycaemia and brain .................................................................................. 24

1.6.1 Severity of hypoglycaemic episodes ........................................................................... 24

1.6.2 Recurrent hypoglycaemic episodes .......................................................................... 25

1.6.3 Duration of hypoglycaemic episodes ........................................................................ 25

1.6.4 Cerebral compensatory mechanisms during hypoglycaemia ................................ 25

1.7 Detection of neuronal injury ............................................................................................... 26

1.7.1 Electrophysiology ........................................................................................................ 26

1.7.2 Cot-side electroencephalogram ................................................................................. 27

1.7.3 Brainstem evoked potentials ....................................................................................... 28

1.7.4 Neuroimaging ............................................................................................................... 29

1.7.5 Pattern of neuronal hypoglycaemic damage ............................................................... 29

1.7.6 The mechanism of neural injury ................................................................................ 30

1.8 Treatment for neonatal hypoglycaemia .......................................................................... 31

1.8.1 Standard treatment ....................................................................................................... 31

1.8.2 Medications .................................................................................................................. 32

1.8.3 Potential new treatments ............................................................................................. 33
1.9 Neurodevelopmental outcome following neonatal hypoglycaemia ........................................ 34
1.10 References ................................................................................. 35

Chapter 2 : Introduction to the studies ................................................................. 46
2.1 Neonatal hypoglycaemia ........................................................................... 46
2.2 References ......................................................................................... 49

Chapter 3 : Cot-side electro-encephalography and interstitial glucose monitoring during insulin-induced hypoglycaemia in newborn lambs ........................................... 51
3.1 Abstract ......................................................................................... 52
3.2 Introduction ..................................................................................... 52
3.3 Materials and methods ....................................................................... 53
  3.3.1 Analysis of blood samples ............................................................ 55
  3.3.2 Continuous glucose monitor ......................................................... 55
  3.3.3 Analysis of EEG ......................................................................... 55
  3.3.4 Statistical analysis ..................................................................... 56
3.4 Results ............................................................................................. 56
  3.4.1 Blood glucose levels .................................................................. 56
  3.4.2 Insulin ...................................................................................... 57
  3.4.3 Alternative fuels ....................................................................... 57
  3.4.4 Clinical changes ....................................................................... 57
  3.4.5 Electro-Encephalogram ............................................................... 58
  3.4.6 Comparison between continuous interstitial and blood glucose levels ........................................... 59
3.5 Discussion ........................................................................................ 60
  3.5.1 Acknowledgements ................................................................... 64
3.6 References ........................................................................................ 64

Chapter 4 : Cot-side EEG monitoring is not clinically useful in the detection of early neurological changes related to mild neonatal hypoglycaemia ........................................... 67
4.1 Abstract ......................................................................................... 68
4.2 Introduction ..................................................................................... 68
4.3 Methods .......................................................................................... 70
4.4 Results ............................................................................................. 72
4.5 Discussion ....................................................................................... 76
4.6 Acknowledgments ........................................................................... 78
4.7 References ........................................................................................ 79

Chapter 5 : Continuous glucose monitoring in newborn babies at risk of neonatal hypoglycemia............................................................... 82
5.1 Abstract ......................................................................................... 83
5.2 Background .................................................................................... 83
5.3 Methods .......................................................................................... 84
5.4 Results ............................................................................................. 86
5.5 Discussion ....................................................................................... 91
5.6 References ........................................................................................ 93

Chapter 6 : A survey of the management of neonatal hypoglycaemia within the Australian and New Zealand Neonatal Network ................................... 95
6.1 Abstract ......................................................................................... 96
6.2 Background .................................................................................... 96
6.3 Method ............................................................................................ 97
6.4 Results ............................................................................................. 98
  6.4.1 Response rate ........................................................................... 98
  6.4.2 Protocols .................................................................................. 98
  6.4.3 Screening ................................................................................ 98
  6.4.4 Diagnosis ............................................................................... 99
  6.4.5 Definition of neonatal hypoglycaemia ........................................ 99
List of Figures

Figure 3-1. Comparison between blood and interstitial glucose levels in 1 lamb ......................... 59
Figure 3-2. Bland-Altman plot of blood glucose and interstitial glucose levels .......................... 60
Figure 4-1. The severity, duration and frequency of low glucose concentrations .................... 73
Figure 4-2. Comparison between interstitial and blood glucose concentrations matched with left, right and occipital aEEG data in a 30-hour period in one baby .................................................. 75
Figure 5-1. Example from 1 baby showing blood and interstitial glucose concentrations and treatment. .................................................................................................................................................................................. 87
Figure 5-2. Bland-Altman plot of the relationship between A, blood and interstitial glucose concentrations overall and B, at glucose concentrations <3.0mmol/L .................................................. 88
Figure 5-3. Differences between blood and interstitial glucose concentrations A, on the first day of monitoring and B, over 7 days of monitoring .................................................................................................. 89
Figure 5-4. The duration of episodes of low interstitial glucose concentrations .................... 90
Figure 7-1. The incidence of neonatal hypoglycemia in babies with different combinations of risk factors .................................................................................................................................................. 123
Figure 8-1. Consort diagram for the Sugar Babies cohort ................................................................ 136
List of Tables

Table 3-1. Heart rate, oxygen saturation and plasma levels of cerebral fuels during the four experimental time periods ................................................. 57
Table 3-2. Amplitude-integrated EEG minimum amplitude and continuity measurements and EEG 90% spectral edge frequency measurements during the 4 experimental time periods .......... 58
Table 4-1. Demographic data for babies studied ......................................................... 72
Table 4-2. Comparison of electroencephalography variables according to gestational age, electroencephalography montage position, and blood glucose concentrations .............. 74
Table 4-3. Plasma concentrations of non-glucose cerebral fuels at study entry and exit and during clinically detected hypoglycemia .............................................................................. 76
Table 5-1. Demographic data for babies studied .......................................................... 86
Table 5-2. Low blood glucose concentrations ................................................................... 90
Table 6-1. Reported screening for neonatal hypoglycaemia .......................................... 98
Table 6-2. Analysers reported to be used for the diagnosis of neonatal hypoglycaemia ........................................ 99
Table 6-3. Blood glucose levels at which respondents reported that treatment would be provided for hypoglycaemia ............................................................................. 100
Table 6-4. First treatment choice for clinical scenario of asymptomatic hypoglycaemic breast fed babies ............................................................................. 100
Table 7-1. Demographic data for babies who did and did not become hypoglycemic and their mothers ........................................................................... 122
Table 7-2. Incides of hypoglycemia in babies with difference risk factors ....................... 124
Table 8-1. Characteristics of mothers and babies at trial entry ........................................ 137
Table 8-2. Primary and Secondary Outcomes in babies randomized to dextrose or placebo gel ... 139
Table 8-3. Rebound and recurrent episodes and duration of hypoglycemia in babies randomized to dextrose or placebo gel ................................................................................. 141
<table>
<thead>
<tr>
<th>Abbreviation/Expression</th>
<th>Symbol/Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine diphosphate</td>
<td>ADP</td>
</tr>
<tr>
<td>Adenosine triphosphate</td>
<td>ATP</td>
</tr>
<tr>
<td>Amplitude integrated electroencephalograph</td>
<td>aEEG</td>
</tr>
<tr>
<td>Appropriate for gestational age</td>
<td>AGA</td>
</tr>
<tr>
<td>Australian and New Zealand Neonatal Network</td>
<td>ANZNN</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>BMI</td>
</tr>
<tr>
<td>Brainstem auditory evoked potential</td>
<td>BAEP</td>
</tr>
<tr>
<td>Brainstem auditory evoked response</td>
<td>BAER</td>
</tr>
<tr>
<td>Children with Hypoglycaemia and their Later Development</td>
<td>CHYLD</td>
</tr>
<tr>
<td>Confidence Intervals</td>
<td>CI</td>
</tr>
<tr>
<td>Continuous glucose monitoring sensor</td>
<td>CGMS</td>
</tr>
<tr>
<td>Day</td>
<td>d</td>
</tr>
<tr>
<td>Decibel</td>
<td>dB</td>
</tr>
<tr>
<td>Electroencephalography</td>
<td>EEG</td>
</tr>
<tr>
<td>Glucose transporter</td>
<td>GLUT</td>
</tr>
<tr>
<td>Grams</td>
<td>g</td>
</tr>
<tr>
<td>Hertz</td>
<td>Hz</td>
</tr>
<tr>
<td>Kilogram</td>
<td>kg</td>
</tr>
<tr>
<td>Kilohm</td>
<td>kΩ</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>LGA</td>
</tr>
<tr>
<td>Magnetic Resonance Imaging</td>
<td>MRI</td>
</tr>
<tr>
<td>Meters squared</td>
<td>m²</td>
</tr>
<tr>
<td>Microvolts</td>
<td>µV</td>
</tr>
<tr>
<td>Milligrams per deciliter</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Milliliters</td>
<td>ml</td>
</tr>
<tr>
<td>Millimoles</td>
<td>mM</td>
</tr>
<tr>
<td>Millimoles per litre</td>
<td>mmol/l or mmol/L</td>
</tr>
<tr>
<td>Minutes</td>
<td>min</td>
</tr>
<tr>
<td>Microvolts squared</td>
<td>µV²</td>
</tr>
<tr>
<td>Monocarboxylate transporter</td>
<td>MCT</td>
</tr>
<tr>
<td>Newborn Intensive Care Unit</td>
<td>NICU</td>
</tr>
<tr>
<td>Number</td>
<td>n</td>
</tr>
<tr>
<td>Ohms</td>
<td>Ω</td>
</tr>
<tr>
<td>Phosphoenolpyruvate carboxykinase</td>
<td>PEPCK</td>
</tr>
<tr>
<td>Relative risk</td>
<td>RR</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>SGA</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>SD</td>
</tr>
<tr>
<td>Week</td>
<td>wk</td>
</tr>
<tr>
<td>Year</td>
<td>y</td>
</tr>
</tbody>
</table>
Chapter 1: Literature review

1.1 History

Blood glucose concentrations were first measured in babies in 1911. Using a method developed by Moeckel and Frank, the blood glucose concentration was measured in seven babies with ages ranging from 9 to 21 days. All babies were fasted for three hours prior to the blood tests. The blood glucose concentrations ranged from 0.076 to 0.098 g/100 ml (4.2 to 5.4 mmol/L), with an average of 0.085 g/100 ml (4.7 mmol/L).

In the early 1950s several authors reported that the blood glucose concentrations of newborn babies were lower than those of children or adults and varied over the first few weeks after birth (Hartmann and Jaudon 1937; Norval, Kennedy et al. 1949; Norval 1950).

In the early 1930s authors suggested a link between low blood glucose concentrations and convulsions followed by poor neurological outcome. Case studies were published reporting an association between low blood glucose concentrations and convulsions in children following removal of the liver, overdoses of insulin and tumours within the islets of Langerhans (Mann and Magath 1922; Gammon and Tenery 1931; Bowen and Beck 1933). Others reported cases of children having convulsions both with and without hypoglycaemia, and questioned whether hypoglycaemia caused convulsions (Darrow 1936).

In the early 1930s scientists were also reporting new findings regarding carbohydrate metabolism, including factors which influence low blood glucose concentrations. These findings caused debate, as some considered that hypoglycaemia was solely attributed to excess insulin, (Harris 1924) whereas others considered that hypoglycaemia resulted from a lack of sufficient glucose (Hartmann and Jaudon 1937). Wauchope was the first to attempt classifying the aetiology of hypoglycaemia, breaking the causes into four categories (Wauchope 1932).

- Factors that cause excess of insulin, such as therapeutic injections, tumours, hyperplasia of the pancreas, and idiopathic causes.

- Factors opposing secretions, including diseases of the suprarenal glands and pituitary tumours.
Factors causing a lack of glycogen, including diseases of the liver, starvation, lactation, muscular exercise, wasting of the muscles.

Factors that interfere with the regulating centre, including nervous disease affecting the pons, or an overactive vagus nerve.

Since this first attempt to classify hypoglycaemia according to causative factors, others have refined the classification and added hypoglycaemia related to specific populations such as neonatal hypoglycaemia. However, the major factors thought to lead to the development of hypoglycaemia remain unchanged from those identified by Wauchope.

In 1937 Hartmann and Jaudon reviewed 286 babies with hypoglycaemia documented over a 15 year period (Hartmann and Jaudon 1937). They suggested that hypoglycaemia could be described as mild, moderate or severe and based these categories on blood glucose concentrations.

- **Mild hypoglycaemia** 2.22 to 2.78 mmol/L
- **Moderate hypoglycaemia** 1.11 to 2.22 mmol/L
- **Severe hypoglycaemia** <1.11 mmol/L

This was the first attempt to define neonatal hypoglycaemia according to a blood glucose concentration. Furthermore, this definition emphasised that hypoglycaemia was an abnormality that could range from mild to severe. The signs of hypoglycaemia included pallor, tremor, twitchiness, sweating, lethargy, floppiness, coma and seizures.

In the same paper the authors reported that hypoglycaemia was common in three different groups of babies. Healthy newborn babies in the first four to five days after birth were the first group to be identified, and the authors concluded that hypoglycaemia in this group was due to immaturity of the regulation systems of the newborn. The second group was babies of diabetic mothers. These babies had more severe clinical signs; some had convulsions and died. But somewhat perplexingly, some of these babies were reported to have low blood glucose concentrations with no clinical signs of hypoglycaemia. The third group was those with recurrent severe hypoglycaemic episodes. These babies frequently convulsed, or collapsed and died. The authors suggested that babies with these clinical signs were insulin hypersensitive primarily because of lack of hormonal control from the adrenal or pituitary glands.
Hartmann and Jaudon reported that death from hypoglycaemia was preventable and should not occur. Early regular feeds, either with milk or sugar water, were considered essential, and if the baby demonstrated clinical signs of hypoglycaemia such as convulsions then administration of intravenous dextrose and/or adrenalin was reported to be lifesaving. Despite this knowledge in 1937, many babies are reported to have died from hypoglycaemia since that time (Cornblath, Odell et al. 1959; Brown and Wallis 1963).

Between the late 1920s and early 1950s multiple studies reported blood glucose concentrations to be lower in babies than in children and adults, with babies who were preterm, low birth weight or of diabetic mothers having the lowest blood glucose concentrations. The consequence of these low blood glucose concentrations for the babies was not clear in these studies.

Nearly 20 years later Cornblath and colleagues reported symptomatic hypoglycaemia presenting on the second or third day after birth in eight babies with significant clinical signs, including seizures. The babies’ birth weights ranged from 1,360 to 3,090 g with gestations from 32 to 39 weeks; six babies weighed less than 2500 g. All the babies’ mothers suffered from toxemia of pregnancy. All eight babies had seizures when hypoglycaemic, with blood glucose concentrations ranging from 1.1 to 1.4 mmol/L, and all immediately stopped seizing when the blood glucose concentration was returned to >2.2 mmol/L with intravenous dextrose. Of the eight babies, one died as a result of sepsis, two had significant neurological damage, and five survived without obvious impairment. The authors recommended further investigation of the impact of hypoglycaemia on neurological outcome.

Similar to the previous report from Hartmann and Jaudon (Hartmann and Jaudon 1937), Cornblath and colleagues also reported asymptomatic hypoglycaemia in five babies. They postulated that babies were able to develop a clinical tolerance to low blood glucose concentrations.

Cornblath suggested that in order to be confident of the diagnosis of clinically significant hypoglycaemia, the baby was required to demonstrate:

- The classical clinical signs associated with hypoglycaemia, including tremor, sweating, lethargy, floppiness, coma or seizures
- A low blood glucose concentration measured by sensitive and precise methods
- The clinical signs which resolve within minutes to hours once normal blood glucose concentrations had been documented.
These three parameters were described by Whipple (Whipple and Fratz 1935) and later named the Whipple's triad. The Whipple’s triad was considered to be important for diagnosis because the clinical signs of hypoglycaemia are not specific and include a range of manifestations that are common in unwell babies (Cornblath, Odell et al. 1959).

Brown and Wallis also reported symptomatic hypoglycaemia in ten babies with weights ranging from 1250g to 3182g and gestations from 34 to 42 weeks. The clinical signs of hypoglycaemia appeared between 6 and 72 hours after birth. Of these ten babies, two died, four survived with evidence of permanent neurological injury on EEG and four survived without any obvious neurological injury. Of the two babies who died, one was not recognised as having hypoglycaemia and thus was treated with sedation. The other was recognised and given intravenous dextrose. However, the intravenous dextrose was reduced, resulting in insufficient glucose administration.

The four babies who survived with no obvious neurological deficits all had risk factors for hypoglycaemia, including growth restriction and being born to mothers who suffered from toxaemia of pregnancy. All four babies were treated with intravenous 10% dextrose and all were closely monitored (Brown and Wallis 1963).

While authors reported both symptomatic and asymptomatic hypoglycaemia, adverse outcome and death were linked to symptomatic hypoglycaemia (Hartmann and Jaudon 1937; Cornblath, Odell et al. 1959; Haworth, Coodin et al. 1963). When asymptomatic hypoglycaemia was recognised, it was reported to be either physiologically normal (Norval, Kennedy et al. 1949; Desmond 1953) or to be associated with a good neurological outcome (Haworth and McRae 1965; Koivisto, Blanco-Sequeiros et al. 1972). It is likely that only the unwell babies had blood glucose concentrations were measured, therefore most asymptomatic hypoglycaemia was not recognised.

In 1974, Pildes and colleagues performed a prospective matched controlled study to evaluate the long term physical, psychological and neurological development of 39 hypoglycaemic babies (<1.6 mmol/L) compared with 41 babies who were not hypoglycaemic. Babies from the hypoglycaemic group had a higher incidence of neurological abnormalities and significantly smaller head circumferences at two, four and six years, compared to the control group. Five of the babies had asymptomatic hypoglycaemia, and all were reported to be normal at five years of age (Pildes, Cornblath et al. 1974). Significant controversy still remains regarding whether or not asymptomatic hypoglycaemia causes harm.
Two seminal papers were published in 1988. In the first Koh and colleagues (Koh, Aynsley-Green et al. 1988) sought to determine neural function in relation to blood glucose concentrations using either brain stem auditory or somatosensory evoked potentials, and also to determine if there was a measurable difference in neural function between children who were symptomatic and asymptomatic during periods of low blood glucose concentrations. The 17 subjects were children admitted for investigation of metabolic disorders or children who had recurrent spontaneous episodes of hypoglycaemia. Only five were babies, with postnatal ages ranging from 1 to 3 days.

All five babies had abnormal evoked potentials during hypoglycaemia (range 0.7 to 2.5 mmol/L) and only one was reported to be symptomatic (drowsy). The blood glucose concentration at which the abnormal evoked potentials were recorded varied between the babies, and the evoked potentials were not always abnormal when blood glucose concentrations were low. Once normoglycaemia was achieved, all the older children, but only two of the babies had normal evoked potentials immediately. Despite normal blood glucose concentrations, three babies continued to have abnormal evoked potentials for periods ranging from 1 to 48 hours.

Koh and colleagues suggested for the first time that the critical blood glucose concentration to maintain neurological integrity is potentially different in each individual. Furthermore, the rate of blood glucose concentration decline or the duration of the hypoglycaemia may influence brain dysfunction. Finally, some of the subjects may have the ability to use alternative cerebral fuels such as ketones. However, this is unlikely to have explained the variation between the babies in this study as all babies were reported to have low concentrations of ketones.

There were no obvious abnormalities of the evoked potentials when the blood glucose concentration was ≥2.6 mmol/L. The authors therefore recommended that a blood glucose concentration of 2.6 mmol/L was a pragmatic safe threshold in babies and children. They also concluded that asymptomatic hypoglycaemia was as harmful to neurological integrity as symptomatic hypoglycaemia. Others have not been able to demonstrate the same findings with evoked potentials and hypoglycaemia (Greisen and Pryds 1989).

The second seminal paper was also published in 1988, by Lucas and colleagues (Lucas, Morley et al. 1988). They examined the incidence and antecedents of low blood glucose concentrations in 661 babies with birthweights less than 1850g, and related the occurrence and persistence of hypoglycaemia to neurodevelopmental outcome at 18mths corrected age. The babies were enrolled in a multicentre trial in five nurseries in southern England to investigate the impact of feeding on early growth in low birth weight babies. Blood glucose
concentrations were measured daily and then weekly until the babies were either discharged or weighed 2000g. There were a total of 6808 blood samples taken on separate days.

The authors reported a strong association between the frequency of low blood glucose concentrations and poor Bayley scores, with babies who had five or more blood glucose concentrations <2.6 mmol/L on separate days during the first two months after birth having lower Bayley scores at 18 months of age. Sixty-seven percent of the babies were reported to have a blood glucose concentration <2.6 mmol/L on at least one occasion. Babies who were <1000g or small for gestational age (SGA) were more likely to have a blood glucose concentration <2.6 mmol/L. The authors suggested that the incidence of hypoglycaemia reported in this study was likely to be an underestimate as the blood glucose concentrations were measured intermittently.

The babies in this study were managed in five different nurseries. The percentage of babies with blood glucose concentration <2.6 mmol/L on more than three days varied from 4% to 31% between nurseries. There was also significant variation between nurseries regarding the treatment provided for hypoglycaemia and the measurement of blood glucose concentrations was not standardised. Furthermore, it is likely that the more unwell babies had more blood glucose concentrations measured.

When this cohort of children was assessed at ages 7.5 to 8 years the strong association between low blood glucose concentrations and neurological outcome was not apparent. The hypoglycaemic group showed only a minor decrease in arithmetic and motor test scores. These findings have cast doubt on the importance of the earlier findings from this study. This may be because the influence of hypoglycaemia was blurred by later events, or effects of the hypoglycaemic insult were transient, or the influence of adversity in early life was able to be overcome in early childhood.

The findings from both the Lucas and Koh papers were consistent in a number of ways. Firstly, blood glucose concentrations greater than 2.6 mmol/L were not associated with either short term or long term neurological dysfunction. Secondly, they suggest that both symptomatic and asymptomatic hypoglycaemia can be harmful to neurological integrity. Finally, hypoglycaemia in a baby is extremely difficult, if not impossible to diagnose on the basis of clinical signs. Despite the flaws in these papers they remain the foundational papers for the widely accepted clinical definition of neonatal hypoglycaemia, which is a blood glucose concentration below 2.6 mmol/L.
1.2 Definition of Neonatal Hypoglycaemia

Despite the widespread acceptance of a blood glucose concentration of 2.6 mmol/L as the threshold for treatment, a rational basis for defining hypoglycaemia has remained elusive. In order to define neonatal hypoglycaemia researchers have focused on a concentration of blood glucose below which there is likely to be functional impairment to organ systems, particularly to the brain. As the blood glucose concentration can be measured easily in clinical practice it seems logical to base the definition on the measurement. However, the measurement itself is a source of difficulty.

Researchers have used four ways to approach the definition; a clinical approach, an epidemiologic approach, an approach based on acute changes in neurophysiological and metabolic-endocrine function, and a neurodevelopmental approach (Deshpande and Ward-Platt 2005). All four approaches are flawed, but comprise the best evidence currently available.

1.2.1 The clinical approach

Historically, hypoglycaemia was diagnosed by clinical signs alone (Mann and Magath 1922; Gammon and Tenery 1931; Wauchope 1932; Bowen and Beck 1933; Whipple and Fratz 1935; Darrow 1936; Hartmann and Jaudon 1937; Desmond 1953; Cornblath, Odell et al. 1959; Brown and Wallis 1963; Haworth, Coodin et al. 1963). However, the signs are not specific to hypoglycaemia. Furthermore, these signs may be present in babies with normal blood glucose concentrations, and completely absent in babies that have severe hypoglycaemia. Therefore the definition of hypoglycaemia based on the clinical approach has not been found to be useful.

1.2.2 The epidemiological approach

The epidemiological approach is based on measuring blood glucose concentrations, initially in normal term babies and latterly in preterm babies, then defining hypoglycaemia by using an empirical cut off of two standard deviations below the mean. The recognition of asymptomatic hypoglycaemia was based on this approach (Cornblath and Reisner 1965; Haworth and McRae 1965; Pildes, Forbes et al. 1967; Koivisto, Blanco-Sequeiros et al. 1972; Cornblath, Schwartz et al. 1990).

Cornblath and Reisner were the first to attempt to define hypoglycaemia using this statistical approach. They used a standardised method of both blood sampling and analysis, and all the babies were term. All 571 babies were fasted for 3.5 to 4 hours, following which they had capillary whole blood for glucose concentrations measured. Of the 571 babies, 179 were healthy and grown appropriately and the remaining 422 were reported as low
birth weight term babies. The authors reported an immediate fall in blood glucose concentration after birth, and a return to what was considered to be adult concentrations by one to two weeks after birth. This finding was consistent with previous reports (Norval, Kennedy et al. 1949; Norval 1950).

Cornblath and Reisener defined hypoglycaemia differently for three groups of babies:

- Blood glucose concentration <20 mg/100ml (<1.1 mmol/L) for low birth weight babies
- Blood glucose concentration <30 mg/100ml (<1.6 mmol/L) for appropriately grown babies in the first 48 hours.
- Blood glucose concentration <40 mg/100ml (<2.2 mmol/L) thereafter.(Cornblath and Reisner 1965)

These definitions were accepted and used in clinical practice (Koh, Eyre et al. 1988).

Later in the 1980s Srinivasan and colleagues measured the plasma glucose concentrations in term babies (37 to 42 weeks) who weighed between 2,500 and 4,000 g and were appropriately grown for their gestation ages (AGA). They found that the plasma glucose concentration was lowest one to two hours after birth, and then rapidly rose in the third hour.

Srinivasan and colleagues suggested a novel change to the definition of neonatal hypoglycaemia which focused on the age of the baby:

- Blood glucose concentration <35 mg/dl (1.9 mmol/L) during the first 3 hours after birth.
- Blood glucose concentration <40 mg/dl (2.2 mmol/L) between 3 and 24 hours of life.
- Thereafter a blood glucose concentration <45 mg/dl (2.5 mmol/L) (Srinivasan, Pildes et al. 1986).

Many authors have identified problems with using the epidemiological approach. Firstly, statistical deviation from the mean may not represent a clinical problem. Secondly, the blood glucose concentrations of a normal population of term babies are likely to represent a continuum, and any single blood glucose concentration is unlikely to represent a threshold of abnormality. Finally, blood glucose concentrations are influenced by feeding patterns of the babies and therefore the findings may simply represent the patterns of feeding

1.2.3 Neurophysiological and metabolic-endocrine function

Until recently it has not been possible to measure neonatal brain function, blood glucose concentrations and alternative cerebral fuels simultaneously in the newborn baby, and it still remains difficult. However, there have been a few studies which have sought to measure brain function and blood glucose concentrations simultaneously in babies. The most notable of these is the previously mentioned study by Koh and colleagues, in which the authors measured brainstem and somatosensory evoked potentials (Koh, Aynsley-Green et al. 1988).

Pryds and colleagues (Pryds, Gresisen et al. 1988) sought to determine changes in cerebral perfusion during hypoglycaemia (<1.7 mmol/L maintained for three hours) in preterm babies, with matched normoglycaemic controls. Cerebral blood flow was two to threefold higher during hypoglycaemia, and rapidly decreased when the blood glucose concentration was corrected. Electroencephalograms (EEG) and visual evoked potentials were not different between hypoglycaemic and normoglycaemic groups. The authors concluded the increased cerebral perfusion supported cerebral metabolic demands, during hypoglycaemia and therefore no changes were seen on either form of brain monitoring.

Two years later the same group sought to repeat the previous findings and also to determine plasma adrenalin and non-adrenalin concentrations in 25 preterm babies. During hypoglycaemia (<1.7 mmol/L) cerebral perfusion was increased, as were plasma adrenalin concentrations. The authors concluded blood glucose concentrations should be maintained above 1.7 mmol/L to avoid increased cerebral perfusion (Pryds, Christensen et al. 1990).

There is also a paucity of evidence regarding metabolic and endocrine function in relation to glucose in newborn babies, and an urgent need to understand the relationship between alternative cerebral fuels and neonatal hypoglycaemia (Hay, Raju et al. 2009). Hawdon and colleagues established normal ranges and interrelationships of blood glucose, ketones and lactate concentrations in the first postnatal week, using a cross-over design in 62 preterm and 156 term babies, and compared findings with 52 older children. Blood glucose concentrations varied more for preterm babies than term babies, and in the first few hours after birth the blood glucose concentration fell faster. Preterm babies had lower overall plasma ketone concentrations which did not increase during hypoglycaemic episodes, unlike most term babies and older children who showed an increase in plasma ketone
concentrations during hypoglycaemia. These findings suggest preterm babies are unable to mount a counter-regulatory response when hypoglycaemic.

In a later longitudinal study investigating metabolic adaptation in 33 small of gestational age (SGA) babies, all receiving treatment or feeds, the authors report SGA babies also were unable to demonstrate an increase in plasma ketone concentrations during hypoglycaemia (Hawdon and Ward-Platt 1993). However, others have shown SGA term babies who are nutritionally compromised can have a counter-regulatory response during hypoglycaemia (de L Costello, Par et al. 2005).

Lactate is also an important alternative cerebral fuel which has been shown to preserve cerebral function during hypoglycaemia in animals, (Hernandez, Vannucci et al. 1980; Vannucci, Nardis et al. 1980; Turbow, Curran-Everett et al. 1995) and in human adults (Maran, Cranston et al. 1994; King, Parkin et al. 1998). In babies two studies have shown a decrease in plasma lactate concentrations with postnatal age (Hawdon, Ward-Platt et al. 1992; de L Costello, Par et al. 2005).

1.2.4 The neurodevelopmental approach

The study that has underpinned this approach to the definition of hypoglycaemia is the previously mentioned retrospective feeding study by Lucas and Morley. In this study, babies with reported blood glucose concentrations <2.6 mmol/L on five different days were more likely to have lower Bayley developmental scores at 18 months than babies without hypoglycaemia (Lucas, Morley et al. 1988). There have been opponents of using this definition because of the lack of standardisation of the blood glucose testing and the loss of the strong association between developmental outcome and hypoglycaemia when the children were older. Furthermore, there was a lack of non-hypoglycaemic control babies in the study and a failure to consider other pathologies (Sinclair 1997).

1.2.5 Variation in the definition

In an attempt to understand the variation between the differing definitions, Koh and colleagues reviewed the definitions of hypoglycaemia in major paediatric and neonatal textbooks and also analysed the responses to a questionnaire sent to 200 paediatricians within the United Kingdom in 1986. The results indicated that there was no agreement on a biochemical definition for neonatal hypoglycaemia among the textbooks. Furthermore, there was disagreement between the paediatricians about the diagnosis and management of neonatal hypoglycaemia, and therefore substantial variation between and within neonatal nurseries (Koh, Eyre et al. 1988).
1.2.6 Current recommendations

In 2000 a group of prominent investigators who were concerned with the paucity of evidence and variation in the management of neonatal hypoglycaemia made recommendations (Cornblath, Hawdon et al. 2000).

Recommendations included:

- All at-risk babies should have blood glucose monitoring using reliable screening analysis to commence within two to three hours after birth. All blood glucose measurements should be measured before feeds, or at any time there are signs associated with hypoglycaemia. There were no recommendations regarding when blood glucose monitoring should be discontinued.

- Babies within the first 24 hours after birth, regardless of birthweight or gestation, with a blood glucose concentration <2.5 mmol/L should have clinical interventions aimed at increasing the blood glucose concentration.

- Babies with blood glucose concentrations <2.0 mmol/L require close surveillance and continued screening. If the blood glucose concentration remains <2.0 mmol/L after a feed or if abnormal clinical signs develop, then intervention aimed at increasing the blood glucose concentration should be provided.

- Babies with blood glucose concentrations of <1.1 to 1.4 mmol/L should have intravenous dextrose administered with the aim of raising the blood glucose concentration to >2.5 mmol/L.

- Babies with recurrent hypoglycaemia or persistent hyperinsulinemic hypoglycaemia should have treatment directed towards a blood glucose concentration of >3.3 mmol/L (Cornblath, Hawdon et al. 2000).

These recommendations have provided pragmatic guidelines for clinicians which have been essentially accepted into clinical practice. However, considerable uncertainty and controversy remain. Following the publication of these recommendations, one of the authors published a paper in the same year recommending differing (lower) operational thresholds (Cornblath and Ichord 2000). There remains no evidence defining the severity, duration, or frequency of hypoglycaemia required before neurological integrity is impaired.

The recommended clinical thresholds for the treatment of hypoglycaemia differ depending on age, (Alberti and Zimmet 1998) with babies having the lowest threshold (Cornblath, Hawdon et al. 2000). In comparison to adults and children, babies have a largest brain to
liver ratio, (Bier, Leake et al. 1977) and this ratio is even greater in babies with growth restriction or prematurity (Hay 1984). The brain/liver ratio is important because the liver is the only source of non-dietary glucose for the brain (Ward-Platt and Deshpande 2005). The lower clinical threshold for treatment of hypoglycaemia therefore seems incongruent with the large brain to liver ratio, suggesting a greater need for glucose.

Tests have been developed for adults to measure cognitive function during hypoglycaemia. Although there is debate as to which is the best test, (Amiel 1998) the majority of adults whose blood glucose concentrations fall to 4 mmol/L begin to demonstrate autonomic activation and inability to concentrate. Furthermore, both adults and children with blood glucose concentrations of 1 mmol/L or less are usually unconscious (Cranston, Lomas et al. 1994; Maran, Lomas et al. 1995; Amiel 1998). However, it is uncommon for babies to be unconscious due to hypoglycaemia.

1.3 Measurement of blood glucose concentrations

The accurate measurement of glucose concentrations is fundamental to the diagnosis of hypoglycaemia. Glucose concentrations are affected by the method of screening, sample site, haematocrit, delays in specimen processing, operator technique, and whether the sample is whole blood or plasma.

Cot-side glucose analysers provide prompt results but are designed for adult diabetics who do not frequently have blood glucose concentrations as low as babies. Studies which have specifically tested the accuracy of bedside glucose analysers at the lower glucose ranges have shown that they both over- and under-estimate blood glucose concentrations (Ho, Yeung et al. 2004). Therefore cot-side analysers should only be used as a screening tool not as a diagnostic tool (Cornblath, Hawdon et al. 2000).

Glucose concentrations also differ with the source of the sample. Arterial blood has a higher blood glucose concentration than venous blood, and capillary sampling can be unreliable when the baby is oedematous or poorly perfused. Plasma glucose concentrations are higher than whole blood glucose concentrations by approximately 14 to 18%, because the red cells are removed. The difference may be greater at lower blood glucose concentrations (<1.6 mmol/L) (Aynsley-Green 1991; Stanley and Caplin 2004). If whole blood is used for the measurement of blood glucose concentrations it is essential that the concentration is measured immediately as the red cells consume glucose. This can be reduced by using fluoride sampling tubes or placing the sample on ice.
1.3.1 Intermittent blood glucose sampling

In clinical practice, blood glucose concentrations are measured in at-risk babies intermittently, commonly 1 to 4 hourly. However, intermittent blood tests may easily miss significant periods of low blood glucose concentrations, for example before feeds. Thus, it is possible that some babies with hypoglycaemia that may threaten brain function are not identified, or alternatively that some babies with only an occasional brief fall in blood glucose concentrations are at no risk of impaired brain function but are inappropriately and invasively treated.

1.3.2 Continuous glucose monitoring

Continuous glucose monitoring has been shown to improve metabolic control in adult and child diabetic patients over the past ten years (Cheyne, Cavan et al. 2002; Cameron and Ambler 2004). A continuous glucose monitor measures interstitial glucose concentrations via a sensor that is placed subcutaneously. In babies the site for the sensor is most frequently the thigh. A number of continuous glucose monitoring systems have been developed. However, the MiniMed Continuous Glucose System (CGMS) is the only system available in Australia and New Zealand.

The MiniMed continuous glucose monitor sensor is a disposable, glucose oxidase based, platinum electrode sensor which converts the interstitial glucose into an electrical signal every 10 seconds, and this is recorded via cable by a pager sized monitor (6 x 9 x 2 cm). Although the monitor records a signal every 10 seconds, the signals are averaged every five minutes, providing a total of 288 readings in 24 hours. The data cannot be viewed in real-time. Glucose concentrations outside the range of 2.2 to 24 mmol/L are considered out of range for the purpose of calibration. However, the monitor records the electrical signals outside these ranges, so that these can be retrieved using the standard instrument algorithm, making the monitor potentially useful in the monitoring of neonatal hypoglycaemia. Continuous glucose monitoring has been shown to be safe in preterm babies (Beardsall, Ogilvy-Stuart et al. 2005; Platas, Lluch et al. 2009) but its role in the management of neonatal hypoglycaemia has not yet been determined.

1.4 Metabolic adaptation

1.4.1 Before birth

Before birth the fetus is entirely dependent on the transfer of nutrients from the maternal circulation. Glucose is the major fetal oxidative substrate. There is a direct relationship between glucose concentrations in the mother and fetus. In humans the fetal blood glucose concentration is 60 to 70% of the maternal concentration (Hauguel, Challier et al. 1983).
Glucose crosses the placenta along a concentration gradient by facilitated diffusion utilising placental glucose transporters, primarily GLUT 1 and GLUT3 (Illsley 2000).

With advancing gestation uterine blood flow increases in order to meet the increasing metabolic demands of the growing fetus. In the third trimester the fetus converts some of the glucose to adipose tissue and glycogen in preparation for the metabolic changes at birth. Studies in sheep demonstrated that reducing uterine blood flow late in pregnancy from 600 to 300 mL/min/kg did not affect fetal glucose uptake. However, a further reduction resulted in decreased fetal glucose uptake, resulting in fetal growth restriction (Wilkening, Battaglia et al. 1985; Kalhan 2004). Studies such as this have not been performed in humans. However, fetuses with poor placental function are frequently growth restricted and at greater risk of neonatal hypoglycaemia.

Lactate is also an important oxidative fuel prior to birth. The majority of the lactate is derived from glucose in both the fetus and placenta. The amount of lactate produced varies between species, with ruminants producing more lactate than the human fetus (Fowden 1994). Other fuels such as amino acids are also actively transported to the fetus against a transplacental gradient. The human placenta is also permeable to small amounts of triglycerides, fatty acids and glycerol (Bloomfield and Harding 2006).

1.4.2 At birth

Immediately after birth the baby must adapt from continuous glucose supply to intermittent feeding and fasting. This normal metabolic and hormonal transition is complex. Endogenous glucose production in the newborn baby has been estimated to be 4 to 5mg/kg.min in the first hours after birth (Kalhan, Savin et al. 1976; Kalhan, Parimi et al. 2001) and glucose production increases in the first few days (Bier, Leake et al. 1977).

A direct relationship has been demonstrated in the newborn between glucose production and the estimated brain weight. Babies have a larger brain to body weight ratio than adults and children (babies 12% compared to adults 2%) (Bier, Leake et al. 1977). In addition, 80% of the total glucose utilisation in the newborn occurs in the brain (Sunehag and Haymond 2002). Although astrocytes store glucose in the perinatal period, hepatic glucose production through glycogenolysis and gluconeogenesis provides the only glucose fuel source until feeding is established (Ward-Platt and Deshpande 2005).
1.4.3 Normal metabolic adaptation

1.4.3.1 Glycogenolysis

Glycogenolysis is the breakdown of glycogen stored in the liver. This breakdown results in the production of glucose-6-phosphate, which can be converted to free glucose by the action of glucose-6-phosphatase. Glycogen is also stored in muscle, but this glycogen cannot be released into the circulation because muscle cells lack glucose-6-phosphatase. Conditions that encourage glycogenolysis include suppressed insulin concentrations, and elevated concentrations of glucagon and adrenalin.

In the third trimester glycogen accumulates in the fetal liver in preparation for birth. The stored glycogen allows the baby to maintain plasma glucose concentrations following birth. However, the glycogen store is limited and is generally exhausted in the first 12 hours after birth in a health term baby if there is not another source of glucose (Shelley 1961; Shelley and Neligan 1966).

1.4.3.2 Gluconeogenesis

Gluconeogenesis then ensures the continued supply of glucose. Gluconeogenesis is the production of glucose from precursors such as lactate, alanine, glutamine and glycerol. The majority occurs in the liver, with a small amount in the kidneys. There are four essential enzymes involved in gluconeogenesis; glucose-6-phosphatase, fructose-1,6-bisphosphatase, phosphoenolpyruvate carboxykinase (PEPCK), and pyruvate carboxylase. These four enzymes are present in the liver at birth in extremely small amounts (Greengard 1977). The process surrounding the complex development of these four enzymes is not well understood (Simmons 2006). A healthy baby is not able to carry out gluconeogenesis in the first few hours after birth due to the requirement to activate PEPCK, which is the rate-limiting enzyme. In fetal sheep, increases in PEPCK are dependent on the peripartum cortisol surge (Fowden, Mijovic et al. 1992). In fetal rats PEPCK can be stimulated by increasing the glucagon/insulin ratio to a state similar to that normally seen after birth in humans (Girard, Caquat et al. 1973).

PEPCK is thought to be produced in the liver in response to the rise in plasma glucagon and fall in plasma insulin concentrations immediately after birth, stimulated by the catecholamine surge (Padbury, Roberman et al. 1982). Newborn babies have been shown to have a catecholamine surge mediated by the process of birth. As PEPCK activity increases there is a parallel increase in gluconeogenesis and tracer studies suggest that in healthy babies gluconeogenesis is occurring two hours after birth (Kalhan, Parimi et al.
PEPCK reaches adult concentrations at approximately 24 hours after birth (Girard 1986).

1.4.3.3 Ketogenesis

Ketogenesis is the production of ketones, β-hydroxybutyrate and acetoacetate, from fatty acid oxidation. In both animal and human studies these substrates have been shown to be used as alternative cerebral oxidative fuels (Kraus, Schlenker et al. 1974; Vannucci and Vannucci 2004).

The newborn brain is capable of extracting and utilising ketone bodies at a rate that is between five and 40-fold greater than that of a child or adult brain (Persson, Settergren et al. 1972). In healthy regularly fed newborn babies ketones supply up to 12% of the cerebral oxygen consumption following a six hour fast (Persson, Settergren et al. 1972; Bougneres, Lemmel et al. 1986; Hawdon, Ward-Platt et al. 1992).

During the first eight hours after birth, healthy and SGA babies have low plasma ketone concentrations, despite having adequate concentrations of precursor free fatty acids (Hawdon, Ward-Platt et al. 1992; Stanley and Caplin 2004). The reason for the low plasma ketone concentrations remains unclear, (Stanley, Anday et al. 1979) but may involve delayed expression of two key enzymes, carnitine palmitoyl-transferase-1 and β-hydroxy-β-methylglutaryl-coenzyme A synthase, which are essential for the first and last steps of hepatic ketogenesis.

1.4.3.4 Lipolysis

Lipolysis is the breakdown of fat which results in the formation of free fatty acids. In the healthy baby there is a surge of glycerol and free fatty acids following birth, in response to the elevated plasma adrenalin and growth hormone concentrations and the suppression of insulin. Fatty acids cannot be used as a cerebral energy source but can be converted in the liver to lactate and ketones.

Lactate is an important energy source for babies during the first few hours of life (Hawdon, Ward-Platt et al. 1992; Medina, Tabenero et al. 1996). The healthy newborn also produces lactate within the brain parenchyma, via glutamate activated glycolysis in astrocytes (Pellerin and Maistretti 1994).

1.4.3.5 The effect of feeding on normal adaptation

Feeding alters the structure and function of the gastro-intestinal tract, and also signals the release of regulatory hormones that are produced in the gut. There are differing metabolic
responses in babies who have received human milk compared to those who have received formula milk. Term breast-fed babies have lower blood glucose and insulin concentrations and higher ketone concentrations over the first few days than babies who have been formula fed (Lucas, Boyes et al. 1981; Hawdon, Ward-Platt et al. 1992; de Rooy and Hawdon 2002). Formula feeding may suppress the ketogenesis (Hawdon, Ward-Platt et al. 1992; de Rooy and Hawdon 2002). The exact mechanism for this is not clear but it is speculated that a factor in breast milk but absent in infant formula augments ketogenesis (de Rooy and Hawdon 2002).

During suckling the baby receives a high lipid, low carbohydrate diet. Both human and rat milk have higher amounts of lipid than other species, and the young have increased blood ketone concentrations during suckling (Anday, Stanley et al. 1981). High blood ketone concentrations have not been demonstrated in lambs, piglets or puppies during suckling. Interestingly, the brains of both lambs and puppies also have a low rate of ketone utilisation when compared with the human baby brain (Williamson and Thornton 2004).

1.4.4 Impaired metabolic adaptation

Neonatal hypoglycaemia results from either normal metabolic demand for glucose in the presence of decreased availability of substrate, or normal substrate availability in the presence of metabolic demand that exceeds the baby’s ability to compensate. The period following birth is a transition period when hypoglycaemia is most common, and is usually transient, resulting from delayed or impaired metabolic adaptation. Persistent hypoglycaemia is often the result of complex endocrine or inborn errors of metabolism disorders.

1.4.4.1 Preterm babies

There are multiple factors that predispose the preterm baby to hypoglycaemia. In the later part of a human pregnancy the fetus accumulates both glycogen and adipose tissue. Preterm babies are born with significantly less glycogen and adipose tissue (Uthaya, Thomas et al. 2005) and therefore have limited ability to release glucose from the liver via glycogenolysis or to produce gluconeogenic precursors via lipolysis. In addition, preterm babies have low concentrations of glucose-6-phosphatase, which is essential for both glycogenolysis and gluconeogenesis. The production of glucose-6-phosphatase may remain low in these babies for some months following birth. Therefore with advancing postnatal age as the feeding interval increases, preterm babies may remain at risk of developing intermittent hypoglycaemia (Hume, McGeechan et al. 1999).
Preterm babies may be even more at risk for neurological damage when hypoglycaemic than term babies, as they are less able than term babies to mobilise alternative cerebral fuels such as ketones (Hawdon, Ward-Platt et al. 1992) in part due to an incomplete counter-regulatory hormone response to hypoglycaemia (Hawdon, Weddell et al. 1993).

1.4.4.2 Growth restricted babies

Growth restricted babies were identified nearly sixty years ago as being at significant risk for hypoglycaemia (Neligan, Robson et al. 1963). Similar to the preterm baby, a growth restricted baby will not accumulate both glycogen and adipose tissue in late gestation, and therefore there is limited ability to release glucose from the liver via glycogenolysis or to produce gluconeogenic precursors via lipolysis.

Ketone and free fatty acid concentrations are reported to be low in growth restricted babies. The poor ketogenic response may be secondary to an inability to mobilise fatty acids from adipose tissue (Hawdon, Ward-Platt et al. 1992; Hawdon and Ward-Platt 1993; Hawdon, Weddell et al. 1993; Ward-Platt and Deshpande 2005). Furthermore, growth restricted babies have been shown to have limited ability to secrete cortisol, adrenalin and noradrenalin in response to hypoglycaemia. This, coupled with a peripheral insensitivity to the actions of glucagon and insulin means growth restricted babies have poorly coordinated counter-regulatory hormone response to hypoglycaemia (Hawdon, Weddell et al. 1993).

Growth restricted babies also often have a larger red cell volume, as a fetal compensatory response to on-going intrauterine hypoxia. This may further increase the risk of hypoglycaemia, since red cells use glucose as an energy source (Stockman and Oski 1978) and the high red cell volume means less plasma available for tissue glucose delivery (Kramer, Oliver et al. 1990; Pallotto and Kilbride 2006).

1.4.4.3 Babies of diabetic mothers

Babies born following a diabetic pregnancy have been shown to have differing body compositions from those from non-diabetic pregnancies and are at increased risk for developing hypoglycaemia (Cordero and Landon 1993; Suevo 1997; Hod, Jovanovic et al. 2003). These babies are frequently overweight for gestation, have increased body fat and are longer.

During a diabetic pregnancy the fetus is exposed to episodic periods of excess glucose from the mother (Cordero and Landon 1993). Insulin does not cross the placenta (Battaglia, Hellegers et al. 1964; Spellacy, Goetz et al. 1964). However, the fetus produces insulin in
response to the excess glucose in order to normalise fetal blood glucose concentrations. After birth, when the umbilical cord is cut, the continuous source of glucose is removed. However, the baby continues to produce excess insulin for several days, which results in an increased risk for neonatal hypoglycaemia (Pedersen 1954; Cordero and Landon 1993).

Hyperinsulinism contributes to hypoglycaemia by increasing cellular glucose uptake and by suppressing hepatic glycogenolysis, gluconeogenesis, adipose tissue lipolysis and hepatic ketogenesis (Cordero and Landon 1993; Stanley and Caplin 2004). Insulin also diminishes the counter-regulatory response to hypoglycaemia (Bloom and Johnston 1972). Thus, babies born following a diabetic pregnancy have limited ability to produce alternative cerebral fuels and may be at greater risk for neurological damage from hypoglycaemia than those from non-diabetic pregnancies.

There appears to be a relationship between poor maternal glucose homeostasis prior to and during labour and delivery and neonatal hypoglycaemia (Weintrob, Karp et al. 1996; Taylor, Lee et al. 2002). Neonatal factors which further increase the risk of hypoglycaemia in these babies include perinatal asphyxia, growth restriction, macrosomia and polycythaemia (Hod, Jovanovic et al. 2003).

Intrauterine growth restriction is more common in diabetic pregnancies than in non-diabetic pregnancies, (Langer, Levy et al. 1989) and occurs at similar rates in gestational and pre-gestational diabetic pregnancies (Weintrob, Karp et al. 1996). The main causes are maternal diabetic nephropathy, hypertension, and the effects of uterine vascular lesions on placental blood flow (Kitzmiller and Combs 1993). The baby from a diabetic pregnancy with growth restriction, particularly when coupled with prematurity, is at greater risk of hypoglycaemia.

### 1.4.4.4 Macrosomia

Babies from both diabetic and non-diabetic pregnancies can be born large for gestational age (LGA). The incidence of macrosomia is increasing (Sinclair, Rowan et al. 2007) and may be in part due the increasing prevalence of diabetes and obesity (Wild, Roglic et al. 2004). Macrosomia increases the risk for neonatal hypoglycaemia (Cordero and Landon 1993; Evers, de Valk et al. 2002).

The precise cause of macrosomia remains unclear. A relationship has been postulated between high maternal glucose concentrations resulting in increased fetal insulin secretion and the production of fat from glucose, glycerol, fatty acids and triglycerides but the studies are conflicting (Jacobson and Cousins 1989; Langer, Levy et al. 1989; Persson and Hanson 1993; Sacks 1993; Hod, Jovanovic et al. 2003). More recently others have
suggested the primary cause of macrosomia is maternal hyperlipidemia causing increased lipid transfer to the fetus (Knopp, Magee et al. 1992; Di Cianni, Miccoli et al. 2005; Catalano 2007; Son, Kwon et al. 2010).

There is no universal definition for macrosomia. A birth weight ≥4000g has been used historically. However, this definition does not allow for the influence of gestational age on birth weight. Therefore the current clinically accepted definition is usually that of large for gestational age e.g. ≥90th percentile (Sacks 1993). This definition also has limitations as birth weight for gestational varies with sex, ethnicity and geographic location (Usher and McLean 1969; Buckfield, Clarkson et al. 1982; Sinclair, Rowan et al. 2007). Customised birthweight centiles have been established which allow for variation in sex, geographic location and maternal factors, including booking weight, height, parity, and ethnicity (Gardosi, Chang et al. 1992; McCowan, Stewart et al. 2004). However, whether customised centiles improve detection of neonatal hypoglycaemia remains undetermined.

1.4.4.5 Maternal obesity

Maternal obesity is common. In Australia, it has been estimated that 35% of pregnant women have a body mass index (BMI) greater than 25/kg/m² (Callaway, Prins et al. 2006). Maternal obesity is linked with poor maternal and perinatal outcomes (Dodd, Grivell et al. 2011). There is an association between increased maternal BMI and neonatal hypoglycaemia (Simmons, Thompson et al. 2000; Doherty, Magann et al. 2006; Sinclair, Rowan et al. 2007; Garcia-Patterson, Aulinas et al. 2012). These babies may be at increased risk because they have been exposed to excess glucose, glycerol, fatty acids and triglycerides in utero and therefore struggle with metabolic transition after birth, but also because obese mothers can have difficulty establishing and maintaining breast feeding (Li, Jewell et al. 2003).

1.5 Other factors causing neonatal hypoglycaemia

1.5.1 Normal substrate availability with increased metabolic demands

An increased metabolic demand commonly occurs in babies who are unwell. Babies suffering from perinatal asphyxia have rapid depletion of substrate stores during the period of anaerobic metabolism. In addition, such babies frequently have hypoxic liver damage, resulting in impaired glyconeogenesis and glycogenolysis (Cornblath and Ichord 2000). Babies with severe sepsis may also have impaired perfusion resulting in less blood glucose delivery to the tissues (Sparrow and Willis 2004).

Hypothermia is common in babies following birth and is associated with hypoglycaemia and poor developmental outcome (Costeloe, Hennessy et al. 2000; Mathur, Krishnamurthy et al.
2005; Buitendijk, de Vries et al. 2008). Hypothermia increases metabolic demand, which depletes substrate due to rapid lipolysis of brown fat stores for thermogenesis, in addition to exhaustion of glycogen stores. In a recently published paper from the Netherlands the authors reported two appropriate for gestational age term babies presenting with hypoglycaemic seizures in the first few days following birth. The only risk factor identified was that both babies were hypothermic for more than six hours. The authors’ recommendations are that babies who remain hypothermic for more than three hours require accurate blood glucose measurements (Buitendijk, de Vries et al. 2008).

1.5.2 Normal metabolic demands with decreased substrate availability

Decreased substrate availability to the tissues can be due to either inadequate delivery or production. An inadequate calorie intake due to poor feeding or inadequate parenteral nutrition increases the risk of neonatal hypoglycaemia when the stored substrates are exhausted (Cornblath and Ichord 2000). It is not uncommon for late-preterm babies to be readmitted to NICU for management of hypoglycaemia due to poor feeding following early discharge (Garg and Devaskar 2006).

1.5.2.1 Congenital hyperinsulinism

Hyperinsulinism is the term given when hypoglycaemia results from inadequate suppression of plasma insulin. Most commonly this is a congenital defect in the regulation of insulin secretion. Hyperinsulinism in infancy is the most common cause of neonatal hypoglycaemia that persists for longer than the first week after birth, and is associated with a high risk of neurological impairment (Hussain, Blankenstein et al. 2007). There are two major types of disease; diffuse changes to the pancreas, characterised by beta-cell hypertrophy and hyperplasia known as nesidoblastosis, and confined focal lesions known as Insulinoma. The incidence varies within differing ethnic groups from, 1 in 2500 in Middle Eastern populations to 1 in 50,000 in Europe (Bruining 1990). Affected babies are often macrosomic and present with seizures.

1.5.2.1.1 Normal insulin secretion

Normally the pancreatic β-cell acts as a highly responsive sensor, allowing insulin to be released by the $K_{\text{ATP}}$ channels as required, to maintain a physiologic glucose balance (Hussain and Aynsley-Green 2003; Stanley and Caplin 2004; Hussain, Blankenstein et al. 2007). At rest the $K_{\text{ATP}}$ channels on the β-cell are open. When the blood glucose concentration increases glucose is transported into the β-cell by the glucose transporter GLUT 2 and undergoes rapid phosphorylation to glucose-6-phosphate catalysed by the enzyme glucokinase. This increases the ratio of ATP/ADP causing the $K_{\text{ATP}}$ channel to
close, resulting in depolarisation of the cell membrane, and allowing the influx of calcium through voltage gated calcium channels. This influx of calcium into the β-cell triggers exocytosis of insulin-containing granules, and insulin is secreted (Hussain and Aynsley-Green 2003; Ogilvy-Stuart and Midgley 2006).

1.5.2.1.2 Pathology of hyperinsulinism

Hyperinsulinism describes conditions caused by inappropriate secretion of insulin (Cosgrove, Shepherd et al. 2004). There are multiple causes of inappropriate insulin secretion, and there is considerable research being done to understand the pathology of hyperinsulinism syndromes. New understanding regarding genetic mutations which result in pathology at the level of the $K_{ATP}$ channels, or expression of the β-cell enzymes glucokinase and glutamate dehydrogenase, has led to greater knowledge about the complexity of hyperinsulinism and has improved the outcome for children with hyperinsulinism (Hussain and Aynsley-Green 2003; Stanley and Caplin 2004; Hussain, Blankenstein et al. 2007).

1.5.2.2 Other endocrine disorders

Neonatal hypoglycaemia secondary to other endocrine disorders is rare. It is caused by imbalance between insulin and counterbalancing hormones growth hormone, cortisol, glucagon, or adrenalin. These babies can present in a similar manner to a baby with hyperinsulinism, and require high doses of glucose to normalise the blood glucose concentration. There is a complex series of diagnostics tests required to confirm the diagnosis, following which life-long treatment is required (Stanley and Caplin 2004; Ogilvy-Stuart and Midgley 2006).

The most common disorders in this category are those associated with hypopituitarism. The incidence ranges between 1 in 4,000 to 1 in 10,000 live births (Ogilvy-Stuart and Midgley 2006). Growth hormone is a 191-amino acid single chain polypeptide that is synthesised, stored and secreted from the pituitary under the influence of other pituitary hormones. Growth hormone-releasing hormone stimulates the release of both growth hormone and somatostatin and peaks in growth hormone correspond with troughs in somatostatin release. Hypoglycaemia would normally stimulate growth hormone release and suppression of somatostatin. Among the biological effects of growth hormone are fatty acid release from adipose tissue, insulin resistance, and increases in blood glucose concentrations.

Cortisol is a counter-regulatory hormone secreted from the zona fasciculata within the cortex of the adrenal gland. The secretion of cortisol is under the control of
adrenocorticotropic hormone from the pituitary gland. One of the primary functions of cortisol is maintenance of blood glucose concentrations through stimulation of hepatic gluconeogenesis, reduction of extrahepatic protein synthesis and inhibition of insulin secretion. Therefore dysfunction of the endocrine pathways between the pituitary and adrenal glands results in hypoglycaemia (Winter 2004). Congenital abnormalities of the pituitary can occur in isolation or in conjunction with other midline abnormalities, such as of the optic nerves or septum pellucidum. Adrenal insufficiency in the newborn period is uncommon. The most frequent causes include inborn errors of counter-regulation hormone synthesis, sepsis, congenital adrenal hypoplasia, and adrenal haemorrhage.

Neonatal hypoglycaemia secondary to defects in gluconeogenesis is also rare. Glucose-6-phosphatase deficiency and glucose-6-phosphate translocase deficiency result in a complete inability of the liver to release glucose. This is because the formation of glucose from glucose-6-phosphate is the common pathway for both glycogenolysis and gluconeogenesis. Babies with these conditions present early with hypoglycaemia, hepatomegaly and acidosis. Other enzyme defects associated with lack of gluconeogenesis include defects in fructose-1, 6-diphosphatase and PEPCK. Both are essential components of the gluconeogenesis pathway (Stanley and Caplin 2004).

1.5.2.3 Glycogen storage diseases

Hypoglycaemia secondary to glycogen storage diseases is rare. Glycogen is stored in both liver and muscle cells. However, only in the liver can glycogen be broken down to free glucose for release into the circulation, because the necessary enzyme glucose-6-phosphatase is only found in the liver. There are two classes of glycogen storage disease (GSD), genetic and acquired, and within these classes are a number of disorders caused by abnormal glycogen synthesis or degradation. Most glycogen storage diseases do not present in the neonatal period. However, the most common presentation in the neonatal period results from a deficiency in glucose-6-phosphatase (von Gierke disease) and accounts for 80% of the cases, babies present with hypoglycaemia, hepatomegaly and lactate acidosis (Thomas, Tsai et al. 2006).

Glycogen synthetase deficiency is a rare autosomal recessive disorder. Affected babies are unable to synthesis glycogen and present with hypoglycaemia and high ketone concentrations following a fast because glycogen stores are absent. However, following a feed because of the inability to synthesise glycogen hyperglycaemia may result (Stanley and Caplin 2004).
1.5.2.4 Fatty acid oxidation defects

Hypoglycaemia secondary to fatty acid oxidation defects is also rare. Inborn errors in fatty acid uptake, activation, and mitochondrial oxidation result in disturbed oxidative phosphorylation and ATP generation. This results in the loss of ketogenesis and the complete inhibition of gluconeogenesis. Babies can present at birth or later in infancy during periods of poor feeding (Stanley and Caplin 2004).

The most common fatty acid oxidation defect is medium chain acyl coenzyme A dehydrogenase deficiency. The incidence is 1 in 8000 live births. Metabolic screening in New Zealand was expanded in 2006 to include fatty acid oxidation disorders (Wilson, Kerruish et al. 2007).

1.5.2.5 Medications

Medications such as valproate given to the mother prior to birth can cause postnatal neonatal hypoglycaemia by reducing the glycogen stores prior to birth and inhibiting glycogenolysis (Ebbesen, Joergensen et al. 2000). Propranolol, a non-selective beta-adrenergic blocker, has also been associated with neonatal hypoglycaemia. The mechanism of action is thought to be related to interruption of glycogenolysis due to suppression of adrenalin (Cissoko, Jonville-Bera et al. 2005).

Medications given directly to a baby following birth such as indomethacin have also been associated with hypoglycaemia. The exact mechanism is not clear, but does not appear to be related to increased insulin concentrations (Lilien, Srinivasan et al. 1985).

1.6 Neonatal hypoglycaemia and brain

The severity, duration, and recurrence of hypoglycaemic episodes required to cause neurological injury remain unclear and until recently the measurement of these parameters has been difficult; this is one reason why evidence is scarce linking hypoglycaemia with neurological impairment.

1.6.1 Severity of hypoglycaemic episodes

The severity of hypoglycaemic episodes may be important in determining neurological outcome. Kahn and colleagues report the neurological outcome of 11 rhesus monkeys who survived (11 to 270 days) following profound insulin-induced hypoglycaemia for up to five hours. Of the 11 animals, 4 were examined as neurologically normal by day 4 and a fifth was reported as normal by nine months of age. The remaining six monkeys were neurologically abnormal. There was no relationship between seizures, severity of the hypoglycaemia and neurological outcome (Kahn and Myers 1971). Stenninger and
colleagues (Stenninger, Flink et al. 1988) compared hypoglycaemic (mean blood glucose concentration <1.5 mmol/L) with non-hypoglycaemic (mean blood glucose concentration 1.9 mmol/L) babies from diabetic mothers and healthy controls at eight years of age. The more severely hypoglycaemic children had the worse long-term outcome overall, but both groups had a poorer outcomes than controls.

1.6.2 Recurrent hypoglycaemic episodes

Recurrent hypoglycaemic episodes have also been linked to poor neurological outcome. Babies with persistent hypoglycaemia have the most severe neurological outcomes and this is likely to be related to both the severity and recurrence of hypoglycaemic episodes (Menni, de Lonlay et al. 2001; Rozance and Hay 2006). Duvanel and colleagues (Duvanel, Fawer et al. 1999) followed up 85 preterm SGA babies of whom 72% were hypoglycaemic (<2.6 mmol/L). Babies with recurrent hypoglycaemic episodes had smaller head circumferences at 18 months of age and lower psychometric scores at 5 years of age. Others have also reported poor neurodevelopmental outcome after recurrent hypoglycaemia including psychomotor delay, epilepsy, and visual impairment (Lucas, Morley et al. 1988; Caraballo, Sakr et al. 2004).

1.6.3 Duration of hypoglycaemic episodes

The duration of hypoglycaemic episodes may also be important in determining neurological outcome (Anderson, Milner et al. 1967; Lucas and Morley 1999; Rozance and Hay 2006). Studies in rhesus monkeys showed individual susceptibility to adverse neurological outcome between monkeys exposed to the same prolonged hypoglycaemic episode (Kahn and Myers 1971). Because blood glucose concentrations are measured intermittently it is difficult to measure the duration of a hypoglycaemic episode. However, continuous interstitial glucose monitoring provides for the first time an opportunity to accurately measure the duration of hypoglycaemia, and therefore may be a useful tool to determine the relationships between duration and neurological outcome.

1.6.4 Cerebral compensatory mechanisms during hypoglycaemia

Glucose enters neurons and astrocytes by facilitated diffusion mediated by two glucose transporters; GLUT1 and GLUT3. Both have been demonstrated in the brains of preterm and term babies (Vannucci and Vannucci 2000; Volpe 2001). During periods of hypoglycaemia there are four mechanisms which may protect the brain. First, glycogen is stored within the astrocytes and this provides a source of glucose when blood glucose is limited (Eyre, Stuart et al. 1994).
Second, the rate at which the brain uses glucose varies with age. Studies using Positron Emission Tomography scanning have shown that the rate of cerebral glucose utilisation at birth is 30% less than in a healthy young adult (Chungani 1998). Cerebral glucose utilisation also varies regionally within the brain depending on postconceptional age. Preterm babies demonstrated higher glucose utilisation in the thalamus and subcortical areas than term babies (Kinnala, Suhonen-Polvi et al. 1996). The regional changes in rates of glucose utilisation in the brain over the first year after birth correspond with the emergence of developmental milestones (Chungani 1998). By one year after birth the glucose utilisation rate in the brain is similar to an adult.

Third, alternative cerebral fuels, particularly lactate and ketones bodies, are transported into the astrocytes by the monocarboxylate transporter 1 (MCT1) and into neurons by monocarboxylate transporter 2 (MCT2). During periods of hypoglycaemia alternative cerebral fuels such as lactate, ketone bodies, pyruvate, amino acids, and glycerol are used to maintain brain function and structure (Hawdon 1999; Volpe 2001; de L Costello, Par et al. 2005).

Fourth, increased cerebral blood flow during hypoglycaemia has been demonstrated in both dogs and preterm babies, and may maintain net substrate delivery (Vannucci, Nardis et al. 1981; Pryds, Gresisen et al. 1988; Pryds, Christensen et al. 1990). More recently authors have shown increased cerebral blood flow to the hypothalamus and forebrain and decreased blood flow to the cerebellum and right par opercularis during hypoglycaemia in both non-diabetic and diabetic adults. This suggests some areas of the brain are more sensitive to changes in glucose concentrations than others (McCrimmon 2012).

1.7 Detection of neuronal injury

1.7.1 Electrophysiology

The degree and duration of the hypoglycaemia required to cause neuronal injury remains unclear. The EEG has been used to measure both the functional and metabolic condition of the brain during hypoglycaemia in both animals and human studies. EEG patterns when hypoglycaemia is induced in animal studies follow a gradual change from a normal frequency to a discontinuous burst-suppression pattern. If the hypoglycaemia continues then the EEG becomes isoelectric. If the blood glucose concentration is returned to within a normal range, the EEG pattern returns to the normal frequency (Volpe 2001).

Compared with adults, newborn rats and dogs require significantly lower glucose concentrations for longer periods of time before changes occur in behaviour or EEG patterns. In newborn dogs with insulin-induced hypoglycaemia, slowing of the EEG was
observed when blood glucose was less than 20% of the baseline concentration (8 mmol/L), and seizures occurred when the blood glucose concentration approached 0.5mmol/L (Vannucci, Nardis et al. 1981).

Reports from animal studies have shown substantial resistance to neuronal injury during insulin-induced hypoglycaemia. In adult rats no neuronal damage was seen one week following the hypoglycaemic insult unless there had been an isoelectric or burst suppression pattern in the EEG during a period of hypoglycaemia (Auer, Olsson et al. 1984). These data suggest no clear correlation between a specific blood glucose concentration and neuronal injury, even though there may be temporary neuronal dysfunction. Furthermore, there may be a relationship between the age of the animal and the influence of hypoglycaemia on neuronal cells.

The human studies have largely been carried out within the diabetic population. Haumont and colleagues (Haumont, Dorchy et al. 1979) showed 80% of diabetic children who reported five or more hypoglycaemic episodes demonstrated EEG abnormalities, including diffuse non-rhythmic slowing in six children, and paroxysmal sharp waves, spikes and bursts of delta waves in a further nine children. Recurrent hypoglycaemia and poor metabolic control has also been linked with EEG abnormalities in adolescents suffering from type1 diabetes. In one study poor control was associated with a global increase in theta activity (Hyllienmark, Maltez et al. 2005).

There are very few EEG studies in babies with hypoglycaemia. In a retrospective case series of four babies, all of whom showed brain injury on MRI, predominantly involving the occipital lobes, ten-lead EEGs were performed on days 2, 5, and 6 when the babies were not hypoglycaemic. These showed seizures and abnormal background which did not localise to the occipital regions (Filan, Inder et al. 2005).

1.7.2 Cot-side electroencephalogram

The Cerebral Function Monitor (CFM) and further advancement to the amplitude integrated EEG (aEEG) has allowed for continuous assessment of EEG in babies within the nursery (de Vries and Hellstrom-Westas 2005). The aEEG is relatively easy to apply and is now frequently used in clinical practice. It is based on a time-compressed semi-logarithmic (linear 0 to 10 µV, logarithmic 10 to 100 µV) display of the peak to peak amplitude values of a filtered and rectified EEG. The EEG is passed through asymmetric band pass filter that strongly enhances intermediate EEG frequencies. Most EEG activity below 2 Hz and above 15Hz is suppressed in order to minimise artefacts from sweating, movements, muscle activity and electrical interference (Hellstrom-Westas and Rosen 2006). This method of
EEG analysis allows for evaluation of seizures and trends in electrocortical background activity using simple pattern recognition and has been demonstrated to be useful in the neonatal nursery (Toet, van der Meij et al. 2002). However, the usefulness of the aEEG in the detection of neuronal injury related to neonatal hypoglycaemia is yet to be determined.

Stenninger and colleagues reported a small pilot study where they sought to detect changes on the CFM related to hypoglycaemia in twelve full term babies from diabetic pregnancies (Stenninger, Eriksson et al. 2001). Periods of hypoglycaemia were detected by both subcutaneous microdialysis and capillary blood. Blood glucose concentrations below 2.2mol/L were treated with intravenous dextrose infusions. There were no changes related to hypoglycaemia detected on the CFM. However, the mean maximum amplitude of the CFM signal was higher and the mean minimum amplitude tended to be lower during normoglycaemic periods than during hypoglycaemia.

There are also a small number of case reviews which have reported decreased aEEG background activity during neonatal hypoglycaemia, with a return to normal when blood glucose concentrations returned to normal (Hellstrom-Westas, Rosen et al. 1989).

1.7.3 Brainstem evoked potentials

The brainstem auditory evoked potential (BAEP) or brainstem auditory evoked response (BAER) reflects electrophysiological activity of a large number of neurons in the brainstem auditory pathway following acoustic stimulation. BAER is technically easier to measure than visual or somatosensory evoked potentials and measures peripheral auditory function and functional brain integrity. BAER has been primarily developed for universal newborn hearing screening and has been shown to be useful in assessment of babies with development disorders in a range of neurological diseases (Wilkinson and Jiang 2006). Visual evoked potentials measure a cortical response elicited by a pattern of visual stimuli. They can easily be measured in the newborn unit and have been found to be predictive of neurological outcome in term babies with perinatal asphyxia, but of less predictive value in preterm babies (Kato and Watanabe 2006). Somatosensory evoked potentials are difficult to measure in babies, and therefore are not a common modality for assessment of neurological function. However, they have been shown to be predictive of cerebral palsy in brain injured babies (Vanhatalo and Lauronen 2006).

Koh and colleagues used brainstem auditory evoked potentials to determine changes in neural function related to blood glucose concentration and reported a blood glucose concentration <2.6 mmol/L was associated a slowing in the auditory evoked potential signal suggesting neural dysfunction (Koh, Aynsley-Green et al. 1988). These findings underpin
current clinical practice. Interestingly, others have tried to repeat this study but have been unable to demonstrate a distinct blood glucose concentration linked to changes in the auditory evoked potential (Greisen and Pryds 1989; Cowett, Howard et al. 1997).

1.7.4 Neuroimaging

Ultrasound scanning remains the most common imaging modality used in the Newborn Intensive Care Unit. However, ultrasound scanning has a lower sensitivity than MRI for detecting the cortical injury in babies with hypoglycaemia (Kinnala, Rikalainen et al. 1999).

Case reports have described the relationship between severe hypoglycaemia and MRI and CT changes (Barkovich, Ali et al. 1998; Traill, Squier et al. 1998; Kinnala, Rikalainen et al. 1999; Alkalay, Flores-Sarnat et al. 2005; Filan, Inder et al. 2005; Balaji, Verghese et al. 2006; Arhan, Gülşen et al. 2011). In all case series the most consistent findings are lesions in the occipital areas of the brain. In the largest reported series of 23 babies, 17 (74%) demonstrated persistent abnormal findings. The majority of the MRI abnormalities (82%) were in the occipital areas, and visual impairment was identified in half of these babies (Alkalay, Flores-Sarnat et al. 2005).

One study investigated sequential neuroradiologic changes in 18 babies aged 1 to 37 days after transient symptomatic hypoglycaemia (Kinnala, Rikalainen et al. 1999). MRI or ultrasonography showed evidence of abnormality in seven (39%) either in the neonatal period or at two months of age. MRI detected more abnormalities than ultrasound scanning. Four babies showed patchy hyperintense lesions in the occipital areas. Other abnormalities included deformations of the frontal horns and mild dilation of ventricles. At two months of age, the changes on MRI had resolved in all but one baby, suggesting that the timing of scanning is important in detection of hypoglycaemic injury.

1.7.5 Pattern of neuronal hypoglycaemic damage

The pattern of brain injury related to hypoglycaemia has been shown to differ from the injury caused by other insults such as hypoxic-ischemic events in animals (Vannucci, Nardis et al. 1980) and human adults (Fujioka, Okuchi et al. 1997; Auer 2004). One pathological study (Anderson, Milner et al. 1967) compared autopsy findings from six babies, three of whom suffered untreated hypoglycaemia and three successfully treated hypoglycaemia. In the untreated babies, the most severe damage was in the cerebral cortex of the parietal and occipital lobes, while the temporal regions were less affected.

The majority of the neuroimaging literature using MRI supports the pathology study and shows that hypoglycaemia is associated with diffuse cortical and subcortical white matter...
damage, with the parietal and occipital lobes affected more severely. Other vulnerable areas include the dentate gyrus, hippocampus and the caudate nucleus (Barkovich, Ali et al. 1998; Traill, Squier et al. 1998; Kinnala, Rikalainen et al. 1999; Alkalay, Flores-Sarnat et al. 2005; Filan, Inder et al. 2005; Arhan, Gülşen et al. 2011). However, interestingly Burns and colleagues (Burns, Rutherford et al. 2008) reported early MRI scans in 35 term babies with symptomatic hypoglycaemia without hypoxic ischaemic encephalopathy and showed that almost all babies had evidence of white matter injury (94%), and only 29% of these babies had a predominately posterior pattern to the injury. In addition, 30% were found to have a haemorrhage. The study was not designed to detect patterns of neural damage related to duration or severity of hypoglycaemia.

There are a number of hypotheses regarding why the occipital lobes may be particularly vulnerable to hypoglycaemic neuronal injury. In dogs, cerebral blood flow to the occipital areas is reduced during periods of hypoglycaemia (Mujsce, Christensen et al. 1989). However, in babies the blood supply to the occipital lobes is from the posterior cerebral arteries, which also supply the brainstem, cerebellar structures, part of the thalamus, posterior temporal lobes and posterior hippocampus. The hippocampus is responsible for higher level functions such as memory and spatial awareness. Studies in rats have demonstrated the hippocampus to be vulnerable to hypoglycaemia (Auer 2004). Hippocampal damage associated with hypoglycaemia has been demonstrated in teenagers and adults who have experienced severe hypoglycaemia (Auer, Hugh et al. 1989; Bjorgaas 2012). Another hypothesis is that the metabolic demands of the brain structures supplied by the posterior cerebral arteries are higher than other areas of the brain (Alkalay, Flores-Sarnat et al. 2005). Further, during the neonatal period there is intense axonal migration and synaptogenesis in occipital lobes and both these processes are sensitive to glucose availability (Volpe 2001).

1.7.6 The mechanism of neural injury

The mechanism of neural injury following neonatal hypoglycaemia is not well defined. Animal studies have shown an accumulation of aspartate which spills into the extracellular space resulting in a complex chain of events causing cell death (Auer and Siesjo 1993). Another possible cause is the reduction in tricarboxylic acid cycle intermediates due to low cerebral glucose availability, leading to decreased energy for mitochondria and incomplete reduction of oxygen, increased mitochondrial free radical generation and cell death (McGowan, Chen et al. 2006).
1.8 Treatment for neonatal hypoglycaemia

1.8.1 Standard treatment

There are very few clinical trials investigating the treatment of neonatal hypoglycaemia. The most common initial treatment for hypoglycaemia is feeding. However, severe and/or persistent hypoglycaemia especially in the presence of clinical signs is most commonly treated with intravenous dextrose.

1.8.1.1 Breast feeding

Breast feeding is recommended by the World Health Organisation for all babies up to six months of age, and the health benefits of breast feeding for both the mother and baby are well recognised. Human studies have shown breast milk volume in the first 24 hours post-partum is low and progressively increases by day 3 (Kulski, Smith et al. 1981; Saint, Smith et al. 1984; Le Huerou-Luron, Blat et al. 2010). Further, the concentration of lactose within breast milk is also low in the first 24 hours and steadily increases over the first three days. Therefore, at-risk babies may be at increased risk of severe and prolonged episodes of hypoglycaemia if they are solely breastfed.

Healthy term breast fed babies in the first days after birth have lower blood glucose concentrations and higher ketone bodies concentrations than those receiving infant formula (Hawdon, Ward-Platt et al. 1992; de Rooy and Hawdon 2002). One possible explanation is that early breast milk has a low carbohydrate concentration and a high fat concentration. The ketone bodies may represent normal adaptive response during the establishment of breast feeding providing alternative cerebral fuels. However, babies at risk of neonatal hypoglycaemia have been shown to have low concentrations of ketone bodies (Hawdon, Ward-Platt et al. 1992; de L Costello, Par et al. 2005; Hay 2012).

One prospective study sought to reduce the incidence of neonatal hypoglycaemia in 84 term babies born to women with gestational diabetes, by establishing breast feeding within 30 minutes of delivery (Chertok, Raz et al. 2009). The blood glucose concentrations were measured at 3 hours of age and showed less hypoglycaemia in babies who were breast fed early. Therefore, it is possible early feeding may reduce the incidence of neonatal hypoglycaemia.

1.8.1.2 Infant formula feeding

Formula is often given to hypoglycaemic babies, although there have been no reported studies of this treatment. The carbohydrate content of formula is significantly higher than
that found in breast milk (Cormack 2003). Therefore, formula milk may be more effective as a treatment for neonatal hypoglycaemia than breast milk.

Two studies from India aimed to prevent hypoglycaemia in both small and large for gestational age babies by feeding. Babies with a blood glucose concentration of >30 mg/dl (1.6 mmol/L) measured by dextrostix (Ames Dextrometer) at less than 30 minutes of age were formula fed, with the treatment group receiving standard formula plus added powdered sugar 1.5 g per 30 ml. In both studies hypoglycaemia was reduced four-fold in the treatment group (Singhal, Singh et al. 1991; Singhal, Singh et al. 1992). The authors recommend early fortified feeding for at-risk babies born in developing countries, where access to accurate blood glucose testing is unavailable. However, formula feeding is not the preferred or recommended method for feeding babies (Williams 1997).

If feeding does not improve the blood glucose concentration the next step is commonly admission to the NICU for intravenous dextrose. A bolus of 200 mg/kg.min of 10% dextrose followed by an intravenous infusion of 8 mg/kg.min increases the blood glucose concentration within one minute, without causing hyperglycaemia (Lilien, Grajwer et al. 1977; Lilien, Pildes et al. 1980).

Intravenous dextrose and glucagon (200 mcg/kg) or intragastric medium chain triglycerides (5 ml/kg) have also been assessed in a randomised controlled trial (Hawdon, Aynsley-Green et al. 1993). Both treatments substantially increased the blood glucose concentration in babies already receiving 5 mg/kg.min intravenous dextrose for hypoglycaemia. Intravenous glucagon also increased the glucose production rate by 2.6 mg/kg.min.

1.8.2 Medications

Medications used for the management of neonatal hypoglycaemia include glucagon, corticosteroids such as hydrocortisone, diazoxide, somatostatin, octreotide and nifedipine.

Glucagon is given intramuscularly in an emergency situation when intravenous access has not been established. Glucagon stimulates adenylate cyclase to produce increased cyclic AMP, and promotes hepatic glycogenolysis and gluconeogenesis which causes blood glucose concentrations to increase (Ogilvy-Stuart and Midgley 2006).

Hydrocortisone is a corticosteroid and increases blood glucose concentrations by promoting gluconeogenesis and decreasing peripheral glucose uptake, in addition to suppressing insulin release (Comblath and Ichord 2000).
Diazoxide is used to treat hyperinsulinism. It is given intravenously and works by blocking the sulfonylurea receptors on the \( \beta \)-cells, which results in opening of the \( K_{\text{ATP}} \) channels and thereby decreasing insulin release.

Somatostatin is a key regulatory peptide that inhibits the secretion of glucagon, insulin, growth hormone and thyrotropin. Somatostatin is used to treat hyperinsulinism, but has a very short half-life and therefore Octreotide, which is a somatostatin analog, is frequently used due to the longer half-life and more potent effects.

Nifedipine for the management of neonatal hypoglycaemia remains a research medication. It acts by blocking the calcium channels in the \( \beta \)-cell and thereby preventing the release of insulin (McGowan 2006; Ogilvy-Stuart and Midgley 2006).

1.8.3 Potential new treatments

Oral carbohydrate is the first line treatment for conscious diabetic patients for the management of hypoglycaemia (Clarke, T et al. 2009). Concentrated glucose gel or honey is commonly administered to the unconscious hypoglycaemic patient when venous access is difficult or glucagon is not available (Clarke, T et al. 2009). Sublingual sugar is also reported to be as effective as intravenous dextrose in treating hypoglycaemia in children with malaria (Barennes, Valea et al. 2005; Graz, Dicko et al. 2008). There are anecdotal reports of improved blood glucose concentrations (Ang, Koh et al. 1990) and decreased need for intravenous dextrose infusion (Bourchier, Weston et al. 1992) following 40% dextrose gel 0.5 ml/kg via the buccal mucosa. Others recommend 40% dextrose gel 0.5–1.0 ml/kg when a hypoglycaemic baby has no venous access (Ogilvy-Stuart and Midgley 2006). In the United Kingdom Hypostop (dextrose gel 40%) is one of the essential medications on all paediatric resuscitation drug trolleys and packs (Perkin and Wey 2004). However, there is very little evidence to support the use of dextrose gel as a treatment for hypoglycaemic newborn babies.

Two conference presentations about 40% dextrose gel provide conflicting findings and differing doses. In the first observational study of 20 babies with hypoglycaemia, blood glucose concentrations increased in 14 babies by a mean of 1.8 mmol/L (range 1.3 to 2 mmol/L) twenty minutes following the administration of 40% dextrose gel 0.5 ml/kg, and at thirty minutes the blood glucose concentration remained above 2.6 mmol/L. The remaining six babies were polycythaemic or oedematous, and these factors were considered to be responsible for treatment failure (Ang, Koh et al. 1990).

The second report is of a randomised trial comparing 40% dextrose gel 1 ml/kg plus a feed with a feed alone in 75 babies greater than 36 weeks’ gestation with a blood glucose
concentration <2.5 mmol/L measured by capillary heel prick using the HemoCue blood glucose meter. The primary outcomes were changes in the blood glucose concentrations at 15 and 30 minutes. Secondary outcomes included the need for intravenous dextrose and the volume of the spontaneous feed following randomisation. There were no significant differences in the blood glucose concentrations of babies in either group at 15 or 30 minutes following treatment. Further, there were no differences between groups in the requirement for intravenous dextrose to treat hypoglycaemia. However, the volume of the subsequent feed was reduced by 5.5 +/- 1.0 ml/kg in babies who received dextrose gel (Troughton, Corrigan et al. 2000). Thus the effectiveness of 40% dextrose gel for treatment of neonatal hypoglycaemia remains uncertain.

1.9 Neurodevelopmental outcome following neonatal hypoglycaemia

The neurodevelopmental consequences of neonatal hypoglycaemia were first described over fifty years ago in a small group of symptomatic babies (Cornblath, Odell et al. 1959). The described consequences include cognitive delay (Pildes, Cornblath et al. 1974; Lucas, Morley et al. 1988; Stenninger, Flink et al. 1988; Duvanel, Fawer et al. 1999) motor delay (Stenninger, Flink et al. 1988; Lucas and Morley 1999), epilepsy and seizures (Menni, de Lonlay et al. 2001; Caraballo, Sakr et al. 2004) visual impairment (Alkalay, Flores-Sarnat et al. 2005; Tam, Widjaja et al. 2008) and behavioural problems (Kerstjens, Bocca-Tjeertes et al. 2012). Further, the physical assessment findings show babies who have experienced severe hypoglycaemia have smaller head circumferences (Duvanel, Fawer et al. 1999; Alkalay, Flores-Sarnat et al. 2005) and the findings from the MRI literature show babies who have experienced symptomatic hypoglycaemia have altered brain structure (Alkalay, Flores-Sarnat et al. 2005; Burns, Rutherford et al. 2008). The duration, severity or number of episodes of hypoglycaemia required to cause neurodevelopmental impairment remains unclear. The studies investigating the relationship between neonatal hypoglycaemia and neurodevelopmental outcome have been performed on babies with other risk factors for neurodevelopmental delay. In addition, studies have differing definitions for hypoglycaemia, have small sample sizes and poor follow-up and the results are conflicting (Griffiths and Bryant 1971; Koivisto, Blanco-Sequeiros et al. 1972; Fluge 1974; Pildes, Cornblath et al. 1974; Lucas, Morley et al. 1988; Stenninger, Flink et al. 1988; Duvanel, Fawer et al. 1999; Lucas and Morley 1999; Brand, Molenaar et al. 2005; Boluyt, van Kempen et al. 2006; Arhan, Gülşen et al. 2011).

Some studies have shown no difference in neurodevelopmental outcome between babies who have normal blood glucose concentrations and those with hypoglycaemia, (Griffiths and Bryant 1971). Others have shown that only babies with seizures have poor
neurodevelopment outcomes, (Koivisto, Blanco-Sequeiros et al. 1972) while others report poorer outcomes for all babies who have been hypoglycaemic (Pildes, Cornblath et al. 1974; Lucas, Morley et al. 1988; Stenninger, Flink et al. 1988; Duvanel, Fawer et al. 1999; Caraballo, Sakr et al. 2004).

Babies suffering from persistent hyperinsulinemia appear to be at highest risk for poor neurodevelopmental outcome. This may be because these babies suffer from severe recurrent hypoglycaemic episodes (Menni, de Lonlay et al. 2001). There is some evidence that prompt diagnosis and management of hypoglycaemia improves neurodevelopmental outcomes in this group (Hussain, Blankenstein et al. 2007).

Burns and colleagues (Burns, Rutherford et al. 2008) investigated patterns of cerebral injury using early MRI scanning and neurodevelopment outcomes in 35 babies with symptomatic hypoglycaemia (median blood glucose concentration 1 mmol/L). Of these, 94% had white matter damage and this was more predictive of neurodevelopmental outcome than the severity or duration of hypoglycaemia. At 18 months 76% had either moderate or severe neurodevelopmental delay, and seizures and visual problems were common. This study suggests that the neurodevelopmental outcome following symptomatic hypoglycaemia is variable, and early MRI scanning may be useful in predicting neurodevelopmental outcomes for affected babies.

1.10 References


Chapter 2: Introduction to the studies

2.1 Neonatal hypoglycaemia

Neonatal hypoglycaemia is important because it is common and linked to both brain damage and death (Cornblath, Odell et al. 1959; Rozance and Hay 2006). Despite awareness of this for the past seventy years there remains a paucity of evidence to guide clinical practice. The definition of neonatal hypoglycaemia has caused considerable controversy, and clinically significant neonatal hypoglycaemia remains undefined (Hay, Raju et al. 2009). It is difficult to know just how many babies are at risk, as published reports have used differing definitions, many have used unreliable analysers to measure the blood glucose concentration, and all have studied specific groups of at-risk babies. Furthermore, once hypoglycaemia is diagnosed, there are no clinical guidelines for management and thus clinicians remain unsure about the best treatment.

There are a number of areas that require careful investigation. Firstly, the duration and severity of hypoglycaemia required to cause brain damage are not well defined, largely because of the difficulties of measuring brain function in babies. Although a blood glucose concentration of <2.6 mmol/L has been recommended as a threshold for treatment in babies at risk, (Cornblath, Hawdon et al. 2000) this threshold for treatment is based on two publications from the 1980s (Koh, Aynsley-Green et al. 1988; Lucas, Morley et al. 1988). Both these publications have important methodological flaws and their relevance to current practice is unclear.

The adoption of a blood glucose concentration <2.6 mmol/L as the threshold for treatment leads to a number of problems for clinical management of hypoglycaemia, as many apparently normal babies have much lower blood glucose concentrations without apparent harm, and hence intervention based on this blood concentration may lead to invasive, expensive and inappropriate treatment of many babies. Cross-sectional studies of blood glucose concentrations at different times after birth in normal term babies suggest that 12% of them will have blood glucose concentrations <2.6 mmol/L in the first 1 to 4 hours after birth, and 10% will continue to have hypoglycaemia during the first six days of life (Srinivasan, Pilides et al. 1986; Hawdon, Ward-Platt et al. 1992). Further, although glucose is normally the major fuel for cerebral oxidative metabolism, under some circumstances alternative fuels can be utilised including lactate, ketones, glycerol, fatty, and some amino acids. Thus, it is likely that some babies with low blood glucose concentrations may be
protected from brain damage by the availability of alternative cerebral fuels. However, the relationship between blood glucose concentrations, alternative fuels and brain function remains undefined.

An additional problem in the management of neonatal hypoglycaemia relates to the rapidly changing blood glucose concentrations in the normal newborn. In clinical practice, blood glucose concentrations are measured intermittently, commonly 3 to 4 hourly. Therefore it is possible that some babies with hypoglycaemia that may threaten brain function are not identified, or alternatively that some babies with only an occasional brief fall in blood glucose concentrations are at no risk of impaired brain function but are inappropriately and invasively treated. Continuous glucose monitoring has been shown to be safe in a small number of extremely preterm babies (Beardsall, Ogilvy-Stuart et al. 2005) and also in the diabetic population, (Cameron and Ambler 2004) but its usefulness in babies at risk of neonatal hypoglycaemia had not been determined.

Ideally, what is needed to resolve these problems is simultaneous measurement of brain function, blood glucose concentration and availability of alternative cerebral fuels, so that we might determine a more rational approach to the diagnosis and management of neonatal hypoglycaemia. The Brainz Monitor (BRMII BrainZ Instruments, Auckland, New Zealand), a cot-side amplitude integrated electroencephalogram (aEEG), is a standard clinical tool within the Newborn Intensive Care Unit for the assessment of babies with neurological dysfunction and potentially might be used to detect changes in brain function related to low glucose concentration. Continuous interstitial glucose monitoring is available, though is not yet in widespread clinical use in babies. Our laboratory has developed methods for measuring alternative cerebral fuels accurately in the very small amounts of blood that can feasibly be taken from newborns.

Therefore, initially, we performed a pilot study in newborn lambs. We sought to determine whether changes in brain function associated with hypoglycaemia could be detected using a clinically applicable cot-side aEEG monitor. We induced hypoglycaemia using insulin in newborn lambs and maintained the hypoglycaemia for up to four hours. The neuro-imaging literature has suggested that the occipital areas of the brain are more sensitive to the damage caused by low glucose concentrations, and therefore we altered the cot-side aEEG to include a third channel which allowed the occipital area of the brain to be monitored (O1-O2 montages). We had two aims: firstly to identify repeatable reversible characteristic changes in brain function as measured using the cot-side aEEG monitor during prolonged insulin-induced hypoglycaemia, and secondly to determine the agreement between continuous interstitial glucose and conventional gold standard intermittent blood
glucose concentrations during hypoglycaemia. We were unable to detect characteristic changes on the cot-side aEEG related to glucose concentrations. However, there was moderate agreement between the two methods of glucose measurement (Chapter 3).

We then moved from the animal laboratory into the clinical practice environment. We aimed to establish the relationship between blood glucose concentrations, alternative cerebral fuels and brain function, as measured by a cot-side aEEG, in newborn babies at risk of hypoglycaemia. Again, we were interested in detecting subtle changes on the aEEG that might assist clinicians to determine which babies are at risk of neurological insult caused by neonatal hypoglycaemia. We found that continuous aEEG monitoring did not appear to be clinically useful in the detection of hypoglycaemia (Chapter 4). However, continuous interstitial glucose monitoring was safe, well tolerated and reliable (Chapter 5).

We also sought to survey current clinical practice in Australia and New Zealand for the management of hypoglycaemia, and particularly aspects of practice about which clinicians remained uncertain. Previous reports from Australia and the United Kingdom (Koh, Eyre et al. 1988; Bonacruz, Arnold et al. 1996; Koh and Vong 1996) have shown considerable variation in the definition, diagnosis and management of neonatal hypoglycaemia. Our findings showed that most clinicians agreed on the threshold for treatment (<2.6 mmol/L). However, the diagnosis was frequently made using unreliable analysers, and once hypoglycaemia was diagnosed clinicians were uncertain about treatment (Chapter 6).

The incidence of neonatal hypoglycaemia is poorly defined, and may be changing as the prevalence of maternal risk factors, such as diabetes and obesity increase (Wild, Roglic et al. 2004). In addition, the management of newborn babies has changed over the past two decades (Cornblath, Hawdon et al. 2000) and there have been no recent reports about the incidence of hypoglycaemia in babies at risk. The current recommended screening regimes are based on few studies and the relevance of these studies to current clinical practice is unclear. We therefore sought to determine the incidence of hypoglycaemia in a cohort of babies at risk, using reliable methods for blood glucose analysis. We were also interested to identify any differences in the incidence of hypoglycaemia between the at risk groups. We found hypoglycaemia was more common than had been previously reported in babies at risk and the incidence was similar in all at risk groups (Chapter 7).

Current treatment for neonatal hypoglycaemia depends on gestational age, birth weight and level of wellness of the baby. If the blood glucose concentration does not improve with feeding, admission to the Newborn Intensive Care Unit is generally indicated for treatment with intravenous dextrose. This requires mother and baby to be separated, which can cause distress and disrupt the establishment of breast feeding. In the survey described in
Chapter 6, we found that one Newborn Intensive Care Unit was using a 40% dextrose gel to treat neonatal hypoglycaemia. There had been anecdotal reports (Ang, Koh et al. 1990; Bourchier, Weston et al. 1992) and one small randomised controlled trial, published in abstract form only (Troughton, Corrigan et al. 2000), of the use of this treatment in neonates. There are potential advantages of an oral treatment such as dextrose gel, including the fact that it is non-invasive, inexpensive and allows the mother and baby to remain together. However, there was not robust evidence upon which to base treatment recommendations. We therefore performed a randomised controlled trial (The Sugar Babies Study) to determine if 40% dextrose gel was more effective than feeding alone in treating hypoglycaemia in late-preterm and term babies in the first 48 hours after birth. We found that babies treated with dextrose gel were less likely to remain hypoglycaemic, less likely to be admitted to the Newborn Intensive Care for the management of neonatal hypoglycaemia and less likely to be formula feeding two weeks after birth (Chapter 8).

Finally, we discuss the implications of our findings for current practice, and potential future research directions.

2.2 References


Chapter 3: Cot-side electro-encephalography and interstitial glucose monitoring during insulin-induced hypoglycaemia in newborn lambs

Published


Keywords: Hypoglycaemia, Insulin, Brain, Diagnostic tests, Neonatal intensive care
3.1 Abstract

Background: The optimal approach to detection and management of neonatal hypoglycaemia remains unclear.

Objectives: We sought to demonstrate whether electro-encephalography (EEG) changes could be detected on the amplitude-integrated EEG monitor during induced hypoglycaemia in newborn lambs, and also to determine the accuracy of continuously measured interstitial glucose in this situation.

Methods: Needle electrodes were placed in the P3–P4, O1–O2 montages. The interstitial glucose sensor was placed subcutaneously. After 30 min baseline recordings, hypoglycaemia was induced by insulin infusion and blood glucose levels were monitored every 5 min. The infusion was adjusted to reduce blood glucose levels by 0.5 mmol/L every 15 min and then maintain a blood glucose level <1.0 mmol/L for 4 h. EEG parameters analysed included amplitude, continuity and spectral edge frequency. The interstitial and blood glucose levels were compared.

Results: All lambs (n = 15, aged 3 to 11 days) became hypoglycaemic, with median blood glucose levels falling from 6.5 to 1.0 mmol/L, p <0.0001. There were no detectable changes in any of the measured EEG parameters related to hypoglycaemia, although seizures occurred in two lambs. There was moderate agreement between the intermittent blood glucose and continuous interstitial glucose measurements in the baseline, decline, and hypoglycaemia periods (mean difference -0.7 mmol/L, 95% confidence interval, CI, -2.8 to 1.4 mmol/L). However, agreement was poor during reversal of hypoglycaemia (mean difference 4.5 mmol/L, 95% CI -1.1 to 10.7 mmol/L).

Conclusions: The cot-side EEG may not be a useful clinical tool in the detection of neurological changes induced by hypoglycaemia. However, continuous interstitial glucose monitoring may be useful in the management of babies at risk of hypoglycaemia.

3.2 Introduction

Neonatal hypoglycaemia is a common problem and has long been linked to both brain damage and death (Cornblath, Odell et al. 1959; Volpe 2001). The duration and severity of hypoglycaemia required to cause brain damage are not well defined. Recently there have been case reports of neonatal hypoglycaemia where computer tomography and magnetic resonance imaging showed a characteristic pattern of brain injury in the cerebral cortex and the subcortical white matter, primarily in the occipital lobes (Volpe 2001; Filan, Inder et al. 2005).
Although severe hypoglycaemia causes electrographic changes including seizures, conventional electroencephalography (EEG) provides only intermittent assessments and is difficult to use in the Newborn Intensive Care Nursery because of the cumbersome nature of the monitoring and the difficulty in interpretation (Rosen 2006). However, in many nurseries, the amplitude-integrated cot-side EEG is a standard clinical assessment tool for babies with hypoxic ischaemic encephalopathy (Hellstrom-Westas and Rosen 2006; Rosen 2006). The clinical utility of this equipment for the identification of hypoglycaemia has not been investigated.

Hypoglycaemia is routinely diagnosed by intermittent blood sampling, commonly 1 to 4 hourly. However, intermittent sampling may miss significant periods of low blood glucose levels, for example before feeds, and the relationship between these measures and brain function has not been defined. Thus it is possible that some infants with hypoglycaemia that may threaten brain function are not identified, or alternatively that some babies with only an occasional brief fall in blood glucose levels are at no risk of impaired brain function but are inappropriately and invasively treated. Ideal management might involve continuous monitoring of blood glucose and cerebral function in each baby at risk of neonatal hypoglycaemia.

Continuous interstitial glucose monitoring has been shown to detect hypoglycaemia and lead to improved metabolic control in diabetic patients (Cheyne, Cavan et al. 2002; Cameron and Ambler 2004). Continuous interstitial glucose monitoring has also been shown to be safe and reliable in a small group of extremely preterm babies (Beardsall, Ogilvy-Stuart et al. 2005). However, its utility and accuracy have not been determined in neonates at risk of hypoglycaemia.

The aim of this study of insulin-induced hypoglycaemia was twofold; firstly, to determine changes in brain function as measured using a clinically applicable cot-side EEG monitor, and secondly, to determine the agreement between continuous interstitial glucose levels and conventional intermittent blood glucose levels.

3.3 Materials and methods

This study was approved by the animal ethics committee of the University of Auckland. Experiments were performed on 15 randomly selected newborn lambs. On the day of the experiment the lambs were weighed and placed in a sling adjacent to the mother’s pen. No sedation, analgesia or anaesthesia was used.

A three-channel cot-side amplitude-integrated EEG monitor (BRMII BrainZ Instruments, Auckland, New Zealand) was designed for the experiment. Seven platinum needle
electrodes were placed; two each in the standard P3–P4, montages, two additional electrodes in the O1–O2 montage, and one reference electrode in the back of the neck. The electrodes were held in place with surgical tape and super-glue under an elastic sleeve.

The continuous glucose monitor sensor (CGMS® system gold TM Medtronic, MiniMed, Northridge, Calif., USA) was inserted subcutaneously in the lamb’s back using the Sensor device according to the manufacturer’s instructions. Both jugular veins were cannulated using 18-gauge intravenous angiocatheters (Teurmo, Surflo®, Tokyo, Japan) and the catheters flushed with heparinised saline (10 U/ml). One catheter provided access for infusions while the other was used for blood sampling. Heart rate and oxygen saturation were continuously recorded from a sensor clip on the lamb’s ear using a Power Lab (AD Instruments Pty Ltd., Bella Vista, Australia). Rectal temperatures were measured as clinically indicated.

A stock solution of 50 units human insulin was made up to 50 ml with 0.9% saline (1 U/ml) (Humulin® R Insulin, Eli Lilly, Indianapolis, Ind., USA). The filled syringes and tubing were kept refrigerated overnight to allow for insulin adsorption to the plastic. At the beginning of the experiment an infusion of 10% dextrose was started at 2.5 ml/kg/h. After a 30-min baseline period, the insulin infusion was then started at 0.5 U/kg/h. The insulin and dextrose infusion rates were adjusted every 5 to 10 min with the aim of reducing the blood glucose level by 0.5 mmol/L every 15 min until the EEG signal showed burst suppression, a flat trace, or the lamb was clinically seizing, or until the blood glucose level was below 1 mmol/L for up to 4 h. Blood samples were taken at 5-min intervals for measurement of blood glucose levels using a Yellow Springs 2300 STAT Plus glucose analyser (Yellow Springs Instruments Inc., Yellow Springs, Ohio, USA). Additional 3-ml blood samples for the measurement of potential alternative cerebral fuels were taken at baseline, every h after that, at the completion of the hypoglycaemic period and at the completion of the experiment.

At the completion of the period of hypoglycaemia, the insulin infusion was stopped, the dextrose infusion was restarted, and boluses of 10% dextrose (5 ml/kg) were given as required to return blood glucose levels to baseline. After a further 15-min period of observation during normoglycaemia, all the monitoring was removed. The lamb was returned to its mother and both animals were observed in the housing pen for 24 h. The total experiment time was up to 7.5 h.
3.3.1 Analysis of blood samples

Blood samples were placed on ice until centrifugation at 4°C and 3,000 g; the plasma was separated and stored at -80°C until analysis. Samples were analysed for lactate, free fatty acids, β-hydroxybutyrate and glycerol using a Hitachi 902 automatic analyser (Hitachi Australia, North Ryde, NSW, Australia). The commercial reagent kits used for analysis were produced by Randox Laboratories Ltd, (Antrim, UK). Human insulin was measured using an Abbott Laboratories IMAX analyser (Abbott Laboratories, Abott Park, Ill., USA).

3.3.2 Continuous glucose monitor

The MiniMed continuous glucose monitor measures interstitial glucose levels through a subcutaneous sensor using a glucose oxidase method. The monitor records the average interstitial glucose level over a 5-min period. There is no real-time read out. Data were downloaded using CGMS® System Solutions™ software, version 3.0C, and a calibration algorithm supplied by the manufacturer was applied to values below 2.2 mmol/L.

We excluded the results of 1 lamb because there were large and uncharacteristic deviations between the glucose measures indicating a faulty sensor (n = 70 paired recordings).

3.3.3 Analysis of EEG

The EEG signals were amplified 5,000 times and bandpass filtered with a first-order high-pass filter with -3 dB, frequency at 1 Hz and a fourth-order low-pass Butterworth filter at -3 dB, frequency at 50 Hz. The signal was digitised at a sampling rate of 256 Hz and the intensity spectra and derived parameters were calculated from 4-second epochs of the digitised signal (Williams and Gluckman 1990). The total EEG intensity (µV²) was calculated on the intensity (power) spectrum between 2 and 20 Hz. Spectral edge frequency was defined as the frequency below which 90% of EEG power existed.

The amplitude was calculated from the bandpass-filtered and rectified signal with an algorithm that generates minimum, maximum and median amplitudes that are functionally equivalent to the cerebral function monitor (Sebel, Maynard et al. 1983). Continuity measures were determined as the percentage of each min during which the amplitude of the raw EEG (assessed at 2-second intervals) was above the determined threshold amplitude (10, 25, 50 or 100 µV). The EEG amplitude, continuity and intensity measurements were averaged and stored to disc at 1-min intervals.

The averaged EEG signal was digitised and analysed in 5-min epochs using Chart File Analyser, beta version 1.74.3 (Liggins Institute, University of Auckland, New Zealand). EEG
data were defined as valid and included in analysis if the electrode impedance was below 10 kΩ per pair, and free from electrical or EMG artefacts. Median values of each quantitative EEG variable were recorded. The raw EEG signals were manually reviewed for seizures by a neurologist.

For analysis, 4 experimental time periods were defined:

1. Baseline: from the beginning of a satisfactory EEG signal to the start of insulin infusion (30 min);
2. Decline: from the start of insulin infusion until the blood glucose level was <1.5 mmol/L (variable, up to 2 h);
3. Hypoglycaemia: from attaining a constant blood glucose level <1.5 mmol/L until the insulin infusion was stopped (variable, up to 4 h), and
4. Recovery: from the end of insulin infusion to the end of the experiment (15 min).

3.3.4 Statistical analysis

Data were divided into four experimental time periods for analyses, and the number of data points in each time period therefore differed for each lamb. To allow for this, median values for each lamb for each period were used in the analyses. Data for different time periods were compared using repeated analysis of variance with Tukey-Kramer HSD correction for multiple comparisons. Bland-Altman plots were used for comparison of blood glucose and interstitial glucose levels.

3.4 Results

Fifteen lambs with a mean weight of 6.1 kg (range 3.4–9.2 kg) were studied at a mean age of 6 days (range 3–11 days). Four lambs died, three between 2 and 12 h after the end of the experiment and one 3 weeks later for unknown reasons. Extensive post-mortem examinations were performed on the 3 early deaths. One lamb had large bilateral intraventricular haemorrhages, and minor haemorrhages in the frontal and parietal lobes. No other abnormalities were identified.

3.4.1 Blood glucose levels

All lambs became hypoglycaemic, with median blood glucose levels falling from 6.5 (range 4.7–8.4 mmol/L) to 1.0 mmol/L (range 0.2–1.8 mmol/L) and returning to baseline levels at the completion of the experiment (levels different during each experimental period, p
<0.0001) (Table 3-1). The time taken to achieve hypoglycaemia varied between lambs, with the median time being 110 min (range 45–260 min).

### Table 3-1. Heart rate, oxygen saturation and plasma levels of cerebral fuels during the four experimental time periods

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Decline</th>
<th>Hypoglycaemia</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>220 (107–293)</td>
<td>248* (88–302)</td>
<td>226 (99–300)</td>
<td>229 (152–287)</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>95 (85–100)</td>
<td>98 (87–100)</td>
<td>98 (88–100)</td>
<td>97 (85–100)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>6.5 (4.7–8.4)*</td>
<td>2.9 (1.1–8.4)*</td>
<td>1.0 (0.2–1.8)*</td>
<td>6.9 (3.8–19.1)*</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>1.6 (1.0–2.5)</td>
<td>1.7 (1.1–3.4)</td>
<td>1.5 (0.1–3.6)</td>
<td>2.1 (0.9–3.7)*</td>
</tr>
<tr>
<td>ßHBA, mmol/L</td>
<td>0.3 (0.1–0.6)</td>
<td>0.2 (0–0.7)</td>
<td>0.2 (0.0–0.6)</td>
<td>0.1 (0.0–0.6)*</td>
</tr>
<tr>
<td>FFA, mmol/L</td>
<td>1.0 (0.4–2.9)</td>
<td>1.1 (0.4–3.0)</td>
<td>1.0 (0.3–3.0)</td>
<td>1.3 (0.2–2.5)</td>
</tr>
<tr>
<td>Glycerol, mmol/L</td>
<td>0.2 (0.1–0.6)</td>
<td>0.2 (0.0–0.5)</td>
<td>0.2 (0.0–0.5)</td>
<td>0.2 (0.0–0.5)</td>
</tr>
</tbody>
</table>

Data are median (range) for 15 lambs * p <0.01 for comparison with all other time periods. See text for explanation of the time periods.

#### 3.4.2 Insulin

A wide range of insulin dosage was required to establish and maintain hypoglycaemia (0.5 U/kg/h to 200U/kg/h). Median plasma insulin levels were 4.4 (1.6–31.5) x 10^3 U/ml after 2 h of infusion, 28.9 (1.9–135.6) x 10^3 U/ml at the end of the hypoglycaemic period and were still 22.9 (3.6–86.4) x 10^3 U/ml at the end of the experiment.

#### 3.4.3 Alternative fuels

The plasma lactate levels did not vary during the first 3 experimental periods, but increased in the recovery phase (p <0.001). Similarly, plasma ß-hydroxybutyrate levels did not vary during the first 3 periods but decreased in the recovery phase (p <0.01). The plasma levels of both free fatty acids and glycerol did not vary during the 4 experimental periods (Table 3-1).

#### 3.4.4 Clinical changes

All lambs showed signs potentially attributable to hypoglycaemia, including jittery movements, tremor, tachycardia, and lethargy, with the tachycardia being most marked during the decline phase of the experiment (p <0.001, Table 3-1). The oxygen saturations were higher in the decline and hypoglycaemic periods of the experiment than both baseline and recovery periods (p <0.0001), but all oxygen saturation recordings were in the normal range. Respiratory distress was noted in 1 lamb after 2.5 h of hypoglycaemia, when the blood glucose level was <1.5 mmol/L, but oxygen saturations remained between 89 and 96%. The respiratory distress continued for more than 4 h until the blood glucose level had returned to normal. Rectal temperatures were measured on all lambs when shivering was seen, and all were within the normal range (38.8–40.3 °C).
Two lambs had electrical seizures, but clinical seizures were detected in only one of these. The lamb with electrical seizures alone had a blood glucose level of 0.5 mmol/L at the time of the seizure and had been hypoglycaemic with a blood glucose level <1.0 mmol/L for 170 min. The seizure was seen in all three EEG channels and lasted for less than one min. The lamb with clinical and electrical seizures had a blood glucose level of 0.9 mmol/L at the time of the seizure and had been hypoglycaemic for 260 min. This lamb had two generalised tonic-clonic seizures each lasting less than one min, two min apart, followed by a postictal period of unresponsiveness lasting approximately 3 min. Both lambs with electrical seizures had plasma levels of lactate, β-hydroxybutyrate, free fatty acids and glycerol at or above the median levels for all lambs studied.

All lambs rested quietly in the sling during the experiment until the recovery phase. When the blood glucose levels had returned to normal, all lambs became restless and appeared to be hungry. Many started struggling to rejoin the mother in the neighbouring pen. When the lambs were reunited with their mothers, feeding commenced immediately and frequent feeding was observed over the next few hours.

3.4.5 Electro-Encephalogram

The median duration of recording was 432 min (range 244–496) of which 370 min (range 214–484) were included in the analysis. There were no significant changes in minimum amplitude, continuity at 50 µV or spectral edge frequency during the experiment (Table 3-2), nor were there any changes in median or maximum amplitude or in continuity at 10, 25, or 100 µV (data not shown). There were no differences between the EEG parameters measured over the left, right, and occipital leads (Table 3-2).

Table 3-2. Amplitude-integrated EEG minimum amplitude and continuity measurements and EEG 90% spectral edge frequency measurements during the 4 experimental time periods.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>Decline</th>
<th>Hypoglycaemia</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum amplitude left µV</td>
<td>9.2 (4.6–16.4)</td>
<td>10.3 (5.5–15.7)</td>
<td>11.5 (7.0–1.9)</td>
<td>11.5 (6.6–30.3)</td>
</tr>
<tr>
<td>Minimum amplitude right µV</td>
<td>9.6 (6.6–12.1)</td>
<td>9.7 (6.9–12.8)</td>
<td>9.9 (7.7–13.6)</td>
<td>10.2 (7.8–14.0)</td>
</tr>
<tr>
<td>Minimum amplitude occipital µV</td>
<td>8.3 (4.9–11.6)</td>
<td>7.6 (5.1–15.6)</td>
<td>8.0 (4.8–18.5)</td>
<td>9.6 (5.2–18.5)</td>
</tr>
<tr>
<td>Continuity left 50µV</td>
<td>40.6 (0–100)</td>
<td>49.6 (5.7–100)</td>
<td>72.7 (2.7–100)</td>
<td>68.9 (0–100)</td>
</tr>
<tr>
<td>Continuity right 50µV</td>
<td>47.0 (0–100)</td>
<td>28.2 (9.3–91.6)</td>
<td>55.6 (12.6–100)</td>
<td>75.2 (2.3–100)</td>
</tr>
<tr>
<td>Continuity occipital 50µV</td>
<td>13.7 (0–100)</td>
<td>39.0 (0–100)</td>
<td>24.7 (0–100)</td>
<td>61.2 (0–100)</td>
</tr>
<tr>
<td>Spectral edge left Hz</td>
<td>12.6 (7.7–16.8)</td>
<td>12.5 (7.3–17.0)</td>
<td>13.1 (6.4–17.2)</td>
<td>14.0 (5.1–17.9)</td>
</tr>
<tr>
<td>Spectral edge right Hz</td>
<td>12.7 (7.2–17.2)</td>
<td>13.2 (9.3–17.5)</td>
<td>11.9 (8.0–16.7)</td>
<td>12.6 (7.8–17.8)</td>
</tr>
<tr>
<td>Spectral edge occipital Hz</td>
<td>14.8 (1.8–18.3)</td>
<td>14.8 (1.8–18.1)</td>
<td>12.5 (1.75–18.3)</td>
<td>15 (1.75–18.4)</td>
</tr>
</tbody>
</table>

Data are median (range) for 15 lambs. See text for explanation of the time periods. There are no differences between time periods for any of the variables.
3.4.6 Comparison between continuous interstitial and blood glucose levels

A total of 1,009 paired blood and interstitial glucose samples were analysed (38 in the baseline phase, 310 in decline, 613 in hypoglycaemia, and 48 in recovery). Initially, the relationship between the blood and interstitial glucose measurements appeared to be very close, with close tracking of the measurements in individual lambs (Figure 3–1).

**Figure 3-1.** Comparison between blood and interstitial glucose levels in 1 lamb. Data plotted from 93 paired blood and interstitial glucose levels. The black line indicates blood glucose levels. The grey line indicates interstitial glucose levels. Experimental time-periods are indicated below the x-axis.

However, the Bland-Altman plot, which determines the level of agreement between two methods of measurement, revealed variation between the experimental phases (Figure 3–2). There was moderate agreement between the intermittent and continuous glucose measurements in the baseline, decline, and hypoglycaemia periods of the experiment (mean difference -0.7 mmol/L, 95% confidence interval, CI, -2.8 to 1.4 mmol/L), with the blood glucose levels being slightly but consistently lower than the continuous interstitial glucose levels (baseline -0.7, CI -2.3 to 0.9 mmol/L, decline -0.8, CI -2.8 to 1.2 mmol/L, hypoglycaemia -0.6, CI -2.7 to 1.5 mmol/L). However, when the blood glucose level remained <1 mmol/L, the blood glucose was usually higher than the interstitial glucose level (Figure 3–2). In the recovery phase, blood glucose levels were significantly higher than interstitial glucose levels (mean difference 4.5 mmol/L, CI -1.1 to 10.7 mmol/L, p <0.0001)
3.5 Discussion

We sought to determine changes in the EEG signal detected using a cot-side EEG monitor associated with insulin-induced hypoglycaemia. Our data show that, while all lambs demonstrated symptoms that could be attributed to hypoglycaemia, and 2 experienced seizures, there were no changes in any of the measured EEG parameters related to insulin-induced hypoglycaemia. We also sought to determine the level of agreement between continuous interstitial glucose monitoring and conventional intermittent blood glucose measurement. These data show that there is moderate agreement between the two methods of measuring blood glucose levels in hypoglycaemic lambs, but that interstitial glucose monitoring may not be reliable during rapid reversal of hypoglycaemia by intravenous glucose infusion.

Hypoglycaemia was achieved in all 15 lambs in our study. However, the time taken and the amount of insulin required in order to achieve hypoglycaemia was variable. In similar studies to ours using puppies (Vannucci, Nardis et al. 1980; Vannucci, Nardis et al. 1981; Mujsce, Christensen et al. 1989) and rat pups (Kim, Yu et al. 2005), hypoglycaemia was
induced using repeated intravenous boluses of 0.2–0.3 and 3 U/kg, respectively, which is much less than in our study. This may be because insulin does not consistently suppress glucose production in newborn lambs. In one study of 3 to 6 and 31 to 35 day old lambs, glucose production continued in all lambs despite insulin infusions of 100 mU.kg\(^{-1}\).min\(^{-1}\) although the older lambs showed a greater response to insulin than the younger group (Gelardi, Rapoza et al. 1999). This relative insulin resistance of young lambs may explain the high doses of insulin required to achieve hypoglycaemia in our study.

Both animal and human newborns have been shown to be able to use alternative cerebral fuels including lactate, ketones, free fatty acids and amino acids, during hypoglycaemia (Kraus, Schlenker et al. 1974; Bougneres, Lemmel et al. 1986; Hawdon, Ward-Platt et al. 1992). We found that during the experimental periods of baseline, decline and hypoglycaemia there was no change in the plasma levels of lactate, β-hydroxybutyrate, free fatty acids, or glycerol, and hence no apparent increase in availability of potential alternative cerebral fuels. This is consistent with the effects of insulin on suppression of alternative fuels (Stanley and Caplin 2004), and also with an earlier study in puppies, in which all puppies had behavioural changes associated with hypoglycaemia, but plasma lactate levels remained unchanged (Vannucci, Nardis et al. 1981). However, in the only similar study in 5 to 7 day old lambs in which hypoglycaemia was rapidly induced using insulin infusion and maintained for 2 h, there was a steady increase in arterial lactate and glycerol levels (Belik, Wagerle et al. 1989). We found significant increases in the plasma lactate levels and a decrease in β-hydroxybutyrate levels only during the recovery phase. This may be related to the use of boluses of intravenous glucose to reverse the hypoglycaemia, potentially exceeding the capability of the citric acid cycle and resulting in the pyruvate produced from the glycolytic pathway being diverted to lactate, while ketogenesis would be inhibited by the glucose infusion.

It is not apparent from this study why two lambs experienced electrical seizures, while others with similar and severer hypoglycaemia did not. There were no differences in the level of alternative fuels between lambs that did and did not experience seizures so that availability of fuels for cerebral oxidative metabolism seems an unlikely explanation. This apparent variability in individual susceptibility to neurological injury during hypoglycaemia has long been recognised in the clinical environment (Hawdon 1999; Cornblath and Ichord 2000), and emphasises the importance of finding a practical approach to individual monitoring of neurological function in babies at risk of hypoglycaemia.

The conventional EEG has been used to measure brain function during hypoglycaemia in both human and animal studies. In animal studies, the EEG patterns change from a normal
frequency to a discontinuous burst suppression pattern. If the hypoglycaemia continues, then the EEG becomes isoelectric. If the blood glucose level returns to the normal range, the EEG pattern returns to the normal frequency (Vannucci, Nardis et al. 1981; Vannucci and Vannucci 2001; Vannucci and Vannucci 2004).

The cot-side EEG is part of the routine care in the management of newborns suffering from asphyxia in many nurseries. However, there are few reports of the use of the cot-side EEG to assess brain function during neonatal hypoglycaemia. One case report has shown epileptogenic activity associated with blood glucose levels between 0.2 and 2.0 mmol/L in a growth-retarded term twin baby using the cot-side cerebral function monitor (Hellstrom-Westas, Rosen et al. 1989). More recently, Stenninger et al. (Stenninger, Eriksson et al. 2001) were unable to demonstrate changes in the amplitude integrated EEG pattern associated with hypoglycaemia in infants of diabetic mothers. However, all babies in this study were treated if the blood glucose levels were 2.0 mmol/L or below so that changes in EEG pattern associated with more severe hypoglycaemia may not have been detected.

There is some evidence from both electrophysiology and imaging of an association between occipital lobe damage and neonatal hypoglycaemia (Barkovich, Ali et al. 1998; Traill, Squier et al. 1998; Kinnala, Rikalainen et al. 1999; Caraballo, Sakr et al. 2004; Alkalay, Flores-Sarnat et al. 2005; Filan, Inder et al. 2005; Miller, Ramaswamy et al. 2005). Therefore, in addition to the standard EEG P3-P4 montages, we placed electrodes in the O1-O2 montages. However, we found no evidence of any difference in EEG measures between differing areas in the brain during insulin-induced hypoglycaemia. This may be because the brain of a lamb is smaller and has a differing blood supply than the brain of a newborn baby, or simply because the limited EEG sampling possible with the limited electrode placement of a cot-side monitor was insufficient to detect any changes that may have occurred, particularly in deeper brain structures. Our findings suggest that the cot-side EEG has limited clinical utility in the identification of neurological changes related to hypoglycaemia.

There are studies supporting the clinical utility of continuous glucose monitoring in children and adults with diabetes (Caplin, Leary et al. 2003; Cameron and Ambler 2004). However, there are few studies evaluating its use in babies, and none in neonatal hypoglycaemia. Beardsall et al. (Beardsall, Ogilvy-Stuart et al. 2005) evaluated the continuous glucose monitor in 16 babies of birth weight <1,500 g, and found the monitor to be safe and reliable for up to 7 days. However, the babies were not often hypoglycaemic and this prevented the authors from evaluating the continuous glucose sensor during hypoglycaemia. Nevertheless, periods in excess of 2 h were reported in which hypoglycaemia was
recorded on the continuous glucose monitor, but not diagnosed clinically, as an intermittent blood sample was not taken. We found the continuous glucose sensor provided consistently low glucose measurements during profound hypoglycaemia in newborn lambs, and usually tracked blood glucose levels well in individual lambs. These findings suggest that the continuous glucose monitor may be clinically useful in the management of babies with hypoglycaemia.

In the first three experimental periods, we found that the interstitial glucose level was slightly higher than the blood glucose level. This may be because in sheep, the red cells are relatively impermeable to glucose, and thus plasma glucose levels are higher than whole-blood glucose levels (Lindsay and Leat 1975). Since glucose in the interstitial space has diffused across the endothelium from the plasma, this higher plasma level may account for the slightly higher interstitial glucose level that we observed.

During the recovery phase of the experiment, when the blood glucose levels increased rapidly, the blood glucose level consistently increased faster than the interstitial glucose levels so that the difference between the two was as large as 10 mmol/L. Interstitial glucose is influenced by the diffusion of plasma glucose across the endothelium, and by the clearance of glucose from the interstitial space. During the recovery phase, boluses of glucose were given intravenously, leading to a rapid rise in blood glucose levels, but insulin levels remained very high, presumably resulting in a high rate of clearance of glucose from the interstitial space. This resulted in a delay between the rise in blood and interstitial glucose levels. A similar lag-time has been well described in previous studies and is reported to be up to 20 min (Rebrin, Steil et al. 1999; Caplin, Leary et al. 2003). In a clinical situation, insulin levels are unlikely to be as high as in this experiment. Nevertheless, relative hyperinsulinaemia is a common cause of neonatal hypoglycaemia, for example in infants of diabetic mothers. Thus, if the interstitial glucose monitor were used in neonates, the potential lag-time would need to be considered when reversing hypoglycaemia with boluses of intravenous dextrose.

In conclusion, our data suggest that the cot-side amplitude-integrated EEG may not be a useful clinical tool in the detection of neurological changes induced by hypoglycaemia, even when additional occipital leads are used. Our data also suggest that there is moderate agreement between blood glucose and continuous interstitial glucose monitoring during hypoglycaemia, but that the agreement is less good when hypoglycaemia is rapidly corrected using intravenous boluses of dextrose. Further studies in babies are needed to establish the utility of continuous interstitial glucose monitoring in the clinical setting.
3.5.1 Acknowledgements

The authors would like to acknowledge the technical assistance of Megan Brownie, Bridget Clark, Mark Oliver, Samantha Rossenrode, Claire Spooner and Eric Thorstensen. This work was funded in part by the Waikato Medical Research Foundation, the Maurice and Phyllis Paykel Trust, and the Rebecca Roberts Scholarship.

3.6 References


Chapter 4: Cot-side EEG monitoring is not clinically useful in the detection of early neurological changes related to mild neonatal hypoglycaemia

Published


Supported by The Auckland and Waikato Medical Research Foundations, the Maurice and Phyllis Paykel Trust and the Rebecca Roberts Scholarship

The authors declare no conflicts of interest
4.1 Abstract

Objectives: Neonatal hypoglycemia is common and can cause brain damage. Cot-side amplitude integrated electroencephalography (aEEG) is widely used in asphyxiated newborns, but remains untested in hypoglycemia. We sought to determine the relationship between EEG patterns and hypoglycemia, using simultaneous cot-side aEEG and continuous interstitial glucose monitoring, and whether non-glucose cerebral fuels modified these patterns.

Study Design: Eligible babies were ≥32 weeks, at risk of hypoglycemia, and admitted to NICU. Electrodes were placed in C3-P3, C4-P4 O1-O2 montages. A continuous interstitial glucose sensor was placed subcutaneously, and blood glucose measured using the glucose oxidase method. Non-glucose cerebral fuels were measured at study entry, exit and during recognised hypoglycemia.

Results: 101 babies were enrolled, with median weight 2179 g and gestation 35 weeks. 24 had aEEG recordings while glucose concentrations were low (<2.6 mmol/L). There were 103 episodes of low glucose concentrations lasting 5 to 475 minutes, but no observable changes in aEEG parameters. Plasma concentrations of lactate, beta-hydroxybutyrate and glycerol were low and did not alter during hypoglycemia.

Conclusions: Cot-side aEEG does not appear to be useful in detection of neurological changes during mild hypoglycemia. Plasma concentrations of non-glucose cerebral fuels were low and unlikely to provide substantial neuroprotection.

4.2 Introduction

Neonatal hypoglycaemia is important because it is common and can cause brain damage (Koh, Aynsley-Green et al. 1988; Lucas, Morley et al. 1988). However, the blood glucose concentration and duration required to cause damage remains unclear (Hay, Raju et al. 2009). This is in part because measuring neurological integrity in babies is difficult, there is little relationship between clinical signs and blood glucose concentrations, and there is an apparent individual susceptibility to hypoglycaemia-induced neurological impairment. Severe hypoglycaemia can cause electrographic seizures and poor neurological outcome (Hellstrom-Westas, Rosen et al. 1989; Burns, Rutherford et al. 2008). However, some babies are able to withstand blood glucose concentrations <1.0 mmol/L without clinical signs or seizures (Koivisto, Blanco-Sequeiros et al. 1972).
Conventional electroencephalography (EEG) is the gold standard for measurement of brain function, and can show marked changes with hypoglycemia in animal studies (Auer, Olsson et al. 1984) and adult diabetics (Tallroth, Lindgren et al. 1990). However it is technically difficult in babies providing only intermittent assessment, and its interpretation requires specialist training. Amplitude integrated cot-side EEG (aEEG) is a standard tool for assessing babies with hypoxic ischaemic encephalopathy (Spitzmiller, Phillips et al. 2007) and seizures. The aEEG allows for continuous recordings, and interpretation is not dependent on the availability of a paediatric neurophysiologist. Two small pilot studies using a single channel EEG Cerebral Function Monitor during neonatal hypoglycemia reported no changes (Pryds, Gresisen et al. 1988), or subtle changes in amplitude (Stenninger, Eriksson et al. 2001). There have also been case reports of decreased aEEG background activity during severe neonatal hypoglycemia (<1.0 mmol/L) (Hellstrom-Westas, Rosen et al. 1989), and changes in quantitative EEG parameters during hypoglycaemia in older children (Bjorgaas, Sand et al. 1998).

Magnetic resonance imaging (MRI) (Alkalay, Flores-Sarnat et al. 2005) and pathology (Anderson, Milner et al. 1967) literature has suggested that occipital regions may be most sensitive to hypoglycaemic damage. Although a novel modified three channel aEEG has been used to measure both parietal and occipital montages in hypoglycaemic newborn lambs (Harris, Battin et al. 2009), we are unaware of any studies reporting aEEG changes in the occipital regions during human neonatal hypoglycaemia.

Hypoglycaemia is routinely diagnosed by intermittent blood sampling, which may miss significant periods of hypoglycaemia (Harris, Weston et al. 2010). Continuous interstitial glucose monitoring has recently been shown to be well tolerated, reliable and safe in newborns (Harris, Weston et al. 2010), and allows potential matching of simultaneous glucose and EEG data.

Non-glucose cerebral fuels including lactate, ketone bodies, glycerol and some amino acids may provide cerebral protection during neonatal hypoglycaemia (Hawdon, Ward-Platt et al. 1992). However, few studies have measured non-glucose cerebral fuels in newborns at risk of hypoglycaemia in the days immediately after birth (Hawdon, Ward-Platt et al. 1992; Hawdon and Ward-Platt 1993; Hawdon, Weddell et al. 1993; de L Costello, Par et al. 2005).

The aim of our study was to determine if there were characteristic aEEG patterns related to neonatal hypoglycaemia detectable using simultaneous cot-side aEEG and continuous interstitial glucose monitoring in at-risk babies admitted to NICU. We also sought to determine if the availability of non-glucose cerebral fuels modified these patterns.
4.3 Methods

Babies included in this study were recruited to the Babies and Blood Sugars Influence on EEG Study (BABIES) study, and details of eligibility, nutritional management and continuous glucose monitoring are provided in the previous report (Harris, Weston et al. 2010). In brief, we studied babies ≥32 weeks gestation, identified as at risk of hypoglycemia and admitted to NICU. Written informed consent was obtained in all cases. The study was approved by the Northern Y Regional Ethics Committee.

All babies were managed according to our NICU guidelines, including early oral feeds with breast milk as soon as it was available, and additional infant formula and intravenous 10% dextrose as required. Hypoglycemia was defined as a blood glucose concentration <2.6 mmol/L, and was initially managed with 40% dextrose gel (200mg/kg), then intravenous 10% dextrose 2ml/kg over 10 minutes then 60 or 90 ml/kg/d (4 - 6 mg/kg.min) if required.

Blood glucose concentration was measured by heel-prick sampling at one hour of age, then before feeds two to four hourly for 12 hours, or in babies receiving intravenous dextrose, 4 hourly for 12 hours, and then as clinically indicated. All blood glucose concentrations were measured using the glucose oxidase method (Radiometer, ABL800Flex, Copenhagen, reading range 0.0 to 60 mmol/L, coefficient of variation 2.1%). A Continuous Glucose Monitor Sensor (CGMS® system gold™ Medtronic, MiniMed, Northridge, CA, USA) was placed into the lateral aspect of the babies' thigh, and the data downloaded using CGMS® system solutions™ software version 3.0C. The interstitial glucose concentrations could not be viewed in real-time, ensuring clinical practice was not influenced by the results. A low interstitial glucose concentration was defined as a single data point (five minute recording) <2.6 mmol/L. Consecutive data points <2.6 mmol/L were defined as a single episode of low glucose concentration. A single blood glucose concentration <2.6 mmol/L was also defined as an episode.

A three channel cot-side aEEG monitor was used (BRMII BrainZ Instruments, Auckland, New Zealand). The screen was altered to display only scenic photos and the impedance of the EEG electrode signal. If there was a clinical requirement to view the EEG signal a password was accessed from the principal investigator to allow the raw EEG and aEEG to be displayed for 12 hours. Seven hydrogel electrodes (Hydro-spot neonatal electrodes, Physiometrix Inc., North Billerica MA, USA) were placed as soon as possible after admission; two each in the standard C3-P3 C4-P4, O1-O2 montage and one reference electrode on the back of the neck.
EEG signals were amplified 5000 times and band-pass filtered with a first-order high-pass filter with -3dB, frequency at 1 Hz and a fourth-order low-pass Butterworth filter at -3dB frequency at 50 Hz. The signal was digitised at a sampling rate of 256 Hz and the intensity spectra and derived parameters calculated from 4-second epochs of the digitised signal (Williams and Gluckman 1990). The total EEG intensity (µV2) was calculated on the intensity (power) spectrum between 2 and 20 Hz. Spectral edge frequency was defined as the frequency below which 90% of EEG power existed. Amplitude was calculated from the band-pass filtered and rectified signal with an algorithm that generates minimum, maximum and median amplitudes functionally equivalent to the Cerebral Function Monitor (Sebel, Maynard et al. 1983). Continuity measures were determined as the percentage of each minute during which the amplitude of the raw EEG (assessed at 2 second intervals) was above the determined threshold amplitude (10, 25, 50 or 100 µV). The EEG amplitude, continuity and intensity measurements were averaged and stored to disk at 1 minute intervals.

The averaged EEG signal was digitised and analysed in five minute epochs using Chart File Analyser, Beta Version 1.74.3 (Liggins Institute, University of Auckland, New Zealand). EEG data were defined as valid and included in analysis if the electrode impedance was below 10 kΩ and free from electrical or EMG artefacts. Median values of each EEG variable were recorded. Samples of raw EEG for each baby were reviewed for seizures by a specialist paediatric neurologist, also classified by inspection by the other investigators (Hellstrom-Westas, Rosen et al. 2007). The samples included any hypoglycemic episode and one hour each side of the episode.

Blood samples were taken at entry and exit to the study, and on up to two further occasions at least four hours apart when the blood glucose concentration was <2.6 mmol/L. Samples were placed on ice until centrifugation and the plasma stored at -80 C until analysis for glucose, lactate, beta-hydroxybutyrate, and glycerol using a Hitachi 902 automatic analyser (Hitachi Australia, North Ryde, NSW, Australia) and commercial reagent kits (Randox laboratories Ltd, Antrim, United Kingdom).

Data were analysed using R 2010 (R Foundation for Statistical Computing, Vienna, Austria). EEG continuity data were arcsine transformed to more closely approximate normality. EEG measures were averaged for each baby for periods of normoglycemia and hypoglycemia, and the means compared using multiple regression analysis. The final mixed model included EEG lead position (centro-parietal vs occipital) and maturity (<37 weeks vs ≥37 weeks) as fixed effects. There were also two random effects to account for the repeated measures in individual babies (baby nested within maturity) and glucose concentration.
(normoglycemia vs hypoglycemia, nested within baby within maturity). Data are presented as mean (SE) or median (range). Non-glucose cerebral fuel concentrations were compared over time using the Kruskal-Wallace test.

4.4 Results

One hundred and one babies were enrolled between December 2006 and February 2009 (Table 4-1). The first blood glucose concentration taken on admission to the NICU was <2.6 mmol/L in three-quarters of the babies (n = 75) (median 2.1 mmol/L, range 0 to 2.5 mmol/L). Ninety babies had high quality EEG data matched to glucose concentrations, providing 5517 hours of data (230 days) (median for each baby 47 h, range 1 to 156 h). However, only one quarter of the babies (n = 24) had low glucose concentrations during this period with matching EEG data. These 24 babies are the subject of this report. They had similar demographic data to those of the entire cohort (Table 4-1), and had multiple risk factors for hypoglycaemia including prematurity (17, 70%), small (6, 25%) or large for gestational age (3, 13%), and infant of diabetic mother (7, 29%). Initially 15 babies (63%) received intravenous dextrose, 7 babies (29%) were formula fed and two (8%) were breast fed, but by the end of the study 16 babies (66%) received breast milk. No baby received medication that might influence the EEG.

<table>
<thead>
<tr>
<th>Table 4-1. Demographic data for babies studied</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Number of babies</td>
</tr>
<tr>
<td>Birth weight (g)</td>
</tr>
<tr>
<td>Gestation (wk)</td>
</tr>
<tr>
<td>Age when recording began (h)</td>
</tr>
<tr>
<td>Duration of interstitial glucose monitoring (h)</td>
</tr>
<tr>
<td>Duration of EEG monitoring (h)</td>
</tr>
<tr>
<td>Duration of matched EEG and interstitial glucose monitoring</td>
</tr>
<tr>
<td>Risk factors for hypoglycaemia*</td>
</tr>
<tr>
<td>Prematurity (32–37 wk)</td>
</tr>
<tr>
<td>Infant of a diabetic mother</td>
</tr>
<tr>
<td>Small for gestational age</td>
</tr>
<tr>
<td>Large for gestational age</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

Values are median (range) or number (%). * Many babies had more than one risk factor.
In the 24 babies there were 15,404 interstitial glucose recordings, of which 844 (5%) were <2.6 mmol/L (median 2.3 mmol/L, range 1.4 to 2.5 mmol/L), and 77 (0.5%) were <2.0 mmol/L (median 1.7 mmol/L, range 1.4 to 2.0 mmol/L). There were 103 episodes of low glucose concentrations, with individual babies experiencing 1 to 23 episodes, with a median duration of 20 minutes (range 5 to 475 min) (Figure 4–1). Only 12 episodes (10%) were detected using intermittent blood glucose measurements. Fifteen babies had repeated episodes of low glucose (range 2 to 23 episodes) and only 3 of these had low glucose concentrations detected by intermittent blood glucose measurement.

Figure 4-1. The severity, duration and frequency of low glucose concentrations

There were 490 blood glucose concentrations measured, of which 44 (9%) were <2.6 mmol/L (median 2.2 mmol/L, range 1.0 to 2.5 mmol/L) and 9 (2%) were ≤2.0 mmol/L (median 1.9 mmol/L, range 1.0 to 2.0 mmol/L). The median number of blood glucose measurements in each baby was 19 (range 3 to 45).

There was a total of 1213 hours of recorded EEG corresponding to simultaneous interstitial glucose measurements. Of these, 104 hours corresponded to interstitial glucose concentrations <2.6 mmol/L, and six hours to glucose concentrations ≤2.0 mmol/L.
Spectral edge frequency decreased with advancing gestation ($p < 0.01$), and continuity was lower in the occipital than parietal EEG ($p < 0.01$) (Table 4-2). Taking these into account, there were no differences in EEG amplitude, continuity or spectral edge frequency between periods of low and normal interstitial glucose concentrations. There were also no differences in EEG parameters between 20 minute periods of low glucose concentration and adjacent 20 minutes of normoglycemia from the same baby. Similarly, there were no observable differences in any aEEG parameters during episodes of normoglycemia or hypoglycemia on visual inspection of the traces (Figure 4–2).

**Table 4-2.** Comparison of electroencephalography variables according to gestational age, electroencephalography montage position, and blood glucose concentrations

<table>
<thead>
<tr>
<th></th>
<th>aEEG</th>
<th>Intensity</th>
<th>Spectral Edge</th>
<th>Continuity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Min mV</td>
<td>Max mV</td>
<td>mV$^2$</td>
</tr>
<tr>
<td><strong>Maturity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37 weeks</td>
<td>17</td>
<td>5.58 (0.27)</td>
<td>15.02 (0.74)</td>
<td>20.76 (2.03)</td>
</tr>
<tr>
<td>≥37 weeks</td>
<td>7</td>
<td>6.76 (0.44)</td>
<td>14.11 (0.77)</td>
<td>24.51 (3.33)</td>
</tr>
<tr>
<td><strong>EEG montage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td>24</td>
<td>6.12 (0.28)</td>
<td>15.10 (0.62)</td>
<td>22.15 (2.02)</td>
</tr>
<tr>
<td>Occipital</td>
<td>20</td>
<td>5.35 (0.29)</td>
<td>13.77 (0.88)</td>
<td>19.59 (2.28)</td>
</tr>
<tr>
<td><strong>Blood glucose concentration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.6 mM</td>
<td>24</td>
<td>6.14 (0.37)</td>
<td>15.06 (0.73)</td>
<td>24.36 (3.00)</td>
</tr>
<tr>
<td>≥2.6 mM</td>
<td>24</td>
<td>5.92 (0.25)</td>
<td>14.76 (0.57)</td>
<td>21.86 (1.74)</td>
</tr>
</tbody>
</table>

*p < 0.01.*

Values are means (SE) n = 24 babies.
Some babies were pale, jittery and clammy during the study but none showed these signs during episodes of low glucose concentrations. On retrospective review of the raw EEG one baby (male, 34 weeks gestation, 1944 g) had 33 asymptomatic electrographic seizures each lasting 15 to 240 seconds over a 30 hour period. This baby had 23 episodes of low interstitial glucose concentrations (total duration 20.4 h) of which 11 episodes (11.9 h) occurred before the first seizure at 63 hours after birth. The lowest interstitial glucose concentration was 2.3 mmol/L and lowest blood glucose was 2.2 mmol/L. Only four of the 33 seizures occurred when the interstitial glucose concentration was <2.6 mmol/L, of which three were isolated to the occipital electrodes and the fourth was on the right side. In total there were eight occipital seizures during a 19 hour period when the glucose concentrations were low (range 2.5 to 4.0 mmol/L). None of the subsequent seizures were occipital.
One baby (male, 40 weeks, 4430 g) had a symptomatic seizure attributed to hypoglycemia before study entry 36 hours after birth (blood glucose 0.8 mmol/L). He suffered repeated episodes of hypoglycemia during the next 24 hours despite treatment, but there were no associated changes on the EEG.

The plasma concentrations of lactate, beta-hydroxybutyrate and glycerol were low in all samples. Plasma lactate concentrations decreased and beta-hydroxybutyrate concentrations increased over the study period, but there were no changes during hypoglycemia (Table 4-3).

**Table 4-3.** Plasma concentrations of non-glucose cerebral fuels at study entry and exit and during clinically detected hypoglycemia (mM)

<table>
<thead>
<tr>
<th></th>
<th>Study entry</th>
<th>During hypoglycemia</th>
<th>Study exit</th>
<th>p value change over time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of baby (h)</strong></td>
<td>24 (1–55)</td>
<td>12 37 (5–76)</td>
<td>23 96 (16–196)</td>
<td>0.004</td>
</tr>
<tr>
<td>Lactate</td>
<td>24 2.8 (1.2–11.1)</td>
<td>12 2.9 (0.9–7.7)</td>
<td>23 1.9 (1.2–3.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Beta-hydroxybutyrate</td>
<td>14 0.02 (0.01–0.28)</td>
<td>6 0.15 (0.03–0.50)</td>
<td>10 0.11 (0.03–0.29)</td>
<td>0.66</td>
</tr>
<tr>
<td>Glycerol</td>
<td>24 0.11 (0.01–0.53)</td>
<td>10 0.14 (0.06–0.31)</td>
<td>23 0.12 (0.05–0.24)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

*Numbers are median (range).*

4.5 Discussion

Our data show that there were no characteristic changes detected by cot-side aEEG related to neonatal hypoglycemia. Furthermore, concentrations of alternative cerebral fuels were low in this group of babies at risk, and are unlikely to provide substantial neurological protection during hypoglycemia.

Deterioration in cerebral metabolism or perfusion can be reflected in the aEEG signal as changes in both amplitude and continuity, whereas a more gradual deterioration is shown in the frequency of the EEG signal (Auer, Olsson et al. 1984). The cot-side EEG monitor has been found to be useful for neurological assessment in other neonatal conditions (K, Ley et al. 2001; Spitzmiller, Phillips et al. 2007), but we were unable to identify changes related to hypoglycaemia. There are a number of possible reasons for this. Firstly, the amount of available data may have limited our power to detect subtle EEG changes. Whilst 45 babies had blood glucose concentrations < 2.0 mmol/L when admitted to the NICU, treatment was commenced immediately. The continuous glucose monitor takes one hour to initialise and the aEEG takes at least 15 minutes to commence using gel electrodes. This meant that were we unable to capture data during the early period of hypoglycemia. Any later clinically recognised episode of hypoglycaemia was also treated promptly, thus limiting data collection during recognised hypoglycemia.
In addition, despite over 200 days of matched EEG and interstitial glucose data, we recorded only 103 hours of hypoglycemia with high quality EEG. A key reason was the prolonged use of the hydrogel electrodes, which required meticulous attention to maintain electrical impedance <10 kΩ per pair. The combination of prompt treatment of hypoglycemia, the length of time taken to initiate monitoring, and the intermittent technical difficulties limited the duration of recorded matched low glucose and aEEG data.

Secondly, the EEG signal is reflective of the voltage, which decreases with the square of the distance that is travelled. Both animal (Auer and Siesjo 1993) and human studies (Hawdon, Weddell et al. 1993) have identified deep structures including the striatum, cingular cortex, dentate gyrus, hippocampus, and caudate nucleus as being sensitive to hypoglycemic damage. Any changes in voltage in these deep structures may not be detected by the skull electrodes of the cot-side EEG monitor. Furthermore the aEEG is a filtered and compressed signal, resulting in loss of detail. The aEEG cannot detect the lower delta or theta frequencies which have been shown to increase during insulin-induced hypoglycemia in both diabetics and non-diabetics (Tallroth, Lindgren et al. 1990).

We added an occipital channel to the standard cot-side aEEG because the occipital regions of the brain may be more sensitive to hypoglycemic damage (Alkalay, Flores-Sarnat et al. 2005). Interestingly, the baby who had asymptomatic seizures experienced eight occipital seizures confined to a 19 hour period which included 7.8 hours of low interstitial glucose concentrations. It is tempting to speculate that for this baby, repeated or prolonged hypoglycemia specifically may have affected occipital cortical function.

We are not aware of any previous reports of prolonged cot-side aEEG monitoring in babies without neurological compromise, and our data demonstrate two aEEG findings unrelated to glucose concentration. Firstly, spectral edge frequency decreased with advancing gestation, in contrast to previous reports of increased spectral edge frequency with advancing gestation (Bell, McClure et al. 1991; Bell, McClure et al. 1991). In our cohort the gestation range was 31 to 40 weeks and the babies were monitored continuously up to seven days, whereas the earlier studies included babies as immature as 26 weeks and monitored only on day three. Secondly, we found that continuity is lower in the occipital than parietal region. This may relate to the regional maturation of the newborn brain, since continuity increases with advancing gestational age (West, Harding et al. 2006) and may predict neurodevelopmental outcome in extremely preterm infants (Bowen, Paradisis et al. 2010).

A novel aspect of this study is the simultaneous measurement of glucose concentrations, alternative cerebral fuels and neurological integrity using accurate and minimally invasive
monitoring devices. Importantly, continuous interstitial glucose monitoring allows measurement of the duration and frequency of episodes of low glucose concentrations, and has been shown to be well tolerated, safe and reliable in newborn babies (Platas, Lluch et al. 2009; Harris, Weston et al. 2010). However, our data show a large number of episodes of low glucose concentration, most of which were not detected using intermittent blood glucose measurement (Harris, Weston et al. 2010). Further, none of the babies in our study demonstrated any signs attributed to hypoglycemia, despite prolonged and repeated episodes of low glucose concentrations and low circulating concentrations of non-glucose cerebral fuels. Our data provide further confirmation that neonatal hypoglycemia cannot be detected clinically without invasive screening.

Non-glucose cerebral fuels may provide neuroprotection to the newborn brain during episodes of hypoglycemia. Lactate is taken up during hypoglycemia in fetal (Turbow, Curran-Everett et al. 1995) and newborn (Hellman, Vannucci et al. 1982) brains of several species, and preserves cerebral function during induced hypoglycemia in adults (Maran, Cranston et al. 1994; King, Parkin et al. 1998). Cerebral uptake is directly related to plasma lactate concentrations (Hellman, Vannucci et al. 1982; Turbow, Curran-Everett et al. 1995). Similarly, both animal (Spitzer and Weng 1972) and human (Bougneres, Lemmel et al. 1986) studies have shown that the fetal and neonatal brain is able to metabolize ketones, and there is a relationship between the cerebral ketone uptake and plasma concentrations (Persson, Settergren et al. 1972). This is also true for glycerol (Sloviter, Shimkin et al. 1966). However, our data show that plasma concentrations of lactate, ketones and glycerol were low in the first few days after birth, perhaps because all babies were known to be at risk and were receiving regular carbohydrate. Nevertheless, alternative cerebral fuels are unlikely to provide substantial neuroprotection during hypoglycemia in these at-risk babies.

We conclude that cot-side aEEG is not clinically useful in the management of mild neonatal hypoglycemia.

4.6 Acknowledgments

We wish to acknowledge the significant contribution of the babies and families who took part. Research nurses Cathy McBride, Paula Middlemiss and Suzanne Butler assisted with recruitment and managed the study in the absence of the primary author.
4.7 References


Chapter 5: Continuous glucose monitoring in newborn babies at risk of neonatal hypoglycemia

Published


Supported by the Auckland Medical Research Foundation, the Waikato Medical Research Foundation, and the Rebecca Roberts Scholarship.

The authors declare no conflicts of interest.
5.1 Abstract

Objective: To determine the usefulness of continuous glucose monitoring in babies at risk of neonatal hypoglycemia.

Study design: Babies ≥32 weeks old who were at risk of hypoglycemia and admitted to newborn intensive care received routine treatment, including intermittent blood glucose measurement using the glucose oxidase method, and blinded continuous interstitial glucose monitoring.

Results: Continuous glucose monitoring was well tolerated in 102 infants. There was good agreement between blood and interstitial glucose concentrations (mean difference, 0.0 mmol/L; 95% CI, -1.1–1.1). Low glucose concentrations (<2.6 mmol/L) were detected in 32 babies (32%) with blood sampling and in 45 babies (44%) with continuous monitoring. There were 265 episodes of low interstitial glucose concentrations, 215 (81%) of which were not detected with blood glucose measurement. One hundred seven episodes in 34 babies lasted >30 minutes, 78 (73%) of which were not detected with blood glucose measurement.

Conclusion: Continuous interstitial glucose monitoring detects many more episodes of low glucose concentrations than blood glucose measurement. The physiological significance of these previously undetected episodes is unknown (J Pediatrics 2010; 157:198-202).

5.2 Background

Neonatal hypoglycemia was first identified as a common condition causing brain damage and death in 1937 (Hartmann and Jaudon 1937). Now more than 70 years later, there is a paucity of data underpinning clinical practice, and the best way to diagnose and treat neonatal hypoglycemia remains unclear.

Blood glucose concentrations fluctuate after birth as the baby adapts to extra-uterine life (Srinivasan, Pildes et al. 1986) and are normally measured intermittently. This means that episodes of hypoglycemia may go undetected, and their duration and severity cannot be assessed. Conversely, if blood glucose concentration is measured when the baby is only transiently hypoglycemic, the baby may be exposed to unnecessary treatment. Although serum glucose measurement is considered the gold standard approach, this is impractical in newborn babies. Therefore, whole blood glucose concentrations are generally measured on samples obtained with capillary heel prick lancing. However, there are a number of factors that interfere with the accuracy of these measurements,(Cornblath, Schwartz et al.
1990; Deshpande and Ward-Platt 2005) heel prick sampling causes pain, and frequently repeated sampling is required (Barker and Rutter 1995).

Continuous interstitial glucose monitoring was initially developed for the management of diabetes mellitus, for which it is safe and reliable, leading to improved metabolic control (De Block, Vertommen et al. 2008). Continuous glucose monitoring also is safe and reliable in extremely low birth weight babies (Beardsall, Ogilvy-Stuart et al. 2005; Beardsall, Ogilvy-Stuart et al. 2007; Platas, Lluch et al. 2009). However, this method of glucose monitoring has not been investigated in larger babies identified as being at risk of neonatal hypoglycemia soon after birth.

There are potential advantages of real-time continuous glucose monitoring, including detecting undiagnosed episodes of hypoglycemia, providing information about the duration and severity of these episodes, allowing evaluation of the baby's response to treatment, and reducing the pain and disturbance of repeated blood sampling. Therefore, we sought to determine the usefulness and reliability of continuous interstitial glucose monitoring in babies admitted to the newborn intensive care unit and identified as being at risk of neonatal hypoglycemia.

5.3 Methods

We studied babies born at ≥32 weeks gestation who were at risk of hypoglycemia and admitted to the Waikato Hospital newborn intensive care unit. Babies remained in the study until they were no longer at risk of hypoglycemia or for 7 days, whichever came first. Babies were excluded from the study when there was a serious congenital abnormality or a skin condition that meant the continuous glucose monitor could not be attached. Whenever possible, consent was sought before birth from pregnant women identified as potentially having a baby at risk because the mother had diabetes mellitus or there was documented concern about either poor or excessive fetal growth or threatened preterm labor. When informed consent was not sought before the birth, the study was discussed with the parents, and informed consent was sought soon after admission to the newborn intensive care unit. The study was approved by the Northern Y Regional Ethics Committee.

All babies were treated according to the clinical guidelines of the newborn intensive care unit. Fluids were provided at 60, 90, 120, and 150 mL/kg on days 1, 2, 3, and 4, respectively. Early oral feeds were commenced with breast milk as soon as it was available. Infant formula was given with parental permission until adequate breast milk was available. When the baby was unable to tolerate feeds, intravenous 10% dextrose was given and gradually reduced as oral feeds were tolerated.
Hypoglycemia was defined as a blood glucose concentration <2.6 mmol/L. Initial treatment for a well baby with hypoglycemia was 40% dextrose gel (200 mg/kg) massaged into the buccal membranes and milk at 7.5 mL/kg (90 mL/kg/day) given two hourly. If the hypoglycemia did not resolve, the dextrose gel was repeated once. Additional measures could include continuous milk and adding Polycose (4 g/100 mL) to the feed.

In an unwell baby or a baby not responding to these measures, intravenous 10% dextrose (2 mL/kg) was given over 10 minutes, followed by intravenous dextrose at 60 or 90 mL/kg/day (4-6 mg/kg/min). If the intravenous dextrose rate increased to >9 mg/kg/min, additional investigations were initiated.

Blood glucose concentration was measured with heel-prick sampling at 1 hour of age, then before feeds 2 to 4 hourly for 12 hours. In babies receiving intravenous dextrose, blood glucose concentrations were measured every 4 hours for 12 hours and then less frequently as clinically indicated. In babies receiving treatment for hypoglycemia, blood glucose concentrations were measured again 30 minutes after treatment.

All blood glucose concentrations were measured with a blood gas analyzer (Radiometer, ABL800Flex, Copenhagen, Denmark) by using the glucose oxidase method (reading range, 0.0-60 mmol/L; coefficient of variation, 2.1%).

We used the Continuous Glucose Monitor Sensor (CGMS system gold, Medtronic, MiniMed, Northridge, California). The CGMS is made up of a platinum glucose-oxidase coated sensor, a cable and a monitor that is a similar size to a pager. We placed the sensor into the lateral aspect of the baby’s thigh with a trigger loaded insertion device and secured it with a clear adhesive dressing. The interstitial glucose concentration is converted into an electrical signal that is stored every 10 seconds. The monitor then averages the signal every 5 minutes, providing 288 interstitial glucose concentration data points per day.

The interstitial glucose concentrations could not be viewed in real-time, ensuring that clinical practice was not influenced by the results. Nursing staff were asked to enter all blood glucose concentrations, feeds and medications for the management of hypoglycemia into the continuous glucose monitor. All blood glucose concentrations entered by the nursing staff were checked for accuracy against the clinical records. Data were downloaded with CGMS system solutions software version 3.0C, and a calibration algorithm supplied by the manufacturer was applied to values <2.2 mmol/L. A low interstitial glucose concentration was defined as a single data point (5-minute recording) <2.6 mmol/L. Consecutive data points <2.6 mmol/L were defined as a single episode of low glucose
concentration. A single blood glucose concentration <2.6 mmol/L was also defined as an episode.

Data were analyzed with JMP software version 7.0 (SAS Institute, Cary, North Carolina) and are presented as means (95% CI) or medians (range).

5.4 Results

There were 102 babies enrolled in the study between December 2006 and February 2009 (Table 5-1). One term baby had a seizure that was attributed to hypoglycemia before enrolling in the study. No other baby had any clinical signs that were attributed to neonatal hypoglycemia. Several babies were reported to be jittery, but none were hypoglycemic at these times.

Table 5-1. Demographic data for babies studied

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>2327 (1032–4960)</td>
</tr>
<tr>
<td>Gestation (wk)</td>
<td>35 (31–42)</td>
</tr>
<tr>
<td>Age at entry to the study (h)</td>
<td>4.8 (1–695)</td>
</tr>
<tr>
<td>Time in study (h)</td>
<td>80 (7–171)</td>
</tr>
<tr>
<td>Male</td>
<td>51 (50)</td>
</tr>
</tbody>
</table>

Risk factors for hypoglycaemia

- Prematurity: 66 (65)
- Infant of a diabetic mother: 31 (30)
- Small for gestational age: 27 (26)
- Large for gestational age: 18 (18)
- Other: 7 (7)

Glucose measurements

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial glucose concentration (mmol/L) n = 97119</td>
<td>4.2 (1.2–13.4)</td>
</tr>
<tr>
<td>Interstitial glucose concentration &lt;2.6 mmol/L</td>
<td>2337 (3)</td>
</tr>
<tr>
<td>Interstitial glucose concentration &gt;8.0 mmol/L</td>
<td>1713 (2)</td>
</tr>
<tr>
<td>Blood glucose concentration (mmol/L) n = 1750</td>
<td>4.1 (1.0–11.5)</td>
</tr>
<tr>
<td>Blood glucose concentration &lt;2.6mmol/L</td>
<td>98 (6)</td>
</tr>
<tr>
<td>Blood glucose concentration &gt;8 mmol/L</td>
<td>31 (2)</td>
</tr>
</tbody>
</table>

Values are median (range) or number (%).

The continuous glucose sensor was well tolerated for as long as 7 days. There were no infections, redness, or edema at the insertion sites. Some, but not all babies appeared to experience brief pain when the glucose sensor was inserted, but not subsequently. Parents also tolerated the continuous glucose monitor well. One family withdrew from the study at 12 hours. Nursing staff found the continuous glucose monitor easy to use.

There was generally good agreement between the interstitial and blood glucose concentrations in individual babies (Figure 5–1).
Figure 5-1. Example from 1 baby showing blood (filled circles) and interstitial (continuous line) glucose concentrations and treatment. Baby was 36 weeks gestation, with a birth weight of 2390 g. There are 9 episodes of low blood glucose concentration and 31 episodes of low interstitial glucose concentrations lasting between 5 and 140 minutes (total time, 19 hours). Only 7 (22%) of these episodes were detected with intermittent glucose measurements.

A Bland-Altman plot of 1750 paired blood and interstitial glucose concentrations also showed good agreement, with a mean difference of 0.03 mmol/L (95% CI, -1.02 to 1.08 mmol/L; Figure 5–2). This agreement was similar even at low glucose concentrations (mean difference for 186 pairs, <3.0 mmol/L -0.18mmol/L; 95% CI,-1.25 to 0.85 mmol/L; Figure 5–2, B), and was maintained for the 7 day monitoring period (mean difference at 7 days, -0.03 mmol/L; 95% CI -0.03 mmol/L; 95% CI -0.97 to 0.85 mmol/L; Figure 5–3). However, the scatter of data was greatest on the first day and particularly in the first 2 hours of monitoring (mean difference, -0.4 mmol/L; 95% CI, -2.0 to 1.2 mmol/L; Figure 5–3).
Figure 5-2. Bland-Altman plot of the relationship between A, blood and interstitial glucose concentrations overall and B, at glucose concentrations <3.0mmol/L.
Figure 5-3. Differences between blood and interstitial glucose concentrations A, on the first day of monitoring and B, over 7 days of monitoring. Data are means and 95% CIs. Figures in brackets show the number of pairs of measurements in each period.

Glucose concentrations <2.6 mmol/L were detected in 45 babies (44%) with continuous interstitial glucose monitoring and in 32 babies (33%) with intermittent blood glucose measurement. The incidence of low glucose concentrations was similar in babies with different risk factors (data not shown).

There were 265 episodes of low interstitial glucose concentrations lasting between 5 and 475 minutes. One hundred seven episodes (40%) lasted >30 minutes (Figure 5–4).
Thirty-five babies (34%) experienced at least one episode lasting >30 minutes, and 21 babies (21%) had repeated episodes lasting >30 minutes. One-third of the babies who were monitored for >24 hours continued to have episodes of low interstitial glucose concentrations despite receiving intravenous dextrose, oral feeds, or both (Table 5-2). One-third of the babies who were receiving full oral feeds also continued to have episodes of low interstitial glucose concentrations, with one-third of these episodes lasting >30 minutes.

**Table 5-2. Low blood glucose concentrations**

<table>
<thead>
<tr>
<th></th>
<th>Blood glucose &lt;2.6 mmol/L</th>
<th>Interstitial glucose &lt;2.6 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Babies</td>
<td>Episodes</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n = 102)</td>
<td>32 (32)</td>
<td>98</td>
</tr>
<tr>
<td>Episodes &gt;30 minutes</td>
<td>34 (33)</td>
<td>107</td>
</tr>
<tr>
<td><strong>After 24 hours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n = 88)</td>
<td>16 (18)</td>
<td>37</td>
</tr>
<tr>
<td>Episodes &gt;30 minutes</td>
<td>20 (23)</td>
<td>61</td>
</tr>
<tr>
<td><strong>On full feeds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n = 87)</td>
<td>16 (18)</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>9 (10)</td>
<td>64 (37)</td>
</tr>
</tbody>
</table>

*Values are numbers (percent)*

Overall, only 50 of the episodes of low interstitial glucose concentrations (19%) were detected with intermittent blood glucose measurements and in only 4 of the 21 babies with
repeated episodes were the episodes detected with intermittent blood glucose measurement.

5.5 Discussion

We determined the usefulness and reliability of continuous interstitial glucose monitoring in babies who were identified as being at risk of neonatal hypoglycemia and admitted to the newborn intensive care unit. Continuous glucose monitoring in this group of babies appears to be safe, well tolerated and easy to use. There is good agreement between continuous interstitial and intermittent blood glucose measurements in 7 days of monitoring. Continuous glucose monitoring detects many more episodes of low glucose concentration than intermittent blood glucose measurement, even in babies being monitored and treated in an intensive care unit.

Like most point-of-care glucose analyzers, continuous interstitial glucose monitoring was developed for use at high glucose concentrations, and most monitors are not able to be calibrated with blood glucose concentrations <2.2 mmol/L. However, earlier studies in sheep and adult humans have suggested that the monitors are accurate at low glucose concentrations (Conrad, Mastrototaro et al. 2004; Harris, Battin et al. 2009). Our data show that the close agreement between blood and interstitial glucose concentrations also applies in newborn babies, and persists for at least 7 days of monitoring with a single sensor, potentially reducing the distress associated with repeated blood sampling or sensor replacement. We report closer agreement between blood and interstitial glucose concentrations than earlier studies in low birthweight babies (Beardsall, Ogilvy-Stuart et al. 2005; Platas, Lluch et al. 2009). This may be in part because ours is the first report in which all blood samples were analysed with the reliable glucose oxidase method rather than less reliable point-of-care methods.

Although there was good agreement between interstitial and blood glucose measurements, there was much greater variability in the measurements in the first 2 hours of monitoring, with some babies showing discrepancies between blood and interstitial glucose concentrations in the first 2 hours and other babies not. Blood glucose concentrations can change rapidly in the first few hours after birth,(Srinivasan, Pildes et al. 1986) and interstitial glucose concentrations can “lag” behind blood glucose concentrations by as long as 20 minutes because of delays in diffusion of glucose from blood into the interstitial space (Caplin, Leary et al. 2003; Reach and Choleau 2008). The interstitial glucose sensor takes a long as 2 hours to stabilize after insertion. Each of these may contribute to the greater variability that we observed during this period.
Episodes of low glucose concentrations were common in the babies that we studied and continued for the 7 days of the study, including in babies who were tolerating full feeds and who normally would not be considered to require intermittent blood glucose measurement. Approximately half the babies had low interstitial glucose concentrations, and one-third of the babies had recurrent episodes; 80% of the episodes of low interstitial glucose concentration were undetected with intermittent glucose measurements. Our findings are consistent with earlier reports of a much higher incidence of low glucose concentrations than was appreciated before the introduction of continuous glucose monitoring in patients with diabetes mellitus (De Block, Vertommen et al. 2008). The NIRTURE study also reported a higher incidence of low glucose concentrations than expected in extremely low birth weight babies (Beardsall, Vanhaesebrouck et al. 2008). Our data suggest that undetected low glucose concentrations are also occurring in the much more common population of babies >32 weeks gestation, despite their being recognized as at risk of hypoglycemia and being monitored and treated in newborn intensive care.

One advantage of continuous glucose monitoring is the ability to measure the duration, severity and frequency of low glucose concentrations in an individual baby. Animal studies investigating the relationship between duration and severity of low glucose concentrations and neurological outcome have been conflicting (Vannucci, Nardis et al. 1980; Vannucci, Nardis et al. 1981; Schrier, Wilhelm et al. 1990; Harris, Battin et al. 2009). In babies, the severity of low glucose concentrations was linked to acute deterioration in the sensory evoked potentials (Koh, Aynsley-Green et al. 1988). Repeated episodes of low glucose concentrations over a number of days were also associated with an increased risk of poor neurological outcome, blindness and epilepsy (Lucas, Morley et al. 1988; Duvanel, Fawer et al. 1999; Tam, Widjaja et al. 2008). Our data demonstrate repeated episodes of low glucose concentrations, both within a single day and over a number of days, in 21% of the babies that we studied.

However, the physiological importance of these previously undetected episodes of low glucose concentrations is unclear. The severity or duration of hypoglycemia required to cause neuronal injury in any given baby is not known, and there is a risk that when continuous interstitial glucose monitoring is quickly adopted into clinical practice it may result in increased treatment for low glucose concentrations, without necessarily changing outcomes. Further research is required into the relationship between the previously undetected episodes of low glucose concentrations and neurological outcome, both in babies at risk of neonatal hypoglycemia and in healthy babies.
5.6 References


Chapter 6: A survey of the management of neonatal hypoglycaemia within the Australian and New Zealand Neonatal Network

Published


Key words: feeding methods; infant, newborn; infant, preterm; infant of diabetic mother; treatment.

What is already known on this topic?

Neonatal hypoglycaemia can cause both brain damage and death. A blood glucose level of <2.6 mmol/L has been suggested as a clinical threshold at which treatment should be provided.

What this study adds

Despite a consensus that neonatal hypoglycaemia was defined as a blood glucose level <2.6 mmol/L, neonatologists frequently reported not treating a baby with a blood glucose level of 2.0 mmol/L. Neonatologists remain uncertain about the relevance of symptoms and the best treatment for babies with hypoglycaemia.

Funding: This work was funded in part by the Auckland Medical Research Foundation, the Waikato Medical Research Foundation, the Maurice and Phyllis Paykel Trust and the Rebecca Roberts Scholarship.

The authors declare no conflicts of interest.
6.1 Abstract

Background: Neonatal hypoglycaemia is a common problem linked to both brain damage and death. There is controversy regarding both the definition of and best treatment for neonatal hypoglycaemia.

Aim: To determine current management of neonatal hypoglycaemia within the Australian and New Zealand Neonatal Network (ANZNN).

Methods: Four questionnaires were sent to the Director of each of the 45 nurseries within the ANZNN. The Director was asked to complete one questionnaire and give the remaining three to other doctors involved with the management of babies with hypoglycaemia in the nursery.

Results: One hundred and eighty surveys were sent and 127 were returned (71%), including at least one from each nursery. Almost all respondents (120, 94%) reported using a protocol to treat hypoglycaemia. Only 2 (2%) reported screening all babies for neonatal hypoglycaemia, with the remainder screening babies at risk. Only 67, (53%) reported that blood glucose levels were tested on an analyser generally considered to be reliable at low levels. Most respondents (99, 78%) reported the clinical threshold for treatment was <2.6 mmol/L. However, when provided with clinical scenarios, respondents reported a variety of interventions, including no treatment.

Conclusion: Doctors within the ANZNN are consistent about definition and screening for neonatal hypoglycaemia. However, frequently, the diagnosis is made using unreliable analysers. There is also wide variation in treatment, suggesting a lack of reliable evidence on which to base practice.

6.2 Background

Neonatal hypoglycaemia is a common problem that has been linked to both brain damage and death (Hartmann and Jaudon 1937; Cornblath, Odell et al. 1959). Magnetic resonance imaging has shown evidence of brain injury following neonatal hypoglycaemia (Filan, Inder et al. 2005; Burns, Rutherford et al. 2008). However, there is a paucity of evidence to inform clinical practice, leading to controversy not only about the definition, but also about the best treatment. Operational guidelines have been developed to guide clinical practice (Cornblath, Hawdon et al. 2000). Treatment is recommended at a blood glucose level of <2.6 mmol/L in babies at risk of delayed metabolic adaption or babies showing abnormal clinical signs. More recently, a blood glucose level of >3.5 mmol/L has been recommended for babies with hyperinsulinism (Hussain, Blankenstein et al. 2007).
However, once neonatal hypoglycaemia has been diagnosed; there is very little evidence to guide treatment choices.

There have been three surveys of the management of neonatal hypoglycaemia published from Australia and the United Kingdom (Koh, Eyre et al. 1988; Bonacruz, Arnold et al. 1996; Koh and Vong 1996). All reported wide variation in the definition of neonatal hypoglycaemia both within and between nurseries, suggesting uncertainty about management.

One survey published in 1996 showed that 90% of Australian Level III nurseries were using unreliable cot-side analysers for the diagnosis of neonatal hypoglycaemia. The authors recommended that all level III nurseries use reliable methods for the measurement of blood glucose levels (Bonacruz, Arnold et al. 1996).

Koh and Vong found significant changes in paediatricians’ reported practice between 1988 and 1996 (Koh and Vong 1996). They reported an increase in the median blood glucose level used to define neonatal hypoglycaemia, attributed to an increased awareness of the risks associated with hypoglycaemia (Koh, Eyre et al. 1988; Lucas, Morley et al. 1988; Cornblath, Schwartz et al. 1990; Aynsley-Green 1991; Cornblath, Hawdon et al. 2000). However, there was uncertainty about the relevance of symptoms.

It has been 12 years since the most recent published survey of the management of neonatal hypoglycaemia. We aimed to determine the current practice for the management of neonatal hypoglycaemia within the Australian and New Zealand Neonatal Network (ANZNN), and to identify areas of practice that remain uncertain.

6.3 Method

Four questionnaires were sent to the director of each nursery within the ANZNN. The director was asked to complete one questionnaire and give the remaining three to other doctors involved in the clinical management of babies with neonatal hypoglycaemia. The director was asked to collect all questionnaires and return them, along with any nursery protocols related to neonatal hypoglycaemia.

The questionnaire included 23 questions related to the use of protocols, screening, and diagnosis, and treatment of hypoglycaemia (6.8 Appendix). There were also five clinical scenarios, and respondents were asked to indicate their preferred first treatment choice. Four described asymptomatic hypoglycaemic babies, while the last described a hypoglycaemic baby with hypoxic ischaemic encephalopathy, fluid restriction, and seizures.
Ethical approval was not sought for the survey. The levels of the Neonatal Units were identified but respondents were not identified. Data were analysed using JMP ® 7.0 2007 (SAS Institute Inc, Cary, NC, USA). Proportions were compared using chi-square test.

6.4 Results

6.4.1 Response rate

One hundred and eighty surveys were sent and 127 were returned (71%). Completed surveys were received from at least one respondent in each of the 45 nurseries who contribute to the ANZNN network, and from all four respondents in 19 of the 45 nurseries (42%). Three surveys had one question unanswered; the remainder were complete.

There were 85 responses (67%) from doctors practising in the 29 Level III nurseries; 64 from Australian nurseries and the remaining 21 from New Zealand nurseries. There were 42 responses (33%) from doctors practising in the 16 Level II nurseries.

6.4.2 Protocols

Forty-four of the 45 nurseries (97%) were reported to have a protocol for the management of neonatal hypoglycaemia, and almost all respondents (120 of 127, 94%) reported using the protocols. Both respondents from one Level III nursery reported no protocol for the management of hypoglycaemia, and five respondents reported having no protocol when others from the same nursery reported using a protocol.

6.4.3 Screening

There was widespread agreement as to which babies were at risk and were, therefore, screened for neonatal hypoglycaemia (Table 6-1). Only two of 127 (2%) respondents reported screening all babies. Eight respondents (6%) reported that screening was dependent on the staff at the time of admission.

Table 6-1. Reported screening for neonatal hypoglycaemia

<table>
<thead>
<tr>
<th>Presentation of baby in hospital</th>
<th>Screened</th>
<th>Not screened</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;37 weeks gestation</td>
<td>106 (83)</td>
<td>20 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Infants of diabetics</td>
<td>125 (98)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Growth restricted babies</td>
<td>122 (96)</td>
<td>4 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>119 (94)</td>
<td>7 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Not feeding well</td>
<td>102 (80)</td>
<td>24 (18)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>105 (83)</td>
<td>21 (16)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unwell for any reason</td>
<td>124 (98)</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>All babies</td>
<td>2 (2)</td>
<td>124 (98)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Values are number (%) of responses. Total responses = 127 from 45 nurseries.
6.4.4 Diagnosis

Almost all respondents (126 of 127, 99%) reported that blood glucose levels were measured by heel prick sampling and that analysis was performed within the nursery (124 of 127, 97%). However, only half (67 of 127, 53%) reported that blood glucose levels were measured using a reliable analyser (i.e. one using the glucose oxidase method). These 67 respondents were from 29 of 45 nurseries (63%). The majority of these were Level III nurseries (27 of 29 (93%)); only two of the 16 (7%) Level II nurseries were reported to be using reliable analysers for the diagnosis of hypoglycaemia. A variety of less reliable analysers were used, of which HemoCue was the most common (Table 6-2).

Table 6-2. Analysers reported to be used for the diagnosis of neonatal hypoglycaemia

<table>
<thead>
<tr>
<th>Analyser</th>
<th>Level III</th>
<th>Level II</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood gas analyser</td>
<td>62 (53)</td>
<td>5 (12)</td>
<td>67 (42)</td>
</tr>
<tr>
<td>Advantage</td>
<td>18 (16)</td>
<td>7 (16)</td>
<td>25 (16)</td>
</tr>
<tr>
<td>HemoCue</td>
<td>4 (3)</td>
<td>14 (33)</td>
<td>18 (11)</td>
</tr>
<tr>
<td>Dextrostix</td>
<td>12 (10)</td>
<td>1 (2)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Super Glucocard II</td>
<td>5 (4)</td>
<td>8 (19)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Precision G</td>
<td>5 (4)</td>
<td>3 (7)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Other analyser</td>
<td>4 (3)</td>
<td>1 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Unsure</td>
<td>6 (5)</td>
<td>4 (9)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Totals</td>
<td>116 (100)</td>
<td>43 (100)</td>
<td>159 (100)</td>
</tr>
</tbody>
</table>

Values are number (%) of responses. Some respondents indicated more than one analyser was used in the same nursery. Total = 159 responses from 127 respondents in 45 nurseries. Blood gas analysers were reported to be used more often in Level III than in Level II nurseries, p < .001.

6.4.5 Definition of neonatal hypoglycaemia

Most respondents reported that they would treat babies with a blood glucose level <2.6 mmol/L. However, there was some variation, particularly soon after birth, with thresholds up to 3.5 mmol/L (Table 6-3). Two-thirds of respondents (79 of 127 (62%)) reported treating an asymptomatic baby with a blood glucose level <2.6 mmol/L in the first 4 h after birth, whereas three-quarters (99 of 127 (78%)) would treat at this blood glucose level after 4 h of age. In contrast, four out of five respondents (105 of 127 (83%)) reported treating a symptomatic baby with a blood glucose level <2.6 mmol/L regardless of the time after birth. Twenty-six respondents (20%) reported that the management of hypoglycaemia was individualised. All indicated multiple factors influencing the threshold for treatment, including the level of illness of the baby (n = 16), the respondent’s preference (n = 14), gestation (n = 15), birth weight (n = 9) and growth restriction (n = 8).
Table 6-3. Blood glucose levels at which respondents reported that treatment would be provided for hypoglycaemia

<table>
<thead>
<tr>
<th>Asymptomatic hypoglycaemia</th>
<th>&lt;2.6 mmol/l</th>
<th>&lt;2.0 mmol/l</th>
<th>&lt;1.7 mmol/l</th>
<th>&lt;1.0 mmol/l</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 h after birth</td>
<td>79 (63)</td>
<td>35 (27)</td>
<td>5 (4)</td>
<td>1 (1)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>&gt;4 h after birth</td>
<td>99 (78)</td>
<td>18 (14)</td>
<td>2 (2)</td>
<td>0</td>
<td>8 (6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptomatic hypoglycaemia</th>
<th>&lt;2.6 mmol/l</th>
<th>&lt;2.0 mmol/l</th>
<th>&lt;1.7 mmol/l</th>
<th>&lt;1.0 mmol/l</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 h after birth</td>
<td>105 (82)</td>
<td>12 (9)</td>
<td>0</td>
<td>1 (1)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>&gt;4 h after birth</td>
<td>104 (83)</td>
<td>11 (8)</td>
<td>0</td>
<td>1 (1)</td>
<td>10 (8)</td>
</tr>
</tbody>
</table>

Values are number (%) of respondents. Total respondents = 127 from 45 nurseries.

6.4.6 Treatment for asymptomatic neonatal hypoglycaemia

6.4.6.1 Standard treatment

In the clinical scenarios, all four babies with asymptomatic hypoglycaemia were reported to be breast feeding well (Table 6-4). The first baby was a healthy term baby with no risk factors for hypoglycaemia. However, 24 of 127 respondents (19%) indicated that they would treat with either formula or intravenous dextrose. Both the preterm baby and the infant of the diabetic scenarios had risk factors for hypoglycaemia. Preterm babies were reported to be more likely to receive treatment than the infant of the diabetic scenarios (109 of 127 respondents (85%) vs. 70 of 127 (55%) (p <0.001)). Formula was reported to be the most common treatment for asymptomatic hypoglycaemia. One hundred and seventeen of 127 respondents (92%) reported that parental consent was required prior to giving infant formula. All 10 who reported that parental consent was not required were from nurseries in which others reported that consent was required.

Table 6-4. First treatment choice for clinical scenario of asymptomatic hypoglycaemic breast fed babies

<table>
<thead>
<tr>
<th>Blood glucose level (mmol/L)</th>
<th>Healthy baby</th>
<th>Preterm baby</th>
<th>Baby of a diabetic mother</th>
<th>Baby of diabetic after initial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>6 (5)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>89 (70)</td>
<td>15 (12)</td>
<td>55 (43)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>3.5</td>
<td>23 (18)</td>
<td>61 (48)</td>
<td>53 (48)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>2.0</td>
<td>0</td>
<td>16 (13)</td>
<td>2 (2)</td>
<td>89 (70)</td>
</tr>
<tr>
<td>1.3</td>
<td>1 (1)</td>
<td>27 (21)</td>
<td>7 (6)</td>
<td>24 (19)</td>
</tr>
<tr>
<td>4.7</td>
<td>8 (6)</td>
<td>5 (4)</td>
<td>8 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>4.7</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
<td></td>
</tr>
</tbody>
</table>

Values are number (%) of respondents. Total = 127 respondents from 45 nurseries. Responses that indicated both breast and formula feeding were included in the formula feed group.
6.4.7 Other treatments

Respondents reported using bolus doses of both 10 and 15% dextrose to treat hypoglycaemia. The most common bolus dose was 2 mL/kg of 10% dextrose, or 200 mg/kg. However, glucose doses ranging from 200 to 500 mg/kg were reported. Respondents also reported using infusions of dextrose ranging from 4.2 mg/kg.min to 13.9 m/kg.min. Other treatment choices included repeating the blood glucose level, consideration of maternal choices or intramuscular glucagon. Twelve of 127 (9%) respondents from four nurseries in New Zealand reported using 40% dextrose gel 200 to 400 mg/kg massaged into the buccal mucosa to reverse asymptomatic hypoglycaemia.

6.4.8 Treatment for symptomatic hypoglycaemia

Almost all respondents (119 of 127 (93%)) reported treating symptomatic hypoglycaemia with intravenous dextrose, either with a bolus (61 of 127 (48%)) or increasing the concentration of dextrose (58 of 127 (45%)). Eight (6%) reported the first treatment choice to be medications, including hydrocortisone, phenobarbitone or no treatment.

6.4.9 Significance of symptoms

The respondents were asked whether asymptomatic hypoglycaemia caused more or less neurological damage than symptomatic hypoglycaemia. Half (61 of 127 (48%)) reported that asymptomatic hypoglycaemia caused less neurological damage, one third (32 of 127 (32%)) reported the risk of damage was similar, and the remainder either did not know (28 of 127 (22%)) or reported that babies with asymptomatic hypoglycaemia were at greater risk (5 of 127 (4%)).

6.4.10 Variation within nurseries

To compare variations in practice within the same nursery, we examined 110 questionnaires from the 31 nurseries (69%), where protocols were used for the management of hypoglycaemia, and from which more one questionnaire was returned.

In all cases, all respondents from the same nursery agreed which babies should be screened for hypoglycaemia. However, there was variation in the reported treatment for hypoglycaemia, particularly for asymptomatic babies. Different thresholds for treatment within the first 4 hour of life were reported from two-thirds of the nurseries (20 of 31 nurseries (65%)), and after 4 hours in half of the nurseries, (17 of 31 nurseries (55%)). The reported thresholds for the treatment of symptomatic hypoglycaemia were more consistent, with variation in only one-third of the nurseries (within the first 4 hours of life 11 of 31 (35%), after 4 hours 9 of 31 (29%)).
6.5 Discussion

Our survey of doctors practising within nurseries in the ANZNN found that all but one nursery have protocols for the management of neonatal hypoglycaemia, and there was agreement that only at-risk babies should be screened. However, more than half the nurseries within the ANZNN are not using reliable analysers to diagnose neonatal hypoglycaemia. Furthermore, there was considerable variation in the reported definition and treatment of asymptomatic hypoglycaemia both within and between nurseries.

In 1996, only 10% of Australian Level III nurseries were reported to be using the more reliable glucose oxidase method for measuring blood glucose levels (Bonacruz, Arnold et al. 1996). Our finding that 27 of the 29 Level III nurseries were using reliable methods reflects a significant practice change over a 12-year period. However, most Level II nurseries continue to use point-of-care glucose analysers, which are likely to lead to both over- and under-estimation of blood glucose levels (Ho, Yeung et al. 2004). This suggests that some babies in Level II nurseries may be receiving unnecessary, invasive and expensive care, while other babies may have undiagnosed hypoglycaemia, potentially placing them at risk of neurological damage.

Ideally, all blood glucose measurements should be performed using reliable laboratory standard analysers (Cornblath, Schwartz et al. 1990; Hawdon, Ward Platt et al. 1994). However, these methods are not available in many Level II nurseries, as blood gas analysers are not immediately available and laboratories are not staffed on a 24 hour basis. Nevertheless, cotside point-of-care analysers should only be used as a screening tool. Every effort should be made to confirm blood glucose levels using a reliable analyser when treatment decisions are necessary.

There has been considerable controversy regarding both the definition and threshold for treatment for neonatal hypoglycaemia. Initially, only symptomatic hypoglycaemia was recognised as being associated with neurological impairment and death (Cornblath, Odell et al. 1959). However, studies of normal term babies immediately after birth (Srinivasan, Pildes et al. 1986) and of preterm babies (Conor Ward 1953) showed that many asymptomatic babies also experienced low blood glucose concentrations, leading to a variety of definitions of hypoglycaemia depending on the maturity and age of the baby (Cornblath and Ichord 2000; Cornblath, Hawdon et al. 2000). Subsequent studies have suggested that asymptomatic hypoglycaemia may also be associated with neurological impairment (Koh, Eyre et al. 1988; Lucas, Morley et al. 1988). As a result, the recommended thresholds for treatment have changed over time, and ideal treatment continues to remain unclear.
The median blood glucose level at which respondents reported that treatment would be provided was the same for all clinical scenarios (<2.6 mmol/L). In 1996, the median definition for hypoglycaemia was reported to be 2.0 mmol/L (Koh and Vong 1996). Eight years earlier (1988), the median definition was <1.1 mmol/L for preterm and growth restricted babies and <2.0 mmol/L for term normally grown babies (Koh, Eyre et al. 1988). The increase in the threshold during the intervening years can perhaps be attributed to the two key papers reporting acute neurological dysfunction and neurodevelopmental delay with blood glucose levels <2.6 mmol/L (Koh, Aynsley-Green et al. 1988; Lucas, Morley et al. 1988).

Our data suggest that a blood glucose level of <2.6 mmol/L is now widely accepted as the threshold for treatment of babies at risk of neonatal hypoglycaemia. However, in response to clinical scenarios, many respondents reported not treating babies with asymptomatic hypoglycaemia and a blood glucose level of 2.0 mmol/L; nearly half reported not treating a baby of a diabetic mother 3 hours after birth, other than to breastfeed, while one-quarter reported not treating a well preterm baby 2 h after birth. These data suggest that the clinical presentation of the baby with asymptomatic hypoglycaemia influences the decision to treat, and may reflect uncertainty about the risk of neurological damage caused by asymptomatic hypoglycaemia.

We found respondents from within the same nursery also reported differing thresholds for treatment, despite using a protocol. This is consistent with findings from a previous survey, which did not differentiate between treatment for asymptomatic and symptomatic hypoglycaemia, but reported that 25 of 41 (61%) special care nurseries in the United Kingdom had respondents using differing thresholds for treatment (Koh, Eyre et al. 1988). The more recent survey from Australia reported 19 of 22 (86%) nurseries had respondents using different thresholds for treating hypoglycaemia (Bonacruz, Arnold et al. 1996). This persisting inconsistency in the approach to treatment for neonatal hypoglycaemia suggests that the paucity of reliable evidence has not been relieved over the last 20 years.

In the clinical scenarios, the most common reported treatment for asymptomatic hypoglycaemia was the administration of infant formula, usually in conjunction with breast feeding. There are reports that supplementation with water or formula adversely affects both the establishment and duration of breastfeeding (Nylander, Lindemann et al. 1991; Blomquist, Jonsbo et al. 1994; Williams 2006). However, others report conflicting findings (Sievers, Clausen et al. 2002). There have been no randomised controlled trials investigating the effects on breastfeeding of briefly supplementing babies at risk of hypoglycaemia with infant formula, and there remains uncertainty about the effect of such
supplements on the duration of breastfeeding (Szajewska, Horvath et al. 2006). Nevertheless, our data suggest that this practice is common in babies at risk of hypoglycaemia in Australia and New Zealand.

Respondents from one Level III and three Level II nurseries in New Zealand reported using 40% dextrose gel as oral treatment for hypoglycaemia. The gel is massaged into the buccal mucosa, and the dextrose is absorbed across the membrane. This treatment has potential advantages; it is oral, inexpensive, and allows the mother and baby to remain together while continuing to establish breastfeeding. However, there is little evidence to support the use of this product (Ang, Koh et al. 1990; Bourchier, Weston et al. 1992; Troughton, Corrigan et al. 2000; Ogilvy-Stuart and Midgley 2006). Randomised trials of the efficacy of this treatment are needed before it is adopted into widespread clinical practice.

We found the majority of respondents reported treating symptomatic hypoglycaemia using intravenous dextrose. The recommended regime is an initial bolus of 200 mg/kg, then an infusion of 10% dextrose at 8 mg/kg.min (Lilien, Pildes et al. 1980). This regime has been shown to improve blood glucose levels within ten minutes without hyperglycaemia, in both symptomatic and asymptomatic hypoglycaemic babies. In the past, bolus doses of 400 mg/kg were recommended, but resulted in rebound hypoglycaemia (Cornblath, Schwartz et al. 1990; Ogilvy-Stuart and Midgley 2006). Our data show that three-quarters of respondents who reported using a bolus gave the recommended dose of 200 mg/kg.

There remains uncertainty about the significance of symptoms related to hypoglycaemia, as is reflected in our data. In a previous survey, 4% of the paediatricians answered that they did not know whether or not a baby with abnormal clinical signs was at more or less risk for neurological damage. We found that of 28 of 126 (22%) answered that they did not know. This uncertainty is likely to persist until careful studies can be performed, such as that proposed by Boluyt and colleagues, (Boluyt, van Kempen et al. 2006) to determine the effect of differing blood glucose levels in the first 3 days after birth on long-term neurodevelopmental outcome.

It is now 70 years since neonatal hypoglycaemia was recognised as a significant cause of neonatal mortality and morbidity (Hartmann and Jaudon 1937). However, its treatment remains controversial. We found that despite the widespread use of protocols to guide care, and apparent consensus that a blood glucose level <2.6 mmol/L required treatment, babies with blood glucose levels of 2.0 mmol/L may not always be treated in Australian and New Zealand neonatal nurseries. Rather, treatment decisions were based on the clinical presentation of the baby. There remains an urgent need for careful clinical investigations.
that will provide those caring for babies with hypoglycaemia reliable evidence on which to base clinical practice.

6.6 Acknowledgements

The authors would like to acknowledge Tracey Kerr for her assistance with mailing out the questionnaires.

6.7 References


6.8 Appendix

6.8.1 Questionnaire
Nursery Protocols and Definitions

1. Does your nursery have a guideline or protocol for the management of hypoglycaemia?
   - [ ] Yes
   - [ ] No

2. Which of the following groups of babies have routine blood glucose monitoring?
   Please tick all that apply in your hospital
   - [ ] All babies following birth
   - [ ] Premature babies <37 weeks gestation
   - [ ] Infants of diabetics
   - [ ] Growth restricted babies
   - [ ] Large for gestational age babies
   - [ ] Babies who are not feeding well
   - [ ] Hypothermic babies
   - [ ] Unwell babies including those suffering from sepsis and asphyxia
   - [ ] Post-operative babies
   - [ ] Other (please specify)

3. Is the threshold for treatment of hypoglycaemia the same for all babies in your nursery?
   - [ ] Yes
   - [ ] No
   If yes, go to question 5

4. If no what is the variation in treatment thresholds related to?
   Please tick all that apply
   - [ ] Birthweight
   - [ ] Gestation
   - [ ] Growth restriction
   - [ ] Level of illness
   - [ ] Consultant preference
   - [ ] Other (please specify)
Diagnosis

5. Are blood glucose levels taken prior to admission to the nursery in infants who are at risk of hypoglycaemia?

- Always
- Sometimes
- Never

6. Following admission to the nursery, when is the first blood glucose level measured?

- Within the first 30 mins
- Within the first hour
- Between 1 and 2 hours
- Between 2 and 4 hours
- Other (please specify)

7. What is the most common blood sample used for measuring a blood glucose level?

- Capillary heel prick
- Venous
- Arterial
8. Are blood samples for measurement of glucose levels tested in your nursery? *as opposed to sending them to the laboratory*

- [ ] Yes
- [ ] No

If no go to question 11

9. If yes which kind of testing is used?

- [ ] Dextrostix
- [ ] Reflolux
- [ ] HemoCue
- [ ] Super Glucocard 2
- [ ] Elite XL
- [ ] Precision G
- [ ] Advantage
- [ ] Glucotrend
- [ ] Blood gas analyser (Glucose oxidase method)
- [ ] Yellow Springs Instruments analyser (YSI)
- [ ] Don’t know
- [ ] Other (please specify)

10. How frequently do you confirm these findings by sending a blood sample to the laboratory?

- [ ] Never
- [ ] Following one low blood glucose level
- [ ] Following two low blood glucose levels
- [ ] Whenever there is concern about a low blood glucose level
- [ ] Other (please specify)
Treatment

11. What is the blood glucose level at which treatment will be given to an asymptomatic baby?

Please tick

*In the first four hours following birth*
A blood glucose level

- [ ] < 1 mmol/l
- [ ] < 1.7 mmol/l
- [ ] < 2.0 mmol/l
- [ ] < 2.6 mmol/l
- [ ] Other (please specify)

*After the first four hours*
Blood glucose level

- [ ] < 1 mmol/l
- [ ] < 1.7 mmol/l
- [ ] < 2.0 mmol/l
- [ ] < 2.6 mmol/l
- [ ] Other (please specify)

12. What is the blood glucose level at which treatment will be given to a symptomatic baby?

*In the first four hours following birth*
A blood glucose level

- [ ] < 1 mmol/l
- [ ] < 1.7 mmol/l
- [ ] < 2.0 mmol/l
- [ ] < 2.6 mmol/l
- [ ] Other (please specify)

*After the first four hours*
Blood glucose level

- [ ] < 1 mmol/l
- [ ] < 1.7 mmol/l
- [ ] < 2.0 mmol/l
- [ ] < 2.6 mmol/l
- [ ] Other (please specify)
13. Does your nursery use dextrose/sucrose gel as a treatment for neonatal hypoglycaemia: e.g. Hypostop, Glucose, Dextrose 40% gel
Please tick

[ ] Yes
[ ] No

If no go to question 16

14. If yes what is the concentration of gel used?
Please specify the brand if possible

[ ] 35%
[ ] 40%
[ ] 50%
[ ] 60%
[ ] 67%
[ ] Don't know
[ ] Other (please specify)

15. What is the dose used?

[ ] 0.5ml/kg
[ ] 1.0 ml/kg
[ ] Other (please specify)

16. Is there a limit to the number of times gel can be given to improve the blood glucose level in a 24h period?

[ ] Yes
[ ] No

If yes what is this limit?

Follow up

17. Are any of the babies treated for hypoglycaemia in your nursery who would not be followed up for other reasons offered developmental follow-up after discharge from the nursery?

[ ] Yes
[ ] No

If yes which babies are offered follow-up?
Practice setting questions

18. In your nursery are you required to get parental permission prior to giving infant formula to a baby?

[ ] Yes
[ ] No

19. A term baby weighing 3.5kg, who is breast feeding well, has a reported blood glucose level of 2.0mmol/l at 5 hours of age.

What would you normally do first?

[ ] No treatment
[ ] Breast feed
[ ] Formula feed
[ ] Dextrose or Sucrose gel
[ ] Dextrose or sucrose gel plus a feed

[ ] Intravenous bolus of dextrose 10% <2ml/kg
[ ] Intravenous bolus of dextrose 10% 2ml/kg
[ ] Intravenous bolus of dextrose 10% >2ml/kg
[ ] Intravenous infusion 10% dextrose 6 to 8ml/kg.h (144–192ml/kg.d)
[ ] Intravenous infusion 10% dextrose >6 to 8ml/kg.h (144–192 ml/kg.d)
[ ] Other (please specify)

When would you repeat the blood glucose measurement?

[ ] Never
[ ] 30 minutes
[ ] 1 hour
[ ] 2 hours
[ ] 3 hours
[ ] Prior to the next feed
[ ] Other (please specify)
20. A baby is admitted to your nursery at 34 weeks gestation and weighing 1.3kg. The blood glucose level is reported to be 2.0mmol/l at two hours of age. The baby is asymptomatic.

What would you normally do first?

- No treatment
- Breast feed
- Formula feed
- Dextrose or Sucrose gel
- Dextrose or sucrose gel plus a feed

- Intravenous bolus of dextrose 10% <2ml/kg
- Intravenous bolus of dextrose 10% 2ml/kg
- Intravenous bolus of dextrose 10% >2ml/kg
- Intravenous infusion 10% dextrose 6 to 8ml/kg,h (144–192ml/kg.d)
- Intravenous infusion 10% dextrose >6 to 8ml/kg,h (144–192ml/kg.d)
- Other (please specify)

When would you repeat the blood glucose measurement?

- Never
- 30 minutes
- 1 hour
- 2 hours
- 3 hours
- Prior to the next feed
- Other (please specify)
21. An infant of a diabetic mother weighing 4.7kg, three hours after birth has a blood glucose level of 2.0mmol/l. The baby is asymptomatic and is reported to have breast fed well since delivery.

What would you normally do first?

- No treatment
- Breast feed
- Formula feed
- Dextrose or Sucrose gel
- Dextrose or sucrose gel plus a feed

- Intravenous bolus of dextrose 10% <2ml/kg
- Intravenous bolus of dextrose 10% 2ml/kg
- Intravenous bolus of dextrose 10% >2ml/kg
- Intravenous infusion 10% dextrose 6 to 8ml/kg.h (144–192ml/kg.d)
- Intravenous infusion 10% dextrose >6 to 8ml/kg.h (144–192ml/kg.d)
- Other (please specify)

When would you repeat the blood glucose measurement?

- Never
- 30 minutes
- 1 hour
- 2 hours
- 3 hours
- Prior to the next feed
- Other (please specify)

This next blood glucose level is reported as 1 mmol/l.
What is your next clinical management?

- No treatment
- Breast feed
- Formula feed
- Dextrose or Sucrose gel
- Dextrose or sucrose gel plus a feed
- Intravenous bolus of dextrose 10% <2ml/kg
- Intravenous bolus of dextrose 10% 2ml/kg
- Intravenous bolus of dextrose 10% >2ml/kg
- Intravenous infusion 10% dextrose 6 to 8ml/kg.h (144–192ml/kg.d)
- Intravenous infusion 10% dextrose >6 to 8ml/kg.h (144–192ml/kg.d)
- Other (please specify)

When would you repeat the blood glucose measurement?

- Never
- 30 minutes
- 1 hour
- 2 hours
- 3 hours
- Prior to the next feed
- Other (please specify)

22. A term infant with hypoxic ischaemic encephalopathy grade II is fitting and unwell. At 12 hours the blood glucose level is 2.0mmol/l. The baby is fluid restricted, receiving 40 ml/kg.d of intravenous 10% dextrose.

What would you normally do first?

- No treatment
- Intravenous bolus of dextrose 10% <2ml/kg
- Intravenous bolus of dextrose 10% 2ml/kg
- Intravenous bolus of dextrose 10% >2ml/kg
- Intravenous infusion 10% dextrose 6 to 8ml/kg.h (144–192ml/kg.d)
- Intravenous infusion 10% dextrose >6 to 8ml/kg.h (144–192ml/kg.d)
- Increase the concentration of dextrose infused
- Other (please specify)
23. Do you believe that a hypoglycaemic baby who is asymptomatic is at more or less risk of neurological damage than a symptomatic infant?

- Don't know
- Asymptomatic baby is at less risk
- The risk of neurological damage is the same
- Asymptomatic baby is at greater risk

24. Additional comments
Chapter 7: Incidence of neonatal hypoglycemia in babies identified as being at risk.

Published


Keywords

Newborn, Infant, Small for gestational age, Large for gestational age, Late preterm, Diabetic mothers, Blood glucose monitoring

Supported by the Auckland Medical Research Foundation, the Waikato Medical Research Foundation, and the Rebecca Roberts Scholarship.

The authors declare no conflicts of interest.
7.1 Abstract

Objectives: Routine blood glucose screening is recommended for babies at risk of neonatal hypoglycemia. However, the incidence of hypoglycemia in those screened is not well described. We sought to determine the incidence of hypoglycemia in babies identified as being at risk, and also to determine differences in incidence between at risk groups.

Study design: Infants (n = 514) were recruited who were born in a tertiary hospital, ≥35 weeks gestation and identified as at risk of hypoglycemia (small, large, infant of a diabetic, late-preterm and other). Blood glucose screening used a standard protocol and a glucose oxidase method of glucose measurement in the first 48 hours after birth.

Results: One-half of the babies (260/514, 51%) became hypoglycemic (<2.6 mM), 97 (19%) had severe hypoglycemia (≤2.0 mM), and 98 (19%) had more than 1 episode. The mean duration of an episode was 1.4 hours. Most episodes (315/390, 81%) occurred in the first 24 hours. The median number of blood glucose measurements for each baby was 9 (range 1-22). The incidence and timing of hypoglycemia was similar in all at risk groups, but babies with a total of 3 risk factors were more likely to have severe hypoglycemia.

Conclusions: Hypoglycemia is common amongst babies recommended for routine blood glucose screening. We found no evidence that screening protocols should differ in different at risk groups, but multiple risk factors may increase severity. The significance of these hypoglycemic episodes for long-term outcome remains undetermined.

7.2 Background

Neonatal hypoglycemia is common and linked to poor neurologic outcome (Lucas, Morley et al. 1988; Cornblath, Hawdon et al. 2000). The definition of neonatal hypoglycemia remains controversial (Rozance and Hay 2010). However, clinical thresholds for treatment have been established, usually <2.2 mM or <2.6 mM, (Cornblath, Hawdon et al. 2000) and clinicians are using these thresholds in clinical practice (Harris, Weston et al. 2009). The incidence of hypoglycemia is estimated to be 5% to 15% in otherwise healthy babies (Cornblath, Hawdon et al. 2000; McGowan, Price-Douglas et al. 2006; Hay, Raju et al. 2009), but there is considerable uncertainty about this. In part this is because the few published papers have used definitions ranging from <1.7 to <2.6 mM (Pildes, Forbes et al. 1967; Lubchenco and Bard 1971; Sexson 1984; Anderson, Shakya et al. 1993; Holtrop 1993; Hume, McGeechan et al. 1999; Agrawal, Lui et al. 2000; Maayan-Metzger, Lubin et al. 2009) and have examined a variety of specific groups of babies at risk (Pildes, Forbes et al. 1967; Lubchenco and Bard 1971; Sexson 1984; Lucas, Morley et al. 1988; Anderson, Shakya et al. 1993; Holtrop 1993; Hume, McGeechan et al. 1999; Agrawal, Lui et al. 2000;
Further, approaches to blood glucose monitoring have been inconsistent and poorly defined, and in many cases have used unreliable screening methods to detect hypoglycaemia (Sexson 1984; Lucas, Morley et al. 1988; Anderson, Shakya et al. 1993; Holtrop 1993; Agrawal, Lui et al. 2000; Maayan-Metzger, Lubin et al. 2009).

Optimum screening approaches for detection of hypoglycemia in at risk babies remain uncertain. It has been suggested that protocols should be individualized for each baby depending on the risk group (Canadian Paediatric Society 2004; Rozance and Hay 2010; Adamkin and Committee on Fetus Newborn 2011). For example, Holtrop (Holtrop 1993) recommended large babies have blood glucose monitoring discontinued 12 hours after birth, and small babies have continued monitoring for 48 hours, whereas Agrawal et al (Agrawal, Lui et al. 2000) and Maayan-Metzger (Maayan-Metzger, Lubin et al. 2009) et al recommended infants of diabetic mothers have blood glucose monitoring for 24 hours. These recommendations are based on very limited evidence and their relevance to current clinical practice is unclear.

The incidence of neonatal hypoglycemia may be increasing as maternal factors known to contribute increase in frequency, including both poor and excessive nutrition, (Henriksen 2006) diabetes, (Wild, Roglic et al. 2004) increasing maternal age, and poor economic conditions. The clinical management of babies at risk of hypoglycemia has also altered over recent decades, with improved identification of babies at risk, improved methods of diagnosis, and a greater focus on early feeding and glucose monitoring. However there are no recent data on the effects of these changes on the incidence of hypoglycemia.

Therefore, we sought to establish the incidence of neonatal hypoglycemia in babies identified as being at risk and receiving routine blood glucose screening using reliable methods. We also sought to identify any differences in incidence between different at risk groups.

7.3 Methods

Babies were enrolled in a randomized controlled trial (The Sugar Babies Study, Australian and New Zealand Clinical Trials Registry Number: 12608000623392). Entry criteria were ≥35 weeks gestation, <48 hours old and identified as being at risk for neonatal hypoglycemia. At risk categories included being the infant of a diabetic mother, late-preterm (35-37 weeks gestation), small (≤10th centile or ≤2500 g), or large (≥90th centile or ≥4500 g) weight at birth, or other reasons identified by the clinical team such as poor feeding. Women identified as likely to give birth to a baby at risk were approached before
birth; those not approached before birth were approached as soon as possible after birth. Babies remained in the study for 48 hours, although those thought to have on-going risk continued to have blood glucose monitoring after this time. Written informed consent was obtained from the parents of each baby and the study was approved by the Northern Y Ethics Committee.

Mothers were encouraged to establish skin to skin contact and breast feeding as soon possible after birth. Babies were encouraged to feed on demand but the interval between feeds was no longer than 3 hours. Women who attended the Maternal Diabetes clinic were encouraged before the birth to express breast milk, which was frozen and later given to the baby. Mothers who wished to breast feed were also encouraged to express breast milk after birth if the baby was sleepy.

Formula fed babies were offered up to 60 ml/kg in the first 24 hours, increasing to 90 ml/kg in the subsequent 24 hours. The first feed was offered within the first hour after birth and then feeds were offered 2 to 4 hourly.

Blood glucose concentrations were measured on capillary blood samples taken by heel-prick lance and analyzed on a blood gas analyzer (ABL800 Flex; Radiometer Medical, Copenhagen, Denmark) using the glucose oxidase method (reading range 0.0–60 mmol/l, coefficient of variation 2.1%). Samples were taken at 1 hour after birth regardless of feeds, then before feeds 3–4 hourly in the first 24 hours, then 3–8 hourly for the next 24 hours. Measurements were discontinued if there were 3 normal blood glucose concentration measurements and no clinical concerns about feeding.

Infants with hypoglycaemia received 200 mg/kg of dextrose gel, or an identical appearing placebo gel, massaged into the buccal mucosa and were encouraged to feed. Babies who did not suckle were given expressed breast milk or infant formula via syringe, cup, or, if admitted to the neonatal intensive care unit, by gastric tube. Blood glucose concentrations were measured again 30 minutes after treatment, and the same gel treatment was repeated once if hypoglycemia persisted. Babies with persistent hypoglycemia after two doses of gel were admitted to neonatal intensive care unit and treated with infant formula, intravenous dextrose, or both.

We defined hypoglycemia as a blood glucose concentration <2.6 mM, and severe hypoglycemia as a blood glucose concentration ≤2.0 mM. An episode of hypoglycemia was as defined as 1 or more consecutive blood glucose concentrations <2.6 mM. The duration of an episode was the time from the first measured blood glucose concentration <2.6 mM
to the first measured blood glucose concentration ≥2.6 mM. A second or subsequent episode was defined as recurrent hypoglycemia.

Population birthweight centiles were calculated using Australian data (Kitchen, Robinson et al. 1983). Customized percentiles were calculated retrospectively using New Zealand percentiles (McCowan, Stewart et al. 2004) and a gestation calculator (Gestation network centile calculator http://www.gestation.net/birthweight_centiles/birthweight_centiles.htm).

Data were analysed using JMP® 8.0 2009 (SAS Institute Inc®, Cary, North Carolina) and are presented as number (percent), median (range), or mean (SD). Comparisons between groups were performed using the Mann-Whitney-U test for parity, Student t test for weights, and Χ² tests for all other variables.

7.4 Results

Five hundred fourteen babies were identified as being at risk of neonatal hypoglycemia and enrolled between November 2008 and November 2010 (Table 7-1). The median number of blood glucose measurements for each baby was 9 (range 1–21), and glucose concentrations ranged from 0.5–8.1 mM. Blood glucose monitoring was discontinued prior to 48 hours after birth in 136 babies (26%). Of the whole cohort 260 (51%) babies became hypoglycemic and 97 (19%) had severe hypoglycemia (Table 7-2). Maternal characteristics were similar in babies who did and did not become hypoglycemic (Table 7-1). Compared to babies who did not become hypoglycemic, those who did become hypoglycemic were more likely to be male. Most babies who became hypoglycemic (205/260, 79%) showed no clinical signs, but 40 babies (15%) were too sleepy to feed when hypoglycemic and 16 (7%) were noted to be jittery.
Table 7-1. Demographic data for babies who did and did not become hypoglycemic and their mothers

<table>
<thead>
<tr>
<th></th>
<th>Recruited</th>
<th>Hypoglycemic</th>
<th>Not hypoglycemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers (n)</td>
<td>481</td>
<td>250</td>
<td>231</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>29.6 (6.4)</td>
<td>29.7 (6.4)</td>
<td>29.6 (6.6)</td>
</tr>
<tr>
<td>Gravidity</td>
<td>2 (0–13)</td>
<td>2 (0–13)</td>
<td>2 (1–12)</td>
</tr>
<tr>
<td>Parity</td>
<td>1 (0–10)</td>
<td>1 (0–10)</td>
<td>1 (0–9)</td>
</tr>
<tr>
<td>BMI at booking (kg/m²)</td>
<td>29 (7.5)</td>
<td>28.5 (7.0)</td>
<td>29.3 (7.9)</td>
</tr>
<tr>
<td>Weight change during pregnancy (kg)</td>
<td>11.9 (7.1)</td>
<td>11.9 (7.3)</td>
<td>11.9 (6.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>199 (42)</td>
<td>98 (39)</td>
<td>102 (44)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>107 (54)</td>
<td>61 (24)</td>
<td>46 (20)</td>
</tr>
<tr>
<td>Oral medication</td>
<td>26 (13)</td>
<td>8 (3)</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Diet controlled</td>
<td>46 (23)</td>
<td>18 (7)</td>
<td>28 (12)</td>
</tr>
<tr>
<td>No treatment</td>
<td>21 (10)</td>
<td>11 (4)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Intended method of feeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>462 (96)</td>
<td>243 (97)</td>
<td>219 (95)</td>
</tr>
<tr>
<td>Infant formula</td>
<td>11 (2)</td>
<td>3 (1)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Combination</td>
<td>8 (2)</td>
<td>4 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Expressed breast milk prior to birth</td>
<td>87 (18)</td>
<td>49 (20)</td>
<td>38 (16)</td>
</tr>
<tr>
<td>Babies (n)</td>
<td>514</td>
<td>260 (51)</td>
<td>254 (49)</td>
</tr>
<tr>
<td>Male</td>
<td>280 (54)</td>
<td>130 (46)</td>
<td>150 (54)*</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3120 (857)</td>
<td>3070 (818)</td>
<td>3171 (894)</td>
</tr>
<tr>
<td>Gestation (wk)</td>
<td>37.4 (1.7)</td>
<td>37.5 (0.7)</td>
<td>37.2 (0.6)</td>
</tr>
<tr>
<td>Singleton</td>
<td>434 (84)</td>
<td>218 (84)</td>
<td>216 (85)</td>
</tr>
<tr>
<td>Vaginal birth</td>
<td>321 (62)</td>
<td>163 (63)</td>
<td>158 (62)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand European</td>
<td>275 (53)</td>
<td>140 (54)</td>
<td>135 (53)</td>
</tr>
<tr>
<td>Maori</td>
<td>150 (29)</td>
<td>79 (30)</td>
<td>71 (28)</td>
</tr>
<tr>
<td>Pacific</td>
<td>16 (3)</td>
<td>6 (2)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>73 (15)</td>
<td>35 (13)</td>
<td>38 (15)</td>
</tr>
</tbody>
</table>

Data are mean (SD), number (%), or median (range). *p = 0.03.

The incidence of hypoglycemia was similar in all risk groups (Table 7-2). The incidence was also similar whether the risk group of “small” babies was defined using the study definition (birth weight <2500 g or population centiles <10th, 77/152, 52%) or using customised centiles <10th, (70/133, 52%). Likewise, the incidence was similar for babies identified as “large” by the study definition (birth weight >4500 g or population centiles >90th, 61/133, 47%) or using customized centiles >90th, (57/118, 48%). Two-thirds of the babies (347/514, 68%) had 1 risk factor for hypoglycemia, 29% (150/514) had 2 risk factors and 3% (17/514) had three risk factors (Figure 7–1). Multiple risk factors did not alter the incidence of hypoglycemia (181/347, 52% in babies with 1 risk factor, 72/150, 48% in those with 2, and 11/17, 65% in those with 3 risk factors, p = 0.37). However, babies with 3 risk
factors were more likely to have severe hypoglycemia (7/17, 41%) than those with 1 (64/334, 19%) or two risk factors (26/150, 17%), (p = 0.05).

**Figure 7-1.** The incidence of neonatal hypoglycemia in babies with different combinations of risk factors

![Venn Diagram showing risk factors and incidence of hypoglycemia](image)

The median duration of hypoglycemic episodes was 1.4 hours (range 0.2-14.5 hours) and was similar in all at risk groups (Table 7-2). One-half of the hypoglycemic episodes occurred within the first 6 hours (187/390, 48%), and three-quarters within the first 24 hours (315/390, 81%). The timing of hypoglycemic episodes was also similar in all at risk groups (Table 7-2). Interestingly, of the babies with hypoglycaemia, 95 (37%) had their first episode after 3 normal blood glucose measurements. Only 15 (6%) of the babies with hypoglycemia had their first episode more than 24 hours after birth. Of the 143 episodes of severe hypoglycemia, 74% (106/143) occurred within the first 6 hours, and 90% 130/143 in the first 12 hours.
Table 7-2. Incides of hypoglycemia in babies with difference risk factors

<table>
<thead>
<tr>
<th></th>
<th>All babies</th>
<th>Infants of diabetic mothers</th>
<th>Late Preterm</th>
<th>Small</th>
<th>Large</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babies (n)</td>
<td>514</td>
<td>202</td>
<td>193</td>
<td>152</td>
<td>133</td>
<td>18</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>260 (51)</td>
<td>98 (48)</td>
<td>103 (54)</td>
<td>77 (52)</td>
<td>61 (47)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>97 (19)</td>
<td>39 (19)</td>
<td>39 (20)</td>
<td>27 (18)</td>
<td>27 (20)</td>
<td>5 (27)</td>
</tr>
<tr>
<td>Recurrent hypoglycemia</td>
<td>98 (19)</td>
<td>31 (15)</td>
<td>37 (19)</td>
<td>32 (21)</td>
<td>25 (19)</td>
<td>5 (27)</td>
</tr>
<tr>
<td>Blood glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>measurements (n)</td>
<td>4664</td>
<td>1714</td>
<td>1901</td>
<td>1514</td>
<td>1120</td>
<td>150</td>
</tr>
<tr>
<td>&lt;2.6 mM</td>
<td>568 (12)</td>
<td>202 (12)</td>
<td>228 (12)</td>
<td>175 (12)</td>
<td>145 (13)</td>
<td>25 (17)</td>
</tr>
<tr>
<td>≤2.0 mM</td>
<td>143 (3)</td>
<td>65 (4)</td>
<td>50 (3)</td>
<td>37 (2)</td>
<td>44 (4)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Hypoglycemic episodes (n)</td>
<td>390</td>
<td>133</td>
<td>155</td>
<td>116</td>
<td>94</td>
<td>25</td>
</tr>
<tr>
<td>In the first 6 h</td>
<td>187 (48)</td>
<td>70 (52)</td>
<td>75 (48)</td>
<td>55 (47)</td>
<td>47 (50)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>In the first 24 h</td>
<td>315 (81)</td>
<td>110 (83)</td>
<td>124 (80)</td>
<td>93 (80)</td>
<td>75 (80)</td>
<td>23 (92)</td>
</tr>
<tr>
<td>24–48 h</td>
<td>75 (19)</td>
<td>23 (17)</td>
<td>31 (20)</td>
<td>23 (20)</td>
<td>19 (20)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Number per baby</td>
<td>1 (1–7)</td>
<td>1 (1–6)</td>
<td>1 (1–7)</td>
<td>1 (1–7)</td>
<td>1 (1–6)</td>
<td>1 (1–4)</td>
</tr>
<tr>
<td>Duration (h)</td>
<td>1.4 (0.2–14.5)</td>
<td>1.4 (0.5–9.0)</td>
<td>1.4 (0.2–7.2)</td>
<td>1.4 (0.5–14.5)</td>
<td>1.4 (0.5–12.2)</td>
<td>1.3 (0.7–3.8)</td>
</tr>
</tbody>
</table>

Data are mean (SD), number (%), or median (range). Many babies had more than one risk factor (see Figure 7-1).

Ninety-eight babies (19%) had 142 recurrent episodes, with a median of 1, (range 1–6) episodes per baby. The frequency of recurrent episodes was similar in all at risk groups (Table 7-2). Of the 142 recurrent episodes, 21 (15%) occurred within 6 hours of the initial episode and 99 (70%) within 24 hours.

Exclusion of the babies who received dextrose gel did not alter the proportion of hypoglycemic babies who experienced severe (52/138, 37%) or recurrent hypoglycemia (49/138, 35%).

7.5 Discussion

We sought to determine the incidence of neonatal hypoglycemia in babies identified as being at risk and also to detect any differences in the incidence related to different risk factors. Our data show that approximately one-half of the babies identified as being at risk actually became hypoglycemic, 37% of these having a blood glucose concentration ≤2.0 mM, and 37% having more than one episode. Most episodes lasted for longer than one hour and occurred in the first 24 hours. The reason for being at risk and the number of risk factors did not affect the incidence of hypoglycemia. However, babies with 3 risk factors had more severe hypoglycemia.

Neonatal hypoglycemia was more common in our cohort than previously reported. There may be a number of reasons for this. First, babies in our study were screened regularly using a consistent standardized approach, thus, increasing the opportunity to detect hypoglycemia. Second, all glucose measurements were analyzed immediately after the
sample was taken using the glucose oxidase method, thus, increasing the accuracy of results.

Third, previous publications have defined hypoglycemia using lower blood glucose concentrations. Pildes et al defined hypoglycemia as a blood glucose concentration <1.7 mM and reported a 6% incidence in small babies (Pildes, Forbes et al. 1967). Lubchenco later reported an overall incidence of 11% in a randomly selected group of babies from a neonatal nursery (Lubchenco and Bard 1971). A decade later using a higher blood glucose concentration of 2.2 mM to define hypoglycemia, Sexson reported an incidence of 29% in admitted at risk babies (Sexson 1984). Not surprisingly, our data show a higher incidence of 51% using a definition of a blood glucose concentration of <2.6 mM, which is the clinical threshold frequently applied in practice (Canadian Paediatric Society 2004; Harris, Weston et al. 2009).

This high incidence occurred despite clinical emphasis on early and frequent feeding in babies at risk. Management included counselling women prior to the birth about the importance both of establishing feeding as soon after birth as possible (within the first hour), and of frequent feeding. Our hospital is a baby-friendly hospital, and the midwives caring for families within the study were experts in establishing and encouraging breast feeding. Ninety-seven percent of the mothers chose to breast feed and a number expressed and stored breast milk prior to the birth, so that this stored milk was available in the first few hours after birth when babies were at greatest risk of hypoglycemia. It is possible that the incidence of hypoglycemia may have been even higher without this attention to early feeding.

The current screening guidelines recommend that the decision to discontinue monitoring should be based on the risk factor for each baby. For example, infants of diabetics and large babies should have monitoring discontinued 12 hours after birth (if the blood glucose is ≥2.6 mM) (Canadian Paediatric Society 2004; Adamkin and Committee on Fetus Newborn 2011) and late preterm babies and small babies after either 24 hours (Adamkin and Committee on Fetus Newborn 2011) or 36 hours (Canadian Paediatric Society 2004). Despite these guidelines, there is significant variation in the screening for hypoglycemia between clinicians and nurseries (Harris, Weston et al. 2009), which may in part be due to the paucity of data to support these recommendations. Our data show babies in different at risk groups have a similar incidence of hypoglycemia, and episodes also occur at a similar time. This suggests that all babies at risk could be monitored using the same screening protocol, thus, simplifying recommendations for clinical practice.
We used a pragmatic approach to identify small and large babies for this study. Customized percentiles have been reported to be better at identifying babies at clinical risk due to impaired growth (McCowan, Stewart et al. 2004), and we, therefore retrospectively applied customized centiles to our data. However, this had little effect on the incidence of hypoglycemia in our cohort. Because the data required to calculate customized centiles (booking weight, height, parity, ethnicity) and computer access to the calculator are not always available when babies are born, it is reassuring that our pragmatic approach appears equally effective in identifying babies at risk of hypoglycemia.

Nineteen percent of the babies in our study suffered from severe hypoglycemia and three-quarters of these episodes occurred the first 6 hours after birth, although episodes continued up to at least 48 hours. Interestingly, babies with three risk factors were more likely to have severe hypoglycemia, though we did not find evidence of a higher incidence of hypoglycemia overall. This may be important, because severity of hypoglycemia has been associated with poor neurological outcome (Anderson, Milner et al. 1967; Rozance and Hay 2006).

The duration of hypoglycemic episodes may also be important in determining neurological outcome (Anderson, Milner et al. 1967; Lucas, Morley et al. 1988; Rozance and Hay 2006). However, measuring duration is difficult using the standard clinical approach of intermittent heel-pricks. We found the median duration of a hypoglycemic episode was 1.4 hours, but of concern, 65 babies had episodes lasting longer than 3 hours and 6 had 2 episodes lasting more than 3 hours. These are likely to be underestimates because intermittent sampling will miss many episodes of hypoglycaemia (Platas, Lluch et al. 2009; Harris, Weston et al. 2010). Continuous interstitial glucose monitoring has been shown to be safe and reliable in babies at risk for neonatal hypoglycemia and may in the future prove a more useful tool to accurately measure the duration of a hypoglycemic episode in relation to later outcome (Beardsall, Ogilvy-Stuart et al. 2005; Platas, Lluch et al. 2009; Harris, Weston et al. 2010).

Recurrent hypoglycemia has been linked with poor neurological outcome (Lucas, Morley et al. 1988; Duvanel, Fawer et al. 1999; Menni, de Lonlay et al. 2001; Caraballo, Sakr et al. 2004). It is, therefore, of concern that 19% of the babies who became hypoglycemic experienced recurrent episodes in the first 48 hours after birth, despite on-going attention to feeding and prompt treatment. There are no previous reports of which we are aware concerning recurrent hypoglycemia in the first 48 hours. However, recurrent episodes have been reported in preterm babies, (Lucas, Morley et al. 1988; Hume, McGeechan et al. 1999) with 1 study showing an association between poor neurological outcome and the number of days on which a baby experienced hypoglycaemia (Lucas, Morley et al. 1988). There is an
urgent need for a well-designed follow up study to determine the developmental outcomes of babies who have experienced early hypoglycemia, and particularly those who experienced recurrent episodes (Hay, Raju et al. 2009).

It is likely that the incidence of hypoglycemia that we report is an underestimate. More than one quarter of babies did not have blood glucose monitoring for the full 48 hours after birth. This was because the study protocol allowed for monitoring to be discontinued after 3 normal glucose measurements and no clinical concerns, as is routine practice in our hospital. The blood glucose measurement is invasive and painful and we do not consider it ethically justifiable to continue to measure blood glucose concentrations in otherwise well babies. Nevertheless, in those whom we did continue to monitor, over one-third of hypoglycemic babies had their first episode after three normal blood glucose measurements, and 6% had a first hypoglycemic episode after 24 hours of age. Previous authors have also shown that hypoglycemic episodes can occur long after the first 48 hours in preterm babies (Lucas, Morley et al. 1988; Hume, McGeechan et al. 1999), suggesting that there may have been others whose first hypoglycemic episode occurred after monitoring was discontinued. Once again, the significance of any such episodes for long-term neurologic outcome remains uncertain, and it is difficult to recommend any changes to current practice before this information is available.

It is also possible our findings may be an underestimate because the babies were recruited to a randomized trial to determine whether dextrose gel was an effective treatment for neonatal hypoglycemia. Receipt of dextrose gel could not have affected the overall incidence of hypoglycaemia, because babies were only randomized after the first hypoglycemic episode, but may potentially have decreased the incidence of severe or recurrent episodes. However, exclusion of babies who received dextrose gel did not change our findings.

We conclude that neonatal hypoglycemia is common in babies currently recommended for routine blood glucose screening, despite recognition of risk factors and early attention to feeding. We found no evidence that screening protocols should differ for different at risk groups, but multiple risk factors may increase the severity of hypoglycemic episodes. The significance of hypoglycemia for long term outcome remains unclear.
7.6 References


Chapter 8: Dextrose gel for treating neonatal hypoglycemia: Randomized placebo-controlled trial (The Sugar Babies Study)

Submitted for consideration to the New England Journal of Medicine

29 October 2012

The Sugar Babies Study was funded from the Waikato Medical Research Foundation, the Auckland Medical Research Foundation, the Maurice and Phyllis Paykel Trust, the Health Research Council of New Zealand, and the Rebecca Roberts Scholarship.

The authors have not conflicts to declare.

Keywords: Infant, small for gestation age, large for gestational age, late-preterm, buccal administration, infant feeding, glucose, glucose oxidase, continuous glucose monitoring
8.1 Abstract

Background: Neonatal hypoglycemia is common and a preventable cause of brain damage. Dextrose gel is used to reverse hypoglycemia in diabetics. However, there is little evidence for its use in babies.

Method: We enrolled 514 babies 35 to 42 weeks gestation, <48 h old and at risk of hypoglycemia, to a randomized, double-blind placebo controlled trial to determine whether 40% dextrose gel massaged into the buccal mucosa is more effective than feeding alone in reversing hypoglycemia. Hypoglycemic babies were randomised to 40% dextrose gel 200 mg/kg (n = 118) or placebo (n = 119) and encouraged to feed. Primary outcome was treatment failure (blood glucose concentration <47 mg/dl (2.6 mmol/l) after two treatment attempts).

Results: Dextrose gel halved the frequency of treatment failure (16 (14%) in dextrose vs. 29 (24%) in placebo group, RR 0.56; 95% CI 0.32 to 0.97; p = 0.03). Babies who received dextrose gel were less likely to be admitted to intensive care for hypoglycemia, (16 (14%) vs. 30 (25%), RR 0.71; 95% CI 0.55 to 0.93; p = 0.03), to receive formula feeds (median 7 vs. 10 feeds; median difference 2; 95% CI 0 to 4; p = 0.04) and to be formula fed at two weeks of age (5 (4%) vs.15 (13%), RR 0.36; 95% CI 0.18 to 0.71; p = 0.04).

Conclusion: Dextrose gel should be considered for first-line treatment for management of hypoglycemia in late preterm and term babies in the first 48 hours after birth.

Australian New Zealand Clinical Trials Registry, ACTRN12608000623392.

8.2 Introduction

Neonatal hypoglycemia is important because it is common, and linked with brain injury and poor neurodevelopmental outcome (Koh, Aynsley-Green et al. 1988; Lucas, Morley et al. 1988; Kerstjens, Bocca-Tjeertes et al. 2012). Neonatal hypoglycemia is reported to affect as many as 5 to 15% of otherwise healthy babies (Cornblath, Hawdon et al. 2000; McGowan, Price-Douglas et al. 2006; Hay, Raju et al. 2009) and is also common in resource-poor countries (Anderson, Shakya et al. 1993; Osier, Berkley et al. 2003). Furthermore, the prevalence is increasing due to the increasing incidence of both preterm birth, (Blencowe, Cousins et al. 2012) and maternal factors known to predispose babies to hypoglycemia including diabetes, (Wild, Roglic et al. 2004) and obesity (Doherty, Magann et al. 2006). There is a paucity of evidence to guide treatment and there have been repeated calls to develop evidence based guidelines for the treatment of neonatal
hypoglycaemia (Williams 1997; Cornblath and Ichord 2000; Hay, Raju et al. 2009; Achoki, Opiyo et al. 2010).

Current treatment choices vary depending on the baby's birth weight and gestational age. In late preterm and term babies, initial management focuses on feeding and increased monitoring, requiring repeated and painful blood tests. If the blood glucose concentration remains low, admission to the Newborn Intensive Care Unit (NICU) for intravenous glucose is usually indicated (Lilien, Pildes et al. 1980). NICU admission usually means that mother and baby are separated, which may delay the establishment of breast feeding.

Another less commonly used treatment is 40% dextrose gel. Potential advantages include keeping the mother and baby together while treatment is provided, ease of administration of the gel, and low cost. Oral carbohydrate is first-line treatment for low blood glucose concentrations in the conscious diabetic child or adult (Clarke, T et al. 2009) and sublingual glucose has been shown to be as effective as intravenous glucose for the treatment of hypoglycemic children with malaria (Barennes, Valea et al. 2005; Graz, Dicko et al. 2008). Two small observational studies in babies between 28 to 42 weeks’ gestation have reported improvement in blood glucose concentrations following massaging dextrose gel 200 mg/kg into the buccal mucosa (Ang, Koh et al. 1990; Bourchier, Weston et al. 1992). However, a randomized trial reported only in abstract, in which 75 hypoglycemic babies on the first day after birth were randomized to a formula feed or a formula feed plus dextrose gel 400 mg/kg, showed no differences in blood glucose concentrations 15 and 30 minutes after treatment. Further, babies randomized to the dextrose gel group suckled a smaller volume during the subsequent feed (Troughton, Corrigan et al. 2000). Therefore, the role of dextrose gel in the management of neonatal hypoglycemia remains unclear.

We sought to determine whether treatment with 40% dextrose gel is more effective than feeding alone in reversing neonatal hypoglycemia in at-risk late preterm and term babies in the first 48 hours after birth.

8.3 Methods

8.3.1 Participants

Eligible babies were born at Waikato Women’s Hospital, a tertiary referral centre, ≥35 weeks’ gestation, ≤48 hours old and identified as being at risk of neonatal hypoglycemia. Risk factors included being the infant of a diabetic mother; late preterm (35 or 36 completed weeks’ gestation); small (birthweight <10\textsuperscript{th} centile or <2,500 g) or large (birthweight >90\textsuperscript{th} centile or >4,500 g); or other reasons such as poor feeding. Exclusion criteria included any prior treatment for neonatal hypoglycemia, serious congenital
malformation, terminal conditions or skin abnormalities which would prevent use of the continuous glucose monitor.

Women identified as likely to give birth to an eligible baby were approached prior to birth; those not recruited before birth were approached as soon as possible after the birth. The study was approved by the Northern Y Ethics Committee, and written informed consent was obtained from the mothers.

8.3.2 Procedures

Blood glucose concentrations were measured according to current clinical guidelines in our hospital (Harris, Weston et al. 2012) on samples obtained by heel lances at one hour after birth, then three to four hourly before feeds for the first 24 hours, then six to eight hourly for the subsequent 24 hours. All blood glucose concentrations were measured using the glucose oxidase method (Radiometer, ABL800Flex, Copenhagen, Denmark, reading range 0.0 to 1,080 mg/dl (0.0 to 60 mmol/l), coefficient of variation 2.1%).

A continuous glucose monitor (CGMS® system gold ™ Medtronic, MiniMed, Northridge, CA, USA) was placed subcutaneously in the lateral thigh as soon as possible after birth, or after recruitment if this was after birth. The monitor remained in place for at least 48 hours or up to seven days until there was no longer clinical concern about hypoglycemia. The interstitial glucose concentrations could not be viewed in real time, ensuring clinical practice was not influenced by the results.

Mothers were encouraged to provide skin to skin contact and breast feed as soon as possible after birth. Prior to birth many mothers expressed and stored breast milk, and when possible babies who did not breast feed adequately were given expressed breast milk by syringe. Babies who were to be formula fed were offered up to 60 ml/kg.d on day 1 and 90 ml/kg.d on day 2.

8.3.3 Randomization and treatment

Babies who became hypoglycemic were randomized to either the dextrose or placebo gel treatment group by computerized allocation using a balanced block design with variable block sizes and stratified by maternal diabetes (yes or no) and birth weight (small, appropriate, or large). The researcher entered demographic data into a computer that provided a randomization number corresponding to a numbered treatment pack containing six labeled syringes, each containing 3 ml of the same gel: either 40% dextrose gel or identical appearing 2% carboxymethyl cellulose placebo gel. Study packs were prepared by the hospital pharmacist, who was the only person holding the randomization schedule.
Clinicians, families and researchers all remained unaware of the treatment group allocation until the data analysis was complete.

The researcher or midwife dried the baby’s mouth with gauze, 0.5 ml/kg (200 mg/kg) gel was massaged into the buccal mucosa, and the baby was encouraged to feed. If feeding was poor, expressed breast milk or formula was given via syringe, according to maternal wishes. The blood glucose concentration was measured 30 minutes after gel administration and if the baby remained hypoglycemic, or hypoglycemia recurred later, treatment was repeated using another syringe from the allocated pack. Up to six doses of gel could be administered over 48 hours.

8.3.4 Outcomes and analysis

The primary outcome was treatment failure, defined as a blood glucose concentration <47 mg/dl (<2.6 mmol/l) 30 minutes after the second of two doses of gel. Secondary outcomes were admission to NICU, frequency and total volume of expressed breast milk, infant formula, intravenous dextrose and gel in the first 48 hours, method of feeding two weeks after birth, incidence of rebound and recurrent hypoglycaemia after successful treatment, time taken to achieve interstitial glucose ≥47 mg/dl following treatment, and total duration of interstitial glucose <47 mg/dl up to 48 hours after birth.

Hypoglycemia was defined as a blood or interstitial glucose concentration <47 mg/dl (<2.6 mmol/l). Episodes of hypoglycemia were defined as one or more consecutive blood glucose concentrations <47 mg/dl or two or more consecutive interstitial glucose concentrations <47 mg/dl. Rebound hypoglycemia was defined as an episode of hypoglycemia within six hours following successful treatment (blood or interstitial glucose ≥47 mg/dl for ≥1 hour following treatment). Recurrent hypoglycemia was defined a further episode of hypoglycemia following successful treatment, within 48 hours after birth.

Babies who failed treatment and remained hypoglycemic were admitted to the NICU and treated with open labeled dextrose gel, infant formula and or intravenous dextrose according to clinical guidelines and clinician preference.

8.3.5 Power calculation

A retrospective review of 91 babies at risk of neonatal hypoglycemia born at our hospital in 2006 found that 51 (56%) became hypoglycaemic, and 9 (20%) remained hypoglycemic after two doses of dextrose gel. Using an one-tailed design (alpha = 0.05, beta = 0.2), and allowing for 5% withdrawals, a sample size of 230 (115 in each group) was required to
detect a reduction in the rate of treatment failure from 35% in the placebo group to 20% in the dextrose gel group.

8.3.6 Data monitoring

An independent data monitoring committee reviewed results after 100 babies had been randomized and recommended the study continue. The safety monitoring committee received reports of serious adverse events (death and seizures), as well as other adverse events (severe hypoglycemia <18 mg/dl (<1 mmol/l), hyperglycemia (two consecutive blood glucose concentrations >144 mg/dl (>8.0 mmol/l)), culture proven sepsis, inflammation or swelling at the insertion site of the continuous glucose monitor).

8.3.7 Statistical analysis

Data from the interstitial glucose monitors were downloaded using CGMS® system solutions™ software version 3.0C, (CGMS® system gold™ Medtronic, MiniMed, Northridge, CA, USA) and recalibrated using a previously reported algorithm (Signal, Le Compte et al. 2012) to optimise accuracy at low blood glucose concentrations using Matlab™ Version 7.14 2012a (The Mathworks; Natick, MA).

Statistical analyses were on an intention to treat basis, and babies for whom primary outcome data were not available were allocated the conservative outcome of treatment failure. Data were analysed using SAS Enterprise Guide® Version 4.3 2010 (SAS Institute Inc®, Cary, NC) and are presented as median (range), mean (SD), relative risk (RR) or median difference and 95% confidence intervals (CI). Normally distributed continuous variables were analysed with t-tests; otherwise a Wilcoxon two sample test was used. Feeding at two weeks of age was analysed using an unordered generalised logistic regression with breast milk as the reference group. Rates of rebound and recurrent hypoglycemia were compared between groups using rate ratios, calculated using OpenEpi Version 2.3.1.(Dean, Sullivan et al.).

8.4 Results

Between December 2008 and November 2010, we approached 1002 women, of whom 588 (59%) gave consent for their baby's participation. Seventy-four of their babies were not enrolled for reasons including not meeting study eligibility criteria after birth, consent withdrawal, not born at our hospital, or researchers not notified in time (Figure 8–1). Of the 514 babies enrolled, 242 (47%) became hypoglycemic and were randomized. Five babies were randomized in error (four treated prior to randomization and one randomized at 50 hours of age), leaving 237 babies; 118 allocated to dextrose, and 119 allocated to placebo gel.
Demographic variables were similar in babies and their mothers who were enrolled but not randomized because they did not become hypoglycemic (data not shown), and in those randomized to dextrose and placebo gel groups, although more boys were randomized to the placebo group (55 vs. 41%) (Table 8-1). Risk factors for hypoglycemia were also similar in both groups.
Table 8-1. Characteristics of mothers and babies at trial entry

<table>
<thead>
<tr>
<th>Maternal characteristics*</th>
<th>Dextrose gel (n=115 (50))</th>
<th>Placebo gel (n = 115 (50))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (y)</td>
<td>29.2 (6.0)</td>
<td>30.2 (6.5)</td>
</tr>
<tr>
<td>Gravidaity</td>
<td>2 (1–11)</td>
<td>2 (1–12)</td>
</tr>
<tr>
<td>Parity</td>
<td>1 (0–7)</td>
<td>1 (0–10)</td>
</tr>
<tr>
<td>BMI at booking (kg/m²)</td>
<td>27 (16–56)</td>
<td>26 (19–66)</td>
</tr>
<tr>
<td>Weight change during pregnancy (kg)</td>
<td>12.2 (8.0)</td>
<td>11.7 (6.8)</td>
</tr>
<tr>
<td>Diabetic women</td>
<td>46 (40)</td>
<td>46 (40)</td>
</tr>
<tr>
<td>Intended method of feeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>114 (99)</td>
<td>109 (95)</td>
</tr>
<tr>
<td>Infant formula</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Combination</td>
<td>0 (0)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Expressed breast milk prior to birth</td>
<td>24 (21)</td>
<td>23 (20)</td>
</tr>
<tr>
<td>Baby characteristics (n)</td>
<td>118</td>
<td>119</td>
</tr>
<tr>
<td>Male</td>
<td>48 (40)</td>
<td>65 (55)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3091 (824)</td>
<td>3031 (782)</td>
</tr>
<tr>
<td>Gestation (wk)</td>
<td>37.4 (1.6)</td>
<td>37.2 (1.6)</td>
</tr>
<tr>
<td>Singleton</td>
<td>100 (85)</td>
<td>99 (83)</td>
</tr>
<tr>
<td>Vaginal birth</td>
<td>73 (62)</td>
<td>74 (62)</td>
</tr>
<tr>
<td>Apgar score at five min &lt;5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blood glucose concentration at time of randomization (mg/dl)</td>
<td>41 (20–45)</td>
<td>41 (16–45)</td>
</tr>
</tbody>
</table>

Ethnicity
- New Zealand European: 63 (53) vs. 64 (54)
- Maori: 34 (29) vs. 37 (31)
- Other: 21 (18) vs. 18 (15)

Identified Risk factors for neonatal hypoglycemia†
- Infant of diabetic mother: 46 (39) vs. 46 (39)
- Late preterm (35 or 36 weeks): 41 (35) vs. 49 (41)
- Birth weight <2500 g: 30 (25) vs. 32 (27)
- Birth weight >4500 g: 12 (10) vs. 10 (8)
- Birth weight <10th centile: 13 (11) vs. 19 (16)
- Birth weight >90th centile: 26 (22) vs. 27 (23)
- Other: 6 (5) vs. 4 (3)

* 3 mothers appear in both columns because one twin was randomized to each treatment group, n= 227 mothers
† many babies had more than one risk factor for hypoglycemia
Values are number (%), mean (SD) or median (range)

There were 432 doses of gel administered, 215 in the dextrose and 217 in the placebo gel group. In both groups babies received a median of two doses of study gel of similar volume, resulting in those randomized to dextrose gel receiving a median of 0.3 (0.2 to 1.0) g/kg dextrose (Table 8-2).

8.4.1 Primary and Secondary Outcomes

Primary outcome data were available for 116 babies (98%) in the dextrose and 118 (99%) in the placebo gel group. Fewer babies in the dextrose group than in the placebo group met the criteria for treatment failure; (16 (14%) in the dextrose and 29 (24%) in the placebo group RR 0.56; 95% CI 0.32 to 0.97; p = 0.04) (Table 8-2).
Overall 98 babies (41%) were admitted to NICU, 46 of these (47%) for treatment of hypoglycemia. NICU admission rates were similar in both treatment groups, but babies who received dextrose gel were less likely to be admitted for hypoglycemia (16 (14%) vs. 30 (25%), RR 0.7; 95% CI 0.6 to 0.9; \( p = 0.03 \)).

Forty babies (17%) required additional treatment with dextrose. Babies randomized to dextrose gel were less likely to receive additional dextrose (12 (10%) vs. 28 (24%), RR 0.43; CI 0.23 to 0.80; \( p = 0.006 \)), but those who did receive intravenous dextrose received similar amounts (Table 8-2).
Table 8-2. Primary and Secondary Outcomes in babies randomized to dextrose or placebo gel

<table>
<thead>
<tr>
<th></th>
<th>Dextrose gel</th>
<th>Placebo gel</th>
<th>Relative risk or median difference</th>
<th>95% Confidence intervals</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babies (n)</td>
<td>118 (50)</td>
<td>119 (50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of study gel (ml/kg)</td>
<td>0.84 (0.43–2.44)</td>
<td>0.97 (0.47–2.49)</td>
<td>0.005</td>
<td>-0.01–0.02</td>
<td>0.45</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>16 (14)</td>
<td>29 (24)</td>
<td>0.56</td>
<td>0.32–0.97</td>
<td>0.04</td>
</tr>
<tr>
<td>Dextrose administered as</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study gel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>118</td>
<td>119</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(g/kg)</td>
<td>0.3 (0.2–1.0)</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open label gel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>6 (5)</td>
<td>13 (11)</td>
<td>0.49</td>
<td>0.19–1.25</td>
<td>0.14</td>
</tr>
<tr>
<td>(g/kg)</td>
<td>0.2 (0.1–0.4)</td>
<td>0.4 (0.2–0.6)</td>
<td>0.14</td>
<td>0.00–0.20</td>
<td>0.10</td>
</tr>
<tr>
<td>Intravenous bolus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>7 (6)</td>
<td>13 (11)</td>
<td>0.75</td>
<td>0.53–1.07</td>
<td>0.24</td>
</tr>
<tr>
<td>(g/kg)</td>
<td>0.2 (0.2–0.2)</td>
<td>0.2 (0.1–1.0)</td>
<td>0.0001</td>
<td>-0.004–0.20</td>
<td>0.96</td>
</tr>
<tr>
<td>Intravenous infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>8 (7)</td>
<td>17 (14)</td>
<td>0.71</td>
<td>0.52–0.96</td>
<td>0.09</td>
</tr>
<tr>
<td>(g/kg)</td>
<td>6.7 (2.0–10.6)</td>
<td>7.7 (3.7–14.6)</td>
<td>2.12</td>
<td>-0.42–5.58</td>
<td>0.10</td>
</tr>
<tr>
<td>Total Intravenous dextrose (g/kg)</td>
<td>7.1 (2.5–10.8)</td>
<td>8.3 (4.2–16.2)</td>
<td>2.55</td>
<td>0.50–5.84</td>
<td>0.09</td>
</tr>
<tr>
<td>Total dextrose from sources other than study gel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>12 (10)</td>
<td>28 (24)</td>
<td>0.43</td>
<td>0.23–0.80</td>
<td>0.006</td>
</tr>
<tr>
<td>(g/kg)</td>
<td>4.5 (0.2–10.8)</td>
<td>6.6 (0.2–16.2)</td>
<td>0.20</td>
<td>-2.1–5.5</td>
<td>0.51</td>
</tr>
<tr>
<td>Total dextrose from all sources</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>118 (100)</td>
<td>119 (100)</td>
<td>0.20</td>
<td>0.19–0.23</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>(g/kg)</td>
<td>0.3 (0.2–11.4)</td>
<td>0.0 (0.0–16.2)</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast feeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>112 (95)</td>
<td>113 (95)</td>
<td>1.00</td>
<td>0.56–1.78</td>
<td>0.98</td>
</tr>
<tr>
<td>Feeds per baby</td>
<td>13 (1–29)</td>
<td>11 (1–24)</td>
<td>-1.00</td>
<td>-3.00–0.00</td>
<td>0.16</td>
</tr>
<tr>
<td>Expressed breast milk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>100 (85)</td>
<td>97 (82)</td>
<td>1.11</td>
<td>0.81–1.53</td>
<td>0.64</td>
</tr>
<tr>
<td>Feeds per baby</td>
<td>4 (1–15)</td>
<td>6 (1–16)</td>
<td>1.00</td>
<td>0.00–2.00</td>
<td>0.02</td>
</tr>
<tr>
<td>Volume (ml/kg)</td>
<td>2.4 (0.1–96.1)</td>
<td>4.7 (0.0–43.6)</td>
<td>1.07</td>
<td>0.14–2.37</td>
<td>0.03</td>
</tr>
<tr>
<td>Infant formula</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>68 (58)</td>
<td>72 (60)</td>
<td>0.94</td>
<td>0.73–1.22</td>
<td>0.69</td>
</tr>
<tr>
<td>Feeds per baby</td>
<td>7 (1–21)</td>
<td>10 (1–24)</td>
<td>2.00</td>
<td>0.00–4.00</td>
<td>0.04</td>
</tr>
<tr>
<td>Volume (ml/kg)</td>
<td>41 (1–162)</td>
<td>58 (2–208)</td>
<td>11.06</td>
<td>-3.01–26.89</td>
<td>0.14</td>
</tr>
<tr>
<td>Admitted to NICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>43 (36)</td>
<td>55 (46)</td>
<td>0.82</td>
<td>0.64–1.05</td>
<td>0.15</td>
</tr>
<tr>
<td>For hypoglycaemia (n)</td>
<td>16 (14)</td>
<td>30 (25)</td>
<td>0.71</td>
<td>0.55–0.93</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Values are number (%), median (range), relative risk or median difference and 95% confidence intervals

Most mothers (98%) intended to breast feed, and 95% of babies were breast fed. Babies in the dextrose gel group received expressed breast milk less frequently than babies in the placebo group (median 4 vs. 6 feeds, median difference 1; 95% CI 0 to 2 feeds; p = 0.02) and received a smaller volume of expressed breast milk (median 2.4 vs. 4.7 ml/kg; median difference 1.1; 95% CI 0.1 to 2.4 ml/kg; p = 0.03). One hundred-forty babies (59%) received formula feeds, with babies in the dextrose gel group receiving fewer formula feeds (median
7 vs. 10 feeds; median difference 2; 95% CI 0 to 4 feeds; \( p = 0.04 \) but there were no differences between groups in the volume of formula feeds. At two weeks of age fewer babies in the dextrose gel group were formula feeding (5 (4%) vs. 15 (13%), RR 0.36; 95% CI 0.18 to 0.71; \( p = 0.04 \)).

There were 175 (74%) babies with continuous glucose monitoring, 88 (75%) in the dextrose and 87 (73%) in the placebo gel group. However, there were only 76 gel treatments (38 in each group) that could be analysed for the secondary outcomes involving continuous glucose monitoring.

Episodes of rebound hypoglycemia were uncommon, and occurred with similar frequency in both groups (Table 8-3). Episodes of recurrent hypoglycemia were less common in babies randomized to dextrose gel than those randomized to placebo when measured by interstitial but not blood glucose concentrations (11 vs. 30 episodes, rate ratio 0.44, 95% CI 0.21 to 0.86; \( p = 0.01 \)). The time taken for interstitial glucose concentration to be restored was similar in both treatment groups (20.3 (0.2 to 215.4) min in the dextrose vs. 22.8 (1.9 to 165.2) min in the placebo group, median difference 4.9 min; 95% CI -4.4 to 19.4 min; \( p = 0.13 \)). The total duration of low interstitial glucose concentrations was not significantly reduced by dextrose gel (Table 8-3).
### Table 8-3. Rebound and recurrent episodes and duration of hypoglycemia in babies randomized to dextrose or placebo gel

<table>
<thead>
<tr>
<th></th>
<th>Dextrose gel</th>
<th>Placebo gel</th>
<th>Rate ratio or median difference</th>
<th>95% Confidence Interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>118 (100)</td>
<td>119 (100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rebound episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes per baby</td>
<td></td>
<td></td>
<td>1.46</td>
<td>0.67–3.26</td>
<td>0.33</td>
</tr>
<tr>
<td>nil</td>
<td>104 (88)</td>
<td>109 (92)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>one</td>
<td>12 (10)</td>
<td>9 (7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>two</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recurrent episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes per baby</td>
<td></td>
<td></td>
<td>0.89</td>
<td>0.55–1.44</td>
<td>0.66</td>
</tr>
<tr>
<td>nil</td>
<td>90 (76)</td>
<td>91 (76)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>one</td>
<td>23 (20)</td>
<td>22 (19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>two</td>
<td>5 (4)</td>
<td>4 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥three</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Interstitial glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>25 (21)</td>
<td>30 (25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rebound episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes per baby</td>
<td></td>
<td></td>
<td>1.20</td>
<td>0.40–3.57</td>
<td>0.73</td>
</tr>
<tr>
<td>nil</td>
<td>20 (80)</td>
<td>25 (83)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>one</td>
<td>3 (12)</td>
<td>3 (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>two</td>
<td>2 (2)</td>
<td>2 (7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recurrent episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes per baby</td>
<td></td>
<td></td>
<td>0.44</td>
<td>0.21–0.86</td>
<td>0.01</td>
</tr>
<tr>
<td>nil</td>
<td>16 (64)</td>
<td>18 (60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>one</td>
<td>8 (32)</td>
<td>4 (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>two</td>
<td>0 (0)</td>
<td>3 (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥three</td>
<td>1 (4)</td>
<td>5 (17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of low interstitial glucose concentrations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>32 (27)</td>
<td>36 (30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (min/baby)</td>
<td>81 (0–840)</td>
<td>164 (0–1064)</td>
<td>48</td>
<td>-7–124</td>
<td>0.23</td>
</tr>
<tr>
<td>Proportion of time (%)</td>
<td>3.0 (0.0–31.8)</td>
<td>6.1 (0.0–37.9)</td>
<td>1.8</td>
<td>-0.2–4.6</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*Over first 48 h after birth for babies with at least 40 h of satisfactory continuous glucose monitoring

Values are number (%) or median and 95% confidence intervals

The gel treatment was well tolerated, with similar numbers of doses reported as tolerated in both groups (213/215 (99%) dextrose and 211/217 (97%) placebo gel doses). Parents also reported the gel treatment was an acceptable and easy treatment for their babies (113/116 (97%) dextrose and 113/118 (96%) placebo gel group).

There were no serious adverse events. Three babies, all in the placebo group, each had one blood glucose concentration of 16 mg/dl (0.9 mmol/l). There were no other adverse events.

Pre-specified sub-group analysis showed no differences in response between babies with different risk factors. If the three babies for whom primary outcome was not available were
excluded, findings remain unchanged (treatment failure 14 (12%) in the dextrose gel and 28 (24%) in the placebo group, RR 0.5; 95% CI 0.28 to 0.90; p = 0.01).

8.5 Discussion

We have shown that treatment with 40% dextrose gel is more effective than feeding alone in reversing neonatal hypoglycemia in at-risk late preterm and term babies in the first 48 hours after birth. Further, babies who received dextrose gel were less likely to be admitted to NICU for management of hypoglycemia, to receive additional dextrose, receive formula feeds, and to be formula fed at two weeks of age. Dextrose gel did not increase the risk of rebound or recurrent hypoglycemia, was well tolerated and was not associated with adverse effects.

Oral carbohydrate is the first line treatment for conscious diabetic patients for the management of hypoglycaemia (Clarke, T et al. 2009). Concentrated glucose gel or honey is commonly administered to the unconscious hypoglycemic patient when venous access is difficult or glucagon is not available. Sublingual sugar is reported to be as effective as intravenous dextrose in treating hypoglycemia in children with malaria (Barennes, Valea et al. 2005; Graz, Dicko et al. 2008). Dextrose gel has been recommended for the management of neonatal hypoglycaemia (Ogilvy-Stuart and Midgley 2006) and there are anecdotal reports of improvement in blood glucose concentration following dextrose gel via the buccal mucosa (Ang, Koh et al. 1990; Bourchier, Weston et al. 1992). However, the only randomized controlled trial using dextrose gel 400 mg/kg did not to show that treatment increased blood glucose concentrations (Troughton, Corrigan et al. 2000). Our study is the first report in babies showing that buccal dextrose gel is a safe effective treatment for the management of hypoglycemia.

One early concern was the possibility that dextrose gel may adversely affect breast feeding, since receipt of any supplements in the neonatal period is reported both to delay the establishment of and decrease the duration of breast feeding (Blomquist, Jonsbo et al. 1994; Dewey, Nommsen-Rivers et al. 2003; Perrine, Scanlon et al. 2012). However, our data show that babies in the dextrose gel group required fewer formula feeds and less expressed breast milk. If the mother’s intention was to breast feed and the baby was hypoglycemic, mothers were encouraged either to feed the baby or express breast milk. Some women may have felt pressured to provide breast milk, which may have negatively affected the establishment of breast feeding. Furthermore, fewer babies in the dextrose gel group received additional dextrose, either intravenously or as open label gel following treatment failure. Thus, babies in the dextrose gel group received less additional clinical intervention, and therefore spent less time separated from their parents. All of these factors
may have contributed to our finding that at two weeks of age formula feeding was less common in babies randomized to receive dextrose gel. We speculate that providing a treatment which allows the mother and baby to remain together while supporting metabolic transition to extra-uterine life may reduce maternal anxiety and support breast feeding establishment in the early post-natal period.

Perhaps surprisingly, continuous glucose monitoring data showed that the time taken for the interstitial glucose concentration to recover following gel treatment was similar in both groups. However, these findings are from a subset of babies who had continuous glucose monitoring, and of these, fewer than half of the treatment episodes were available for analysis. There were two reasons for this. Firstly, although the continuous glucose monitor was placed as soon after birth as possible, it takes one hour to initialise. This meant that in 152 cases the first gel treatment was given before continuous glucose data were available. Secondly, there were 24 episodes of hypoglycemia when, although the blood and interstitial glucose concentrations were <47 mg/dl at the time of diagnosis of the hypoglycemic episode, the interstitial glucose concentration was ≥47 mg/dl at the time of gel administration and therefore the secondary outcomes could not be determined.

One potential risk of administering dextrose gel is the possibility of causing rebound hypoglycemia secondary to stimulation of insulin secretion. Lilien and colleagues reported that a mini-bolus of 200 mg/kg intravenous dextrose improved blood glucose concentrations without rebound hyperglycemia (Lilien, Pildes et al. 1980). We chose the same dose for buccal glucose administration, and also found that rebound hypoglycemia was uncommon and occurred with similar frequency in both groups. However, consistent with the overall findings that dextrose gel reduced treatment failure, recurrent hypoglycemia was less common in babies who received dextrose gel when measured by continuous interstitial glucose monitoring, despite these babies receiving less frequent feeds. Furthermore, babies who received dextrose gel appeared to spend less time hypoglycemic overall than babies who received placebo gel, although this finding did not reach statistical significance.

Babies enrolled in this trial were similar to the majority of babies who are at risk of hypoglycemia in the immediate neonatal period. Although dextrose gel did not decrease admission to NICU in this study, most likely because babies were admitted for a variety of reasons other than hypoglycemia, it did reduce admission for hypoglycemia. This suggests that, in babies at risk of hypoglycemia but without other co-morbidities, dextrose gel treatment may potentially avert the need for NICU admission, reducing costs and keeping mother and baby together. We cannot extrapolate from our data whether dextrose gel may
be effective treatment in babies of other gestational or postnatal ages. Neither can we
determine if the dose we have used is the ideal dose. Further randomized studies are
needed to clarify these issues.

Dextrose gel treatment has a number of advantages including ease of administration and
low cost. Babies tolerated both the administration of the gel and the gel itself. Both parents
and staff reported gel treatment to be acceptable and simple to administer. Dextrose gel is
inexpensive and can be purchased commercially for approximately US $70/100 ml or $2
per baby, can easily be made in the hospital pharmacy, and is stable at room temperature.
Therefore, dextrose gel may also be useful in resource-poor settings where hypoglycemia
is common and under diagnosed (Anderson, Shakya et al. 1993; Osier, Berkley et al. 2003;
Allen and Jeffery 2006).

We have shown that dextrose gel is an effective, well tolerated and acceptable treatment
for neonatal hypoglycemia. Dextrose gel should be considered as first line management of
late preterm and term hypoglycemic babies in the first 48 hours after birth.

8.6 Acknowledgements

We wish thank all the Sugar babies and their families for being part of the study and the
staff at Waikato Women’s Hospital, particularly the Research Nurses Catherine McBride
and Paula Middlemiss. We acknowledge the support of the Independent Data and Safety
Monitoring Committee: Caroline Crowther, Frank Bloomfield and David Graham. Members
of the CHYLD data team have assisted with data entry and the analyses: Greg Gamble,
Janine Paynter, Pei Wen Chen, Tineke Crawford, Yann Henry, Grace Knight and Rebecca
Young. The Sugar Babies Study was funded from the Waikato Medical Research
Foundation, the Auckland Medical Research Foundation, the Maurice and Phyllis Paykel
Trust, the Health Research Council of New Zealand, and the Rebecca Roberts Scholarship.

8.7 References


277.


Chapter 9: Implications for practice and future research

9.1 Measurement of neurological function

Determining the relationship between neurological function and blood glucose concentration in clinical practice has been difficult. Ideally we need to detect changes in neurological function related to low glucose concentrations prior to injury occurring. The only cot-side tool widely used in the assessment of neurological function in babies is the amplitude integrated electroencephalography (aEEG) monitor. Conventional EEG is a gold standard for measuring brain function and changes have been reported in qualitative and quantitative EEG parameters associated with low glucose concentrations (Auer, Olsson et al. 1984; Tallroth, Lindgren et al. 1990; Bjorgaas, Sand et al. 1998). However, standard EEG is not practical in the Newborn Intensive Care Unit and provides only intermittent monitoring. There have been case reports showing decreased background activity and burst suppression during profound hypoglycaemia using the cot-side aEEG (Hellstrom-Westas, Rosen et al. 1989; ter Horst, Brouwer et al. 2004). We therefore sought to determine if the cot-side aEEG could be useful in the assessment of neurological function related to low glucose concentrations.

We were aware from the pathological and the magnetic resonance imaging literature that the occipital lobes of the brain may be particularly sensitive to the injury caused by low glucose concentrations. Therefore we altered the cot-side aEEG monitor to allow for detection of signal from the occipital areas of the brain.

In our first pilot study we induced low glucose concentrations using insulin in newborn lambs, seeking to identify characteristic changes in the aEEG associated with the changes in blood glucose concentrations. In our second study, the BABIES Study, we sought to undertake similar measurements in babies to determine the relationship between brain function using the cot-side aEEG and blood and interstitial glucose concentrations, while also measuring plasma concentrations of alternate cerebral fuels.

There were no changes related to blood glucose concentrations in either the lamb or BABIES study on any aEEG parameter analysed, including amplitude, continuity, and spectral edge frequency. There were also no differences when we compared these findings from the left and right P3-P4 and occipital O1-O2 montages (Harris, Battin et al. 2009; Harris, Weston et al. 2011). Our findings show the current automated analysis parameters
on the cot-side aEEG do not detect characteristic changes related to hypoglycaemia and therefore are not useful for this purpose. However, a recent small study in extremely preterm babies has reported increased interval between bursts of electrical activity in the EEG associated with low blood glucose concentrations (Wikstrom, Lundin et al. 2011). In the future it may be possible to reanalyse our data using interburst interval analysis or other quantitative EEG parameters that may prove more useful in detecting altered brain function during hypoglycaemia.

One reason why we failed to detect changes in aEEG associated with hypoglycaemia may be that episodes of severe hypoglycaemia were uncommon in our study. Babies were treated immediately hypoglycaemia was diagnosed and in the 24 babies with matched aEEG and low glucose concentrations, the lowest glucose concentration ranged from 1.5 to 2.5 mmol/L. Others have reported decreased aEEG background when the blood glucose concentration falls below 1.5 mmol/L (Hellstrom-Westas, Rosen et al. 1989) and burst suppression when the blood glucose concentrations are <1.0 mmol/L (ter Horst, Brouwer et al. 2004). Thus it is possible that more severe hypoglycaemia than we observed may result in detectable changes in the cot-side aEEG. However, we were seeking to detect subtle changes that might be useful for clinical staff in identifying babies at risk of neurological injury before such injury occurred, and it is clear from our data that cot-side aEEG is not clinically useful for this purpose.

Compared to the amount of matched aEEG and interstitial glucose data we collected during normoglycaemia (>200 days), we had only a small amount of matched data during hypoglycaemia (103 hours). There were several reasons for this, including prompt treatment of hypoglycaemia, the time required to set up and initialise the continuous aEEG and glucose monitoring (>1 hour), and difficulty in maintaining good attachment of the gel electrodes, particularly to the occipital area. Needle electrodes are commonly used in clinical practice for recording EEGs, are quickly inserted, provide a superior signal quality and require less attention. After experiencing considerable difficulty with gel electrode attachment resulting in the loss of EEG data during episodes of hypoglycaemia, we obtained approval from the ethics committee for an amendment to our protocol to include the use of needle electrodes for babies in whom gel electrodes proved unsatisfactory. We used needle electrodes in four babies, and in each case obtained immediate good quality EEG data for up to 72 hours without evidence of adverse effects at the insertion sites. We would therefore recommend that future investigators should consider using needle electrodes for prolonged EEG recordings in babies who are not encephalopathic. However, it is unlikely that collecting more EEG data would alter our conclusions. A retrospective power calculation using a two-tailed design with alpha = 0.05 and beta = 0.2, showed that
we had 80% power to detect a difference in EEG parameters between hypoglycaemic and non-hypoglycaemic periods of 15% for aEEG min, 23% for intensity, 10% for spectral edge frequency and continuity 25µV, and 19% for continuity 50µV. Differences smaller than these are unlikely to be clinically useful for diagnostic purposes.

When we reviewed the raw EEG we found two lambs had experienced electrical seizures during hypoglycaemia; one had an associated clinical seizure. Some hours after the experiment was complete another lamb had a clinical seizure. One baby also had 33 asymptomatic seizures following repeated and prolonged episodes of hypoglycaemia, with the majority of the seizures occurring when the interstitial glucose concentration was >2.6 mmol/L.

Although others have reported seizure activity following hypoglycaemia (ter Horst, Brouwer et al. 2004), our focus was on detecting changes on the EEG at the time of low glucose concentrations, and it is likely that our findings are an underestimate of asymptomatic late seizure activity. This is because we only reviewed the raw EEG to detect seizures in babies who had matched EEG and low interstitial glucose recordings. Since the interstitial glucose monitor requires one hour for initialising, we were unable to measure episodes of low interstitial glucose concentration until at least an hour after admission to NICU. However, 75 babies were hypoglycaemic prior to admission and of these 61 babies (81%) had good quality EEG data soon after admission, but only 21 (28%) had matched EEG and low glucose concentration data and thus were reviewed for seizure activity. We therefore plan further analysis of the EEG data to determine the incidence and time of onset of asymptomatic seizure activity in babies who have been hypoglycaemic. Further, all babies studied are being invited to join a follow-up study which examines neurodevelopmental outcomes at 2 and 4.5 years and thus we will be able to determine if there is a relationship between asymptomatic electrical seizures in the first week after birth and later outcomes.

Most reports about the usefulness of aEEG monitoring are about neurologically abnormal babies. There are three small reports from neurologically healthy late-preterm and term babies and reported reference ranges showing changes in aEEG parameters with advancing postnatal age (Verma, Archbald et al. 1984; Thornberg and Thiringer 1990; Korotchikova, Connolly et al. 2009). All of these have analysed short periods of aEEG recording, and the earlier reports only used single channel aEEG measurements. We have more than 200 days of aEEG recordings (and other physiological clinical parameters) in babies with no clinical evidence of encephalopathy from soon after admission to the Newborn Intensive Care for up to a week after birth. Further analysis of these data to determine longitudinal changes in aEEG parameters and sleep wake cycling has the
potential to provide additional normative data for comparison with aEEG measurements in babies suspected of having encephalopathy.

9.2 Alternative cerebral fuels

Glucose is normally the major fuel for cerebral oxidative metabolism. Under some circumstances alternative fuels can be utilised including lactate, ketones, glycerol, fatty acids and some amino acids. However, the relationship between blood glucose concentrations, alternative fuels and brain function remains undefined.

Although it is likely that some babies with low blood glucose concentrations may be protected from brain damage by the availability of alternative cerebral fuels (Rozance and Hay 2006), there is only a small body of evidence to support this contention. Hawdon and colleagues (Hawdon, Ward-Platt et al. 1992) reported concentrations of alternative cerebral fuels from heel prick blood samples in the first week after birth, and found variation in these concentrations dependent on gestational age and milk type. Term babies had higher concentrations of alternative cerebral fuels than preterm babies, and breast fed babies had higher concentrations of ketones than those fed infant formula. Interestingly, none of the preterm and only some term babies were able to demonstrate a ketogenic response to hypoglycaemia regardless of feeding type. There have been a number of reports showing the concentrations of alternative cerebral fuels are low in babies at risk of neonatal hypoglycaemia (Koh, Aynsley-Green et al. 1988; Hawdon, Weddell et al. 1993; de L Costello, Par et al. 2005). There are also two small reports suggesting early use of infant formula, a common treatment for neonatal hypoglycaemia, may inhibit ketogenesis (Hawdon, Ward-Platt et al. 1992; de Rooy and Hawdon 2002).

Measuring alternative cerebral fuels in babies commonly requires a large blood sample and rapid analysis, and is therefore not routinely undertaken in clinical practice. Our laboratory developed techniques which allowed us to analyse alternative cerebral fuels in small amounts of blood. In both the lamb study and BABIES study we found the concentrations of alternative cerebral fuels were low during episodes of hypoglycaemia. We induced hypoglycaemia in the lambs using insulin and the high concentrations of insulin would have prevented the lambs from producing alternative fuels. However, many babies at risk also cannot produce alternative cerebral fuels soon after birth when the majority of the hypoglycaemic episodes occur. The infant of the diabetic mother, for example, has transient hyperinsulinism and small for gestational age and preterm babies have limited fat stores from which to produce ketones (Ward-Platt and Deshpande 2005; Hay 2012).
A few studies have shown that healthy breast fed babies have lower blood glucose and higher ketone body concentrations than formula fed babies (Hawdon, Ward-Platt et al. 1992; de Rooy and Hawdon 2002). The mechanism for this is unclear but it has been speculated that the high fat content in human breast milk encourages ketogenesis. However, this has led to an assumption in clinical practice that breast fed babies at risk of hypoglycaemia are protected from neurological insult because of the availability of alternative cerebral fuels (de Rooy and Hawdon 2002; de Rooy and Johns 2010). Our data do not support these assumptions. Rather, our data show that breast fed babies at risk of hypoglycaemia have low concentrations of alternative cerebral fuels soon after birth, and that during episodes of hypoglycaemia concentrations of alternative fuels remain low. Thus, exclusively breast fed babies at risk of hypoglycaemia may also be at risk for neurological injury, particularly as the volume of breast milk produced in the first 48 hours after birth is also low (Saint, Smith et al. 1984).

9.3 Measurement of blood and interstitial glucose

The measurement of blood glucose concentrations is fundamental to the diagnosis of hypoglycaemia but fraught with difficulties. Currently, blood glucose concentration is measured intermittently, usually 3 to 4 hourly initially; most frequently the sample is taken from a heel-prick lance which causes pain. The majority of babies are distressed by the sampling, and most parents find blood sampling from their babies a stressful event. Further, the technique of taking a blood sample from a baby requires skill; the foot needs to be warmed, and the depth and angle of the heel-prick needs to allow for blood to flow freely. It is essential that the sample is analysed immediately to avoid inaccurate results, and not uncommon for samples to have to be repeated. Coupled with these technical difficulties, the very nature of the intermittent sampling means that episodes of hypoglycaemia potentially are missed. Ideally what is needed is a non-invasive continuous approach to measuring blood glucose concentrations.

9.3.1 Initialisation of continuous glucose monitors

Continuous interstitial glucose monitoring is a less invasive method of measuring glucose concentrations that was developed for the diabetic population and has been shown to be safe, reliable and lead to improved metabolic control (De Block, Vertommen et al. 2008). However, the sensor is placed subcutaneously and four blood glucose measurements are required in each 24 hour period for calibration purposes. Following the insertion of the sensor, data collection is delayed for an hour while the monitor initialises. This means that at best interstitial glucose concentration can be measured starting from 70 to 90 minutes after birth, and therefore it is impossible to measure the initial decrease in glucose.
concentrations soon after birth (Harris, Weston et al. 2010). However, this may not be important, and may even be an advantage, as blood glucose concentrations normally decrease after birth in healthy newborns, reaching a nadir at one to two hours of age, and then increase (Srinivasan, Pildes et al. 1986). Therefore, normal physiological changes will not be detected by interstitial glucose monitoring, and this may reduce unnecessary treatment. However, episodes of low glucose concentrations beyond the first two hours after birth could be detected. Since later or prolonged low glucose concentrations representing failure of metabolic adaptation may be associated with neurodevelopmental impairment, real-time continuous glucose monitoring might allow for prompt recognition and management of these later more significant episodes while avoiding early over-treatment.

9.3.2 Potential advantages

Continuous glucose monitoring was first reported to be used with babies in 2005 (Beardsall, Ogilvy-Stuart et al. 2005) and has been shown to be safe and reliable in very low birth weight infants (Beardsall, Vanhaesebrouck et al. 2008; Platas, Lluch et al. 2009). However, continuous glucose monitoring had not been investigated in larger babies at risk of neonatal hypoglycaemia. There are potential advantages in continuous glucose monitoring over the current intermittent heel prick measurements. Continuous monitoring may detect otherwise undiagnosed episodes of hypoglycaemia, and provides for the first time, measurement of the severity, duration and recurrence of hypoglycaemic episodes, allowing for evaluation of the baby's response to treatment. Further, fewer heel-prick glucose measurements are needed, so that babies experience less repetitive pain. We therefore sought to determine the usefulness of continuous glucose monitoring in babies at risk of hypoglycaemia.

9.3.3 Agreement and accuracy

Continuous glucose monitoring was designed to measure high concentrations of glucose in diabetics. Evidence about its reliability during hypoglycaemia is scarce and there have been no investigations in babies. Our initial investigations therefore sought to determine the accuracy of continuous interstitial glucose monitoring during hypoglycaemia by comparing the results with conventional gold standard intermittent blood glucose measurement using the glucose oxidase method. We did this in newborn lambs during insulin-induced hypoglycaemia, as it would be unethical to induce hypoglycaemia in babies.

When we compared blood and interstitial glucose concentrations in individual lambs the results of the two methods of glucose measurement were very similar. However, when results for all lambs with paired blood and interstitial glucose concentrations were assessed, we found only moderate agreement, with a mean difference of -0.7 mmol/L (95% CI -2.8 to
1.4 mmol/L). This difference suggests that continuous glucose monitoring may not be accurate enough to be useful in the management of babies with neonatal hypoglycaemia. However, the red blood cells in lambs are less permeable to glucose than are human red cells, and we found a closer agreement between continuous glucose monitoring and blood glucose measurements in babies than in lambs (mean difference 0.0 mmol/L, 95% CI -1.1 to 1.1 mmol/L). This suggests continuous glucose monitoring may be sufficiently accurate to be useful in clinical practice, with the potential to provide the clinician with immediate access to data about the severity, duration, and recurrence of hypoglycaemic episodes as well as response to treatment.

Our data show continuous glucose monitors provide reasonably accurate measurements of interstitial glucose concentrations, showing trends over time and response to treatment. Beardsall and colleagues have recently reported a case study showing the usefulness of this approach in informing treatment decisions, leading to improved glucose control and also reducing the requirement for heel-prick blood sampling (Beardsall, Pesterfield et al. 2011). It is possible that the use of continuous glucose monitoring in clinical practice could contribute to improved outcomes, as the availability of continuous real-time data may allow for prompt diagnosis and treatment, which has been shown to improve neurological outcome for babies with ongoing metabolic dysfunction (Hussain, Blankenstein et al. 2007).

9.3.4 The Lag-time

In the lamb experiment the agreement between blood and interstitial glucose was poor during the recovery phase of the experiment, when the lamb received a rapid bolus of intravenous dextrose. The blood glucose concentration consistently increased swiftly, and the interstitial glucose concentration increased over 10 to 20 minutes. The delay between blood and interstitial glucose concentrations has been previously described and has been termed ‘lag-time’ (Rebrin, Steil et al. 1999; Caplin, Leary et al. 2003). This lag-time would be expected to be important during correction of hypoglycaemia with a bolus of intravenous dextrose, and clinicians would need to be aware of it if using a continuous glucose monitor. However, this need not be a disadvantage as continuous glucose monitors provide real-time data which allow the clinician to observe a baby’s response to treatment. Further, it is routine in clinical practice following an intravenous bolus of dextrose for the blood glucose concentration to be measured 30 minutes following treatment. Our data show the discrepancy between interstitial and blood glucose concentrations measurements after a bolus of dextrose had resolved within 30 minutes in both lambs and babies.
9.3.5 Detection of low glucose concentrations

Continuous interstitial glucose monitoring detected many more episodes of low glucose concentrations than intermittent blood glucose measurement, with many episodes lasting longer than 30 minutes, and many babies having more than one episode. Furthermore, we found babies were continuing to have episodes of low glucose concentrations beyond the time when clinicians would have previously assumed that the risk of hypoglycaemia had passed; for example when babies were tolerating full oral feeds.

Previous publications have also reported that continuous interstitial glucose monitoring detects many more episodes of low glucose concentrations in the first week after birth in very low birth weight babies (Beardsall, Vanhaesebrouck et al. 2008; Platas, Lluch et al. 2009). These findings are concerning because neonatal hypoglycaemia is linked with poor neurological outcome, and many at-risk babies appear to be having undetected episodes that are not treated. However, although it is clear that babies with prolonged and severe hypoglycaemia may have poor neurological outcomes (Lucas, Morley et al. 1988; Stenninger, Flink et al. 1988; Duvanel, Fawer et al. 1999; Menni, de Lonlay et al. 2001; Caraballo, Sakr et al. 2004), there is very little evidence that treating low glucose concentrations in babies improves neurodevelopmental outcomes, particularly if episodes are neither prolonged nor severe. Thus, introducing continuous glucose monitoring for all at-risk babies is likely to increase the diagnosis and therefore treatment of low glucose concentrations, but may not improve outcomes; in fact the resulting prolonged hospitalisation and separation from parents may cause harm.

Babies from both the BABIES and Sugar Babies studies are being invited to join our follow up study (The CHYLD Study, Children with Hypoglycaemia and their Later Development) which aims to determine neurodevelopmental outcome at 2 and 4.5 years of babies at risk of neonatal hypoglycaemia. Our hypothesis is that neuropsychological development of 2 and 4.5 year old children is related to the severity, duration and frequency of low glucose concentrations in the neonatal period. We expect that an increased understanding of the actual risks associated with different patterns of hypoglycaemia will contribute to the ongoing discussion concerning the appropriate management of babies at risk of hypoglycaemia. Further, we hope to be able to identify babies for whom intervention is not necessary, thereby reducing the rate of iatrogenically lengthened hospital stays.
9.3.6 Further investigations

9.3.6.1 Continuous glucose monitoring in healthy newborn babies

Use of continuous interstitial glucose monitoring has only been reported in babies identified to be at risk of either hypo- or hyperglycaemia (Beardsall, Ogilvy-Stuart et al. 2005; Platas, Lluch et al. 2009; Harris, Weston et al. 2010; Beardsall, Pesterfield et al. 2011). Previous cross-sectional studies of blood glucose concentrations at different times after birth in normal term babies suggest that 12% of them will have blood glucose concentrations <2.6 mmol/L in the first one to four hours after birth, and 10% will continue to have hypoglycaemia over the first six days (Srinivasan, Pildes et al. 1986). It would be useful to determine longitudinal changes in glucose concentrations after birth in healthy late preterm and term babies using continuous glucose monitoring to better define physiological changes in different groups of babies.

There is little doubt that these data would be useful, but this type of data collection is fraught with ethical challenge. There is little potential benefit to the individual baby and a risk of potential harm, as otherwise healthy newborn babies would be required to undergo both intermittent and continuous glucose monitoring. Both methods of analysing glucose concentrations cause brief pain when the skin is punctured. All babies would require four blood glucose samples taken daily, in addition to the insertion of the continuous glucose sensor. Further, if episodes of low glucose concentrations were detected, researchers may feel obliged to provide treatment because of the link with neurodevelopmental impairment. This would have the potential to add further harm such as via disruption of breast feeding and separation of mother and baby, and would also defeat the intended purpose of the study to observe physiological changes.

9.3.6.2 Glucose concentrations and feeding

Our survey showed that feeding was the most common treatment for hypoglycaemia (Harris, Weston et al. 2009). However, there was considerable variation in both the volume and frequency of formula feeds offered to babies, suggesting clinicians are unsure about the best feeding regime. There is a paucity of evidence about the effect of feeding on blood glucose concentrations and the published reports have flaws, including the method used to analyse the blood samples. However, taken together the findings from these reports suggest factors such as gestation, post-natal age, and the type and volume of milk may determine changes in blood glucose concentrations after feeding (Beard, Panos et al. 1966; Lucas, Bloom et al. 1978; Lucas, Boyes et al. 1981; Hawdon, Ward-Platt et al. 1992; Sweet, Hadden et al. 1999). Beard and colleagues reported that starved preterm and term babies demonstrated a progressive decrease in blood glucose concentrations with advancing
postnatal age up to 72 hours (Beard, Panos et al. 1966) and others have shown that blood glucose concentrations decrease between feeds (Lucas, Boyes et al. 1981; Hawdon, Ward-Platt et al. 1992). It would be useful to determine the relationship between feeding and blood glucose concentrations, as this could contribute to the development of improved feeding regimes, and reduce episodes of hypoglycaemia.

Continuous glucose monitoring has been used to detect changes in blood glucose concentrations related to feed type and volume in diabetic adults and children, and these findings have contributed to changes in management which have improved metabolic control (Melanson, Westerterp-Plantenga et al. 1999; White and Jones 2011). We are planning further exploration of our data to describe the relationship between feeding and blood and interstitial glucose concentrations in babies who did and did not become hypoglycaemic. This analysis could contribute to evidenced based feeding and blood sampling regimes in babies at risk, which in turn may prevent episodes of hypoglycaemia while minimising blood tests.

9.3.6.3 Glucose concentrations and dextrose gel

Our data show that dextrose gel improved the blood glucose concentrations. However, we are yet to determine the time of onset and duration of effect of the dextrose gel. Seventy-five percent of the randomised babies had useful continuous glucose monitoring data, and these data will help us determine if the effect of dextrose gel differs depending on postnatal age, gestation, identified risk factors, and feeding. Findings from these analysis may also help to determine the optimal interval and frequency for repeat blood glucose concentration measurements following treatment.

9.4 Incidence of neonatal hypoglycaemia and screening

Prior to our study there were no published data about the incidence of neonatal hypoglycaemia in babies commonly identified as being at risk in the first 48 hours (Harris, Weston et al. 2012). We sought to determine the incidence of hypoglycaemia in a cohort of at-risk babies who were being screened using a reliable method of analysis for blood glucose concentrations in the first 48 hours after birth.

We used our local screening protocol for the Sugar Babies Study and this protocol differs from published recommendations (Canadian Paediatric Society 2004; Adamkin and Committee on Fetus Newborn 2011) in two ways. Firstly, the published guidelines recommend an individualised screening regime depending on the identified at risk group. For example, it is recommended that large babies and infants of diabetics have glucose measurements discontinued 12 hours after birth. Secondly, both guidelines recommend a
lower blood glucose concentration for treatment when the baby is less than four hours old, whereas our protocol used the same clinical threshold for treatment (<2.6 mmol/L) regardless of postnatal age. Our data show the incidence of hypoglycaemia was similar in all at risk groups in the first 48 hours after birth, and no evidence to support discontinuing blood glucose monitoring after 12 hours. Screening all at-risk babies using the same protocol may be useful for the clinical team, as it would support consistency of care. However, without evidence that diagnosis and treatment of neonatal hypoglycaemia improves the outcome for at-risk babies, increasing the recommended duration of blood glucose screening would be difficult to justify.

Neonatal hypoglycaemia was common in our cohort, with half the babies becoming hypoglycaemic. Further, our reported incidence may be an underestimate because blood glucose monitoring was to be discontinued after three blood glucose measurements >2.6 mmol/L unless there was clinical concern about the risk of hypoglycaemia. Amongst the hypoglycaemic babies, 95 (37%) had their first episode of low glucose concentrations after three blood glucose concentrations >2.6 mmol/L, suggesting that other babies may also experience undetected episodes of hypoglycaemia after screening is discontinued.

Although it is clear that blood glucose monitoring for hypoglycaemia should start soon after birth, since this is when most hypoglycaemia occurs, the best time for monitoring to be discontinued remains unclear. Of the babies who had episodes of hypoglycaemia in the first 24 hours, 20% continued to have episodes in the next 24 hours. Others have shown preterm babies continue to have episodes up to one month after birth (Lucas, Morley et al. 1988; Hume, McGeechan et al. 1999). Further, findings from the BABIES Study using continuous glucose monitoring show that some babies from each at risk group continued to have episodes of low glucose concentrations after 48 hours of monitoring, and many of these episodes lasted longer than 30 minutes. As most episodes were undetected by intermittent blood glucose measurements, many babies may experience undiagnosed and untreated episodes of hypoglycaemia. Our studies were not designed to determine how long babies continued to have episodes of low glucose concentrations, and a specifically designed study involving prolonged monitoring would be required to determine the best time to discontinue blood glucose monitoring.

9.5 Treatment

9.5.1 Survey

We sought to determine the current management of neonatal hypoglycaemia within the Australian and New Zealand Neonatal Network (ANZNN). Publications prior to ours from the United Kingdom and Australia had reported significant variation between clinicians in
screening, diagnosis, and management of hypoglycaemia. Our data show that respondents within the ANZNN agreed that treatment should be provided when the blood glucose concentration was <2.6 mmol/L. These findings suggest the Koh and Lucas publications from 1988 still underpin current clinical practice (Koh, Aynsley-Green et al. 1988; Lucas, Morley et al. 1988).

However, we were concerned to find that over half of the respondents reported blood glucose measurements are made using point-of-care analysers designed for diabetics and not for the diagnosis of neonatal hypoglycaemia. Point-of-care analysers have been shown to be inaccurate for the assessment of glucose concentration in babies (Bonacruz, Arnold et al. 1996; Ho, Yeung et al. 2004; Hay, Raju et al. 2009; Beardsall 2010). However, they are attractive to clinicians because they provide a prompt result and are relatively inexpensive when compared with the gold standard laboratory analysers. This means that many babies within the ANZNN may be treated unnecessarily, and of more concern, many may not receive treatment when required. There remains an urgent need for an accurate point-of-care analyser to be developed for babies.

9.5.2 The Sugar Babies Study

We found our nursery was the only nursery which had a protocol for the treatment of asymptomatic hypoglycaemia with 40% dextrose gel. This treatment was established in the Waikato Newborn Intensive care in 1991 and the following year in postnatal areas. The clinicians in our nursery were confident that dextrose gel reversed hypoglycaemia, and oral carbohydrate is the first line treatment for hypoglycaemic children and adults (Clarke, T et al. 2009). However, the available evidence about the use of 40% dextrose gel in babies is conflicting (Ang, Koh et al. 1990; Bourchier, Weston et al. 1992; Troughton, Corrigan et al. 2000).

We therefore performed a randomised controlled trial (The Sugar Babies Study) to determine if 40% dextrose gel was more effective than feeding alone in late-preterm and term babies in the first 48 hours after birth. These babies represent the majority of babies affected by neonatal hypoglycaemia.

We have shown that 40% dextrose gel is an effective, simple, well tolerated treatment for neonatal hypoglycaemia. Furthermore, treatment with dextrose gel did not disturb the establishment of breast feeding. Ours was a single centre randomised controlled trial to determine the effectiveness of dextrose gel. However, to determine efficacy in differing circumstances a multicentre randomised control trial is required. Factors that might alter responses in such a trial include differing populations of babies at risk, and differing clinical
management of both mothers and babies, including screening and feeding regimes. In our study we also paid meticulous attention to the timing and mode of administration of dextrose gel and we do not know how important these factors are in determining response to treatment. Other trials are also needed to investigate the effectiveness of differing doses of dextrose gel and in younger gestational ages than those in our study.

We have recently registered the title “Oral dextrose gel for the management of hypoglycaemia in newborn infants” with the Cochrane Library for a systematic review using pre-determined primary and secondary outcome measures. Following completion of the systematic review we hope to develop and implement a clinical guideline for the use of dextrose gel. Further investigation into the effectiveness of dextrose gel in different settings should be encouraged, and in time the findings from a meta-analysis would provide comprehensive evidence about the efficacy of dextrose gel as treatment for neonatal hypoglycaemia.

Dextrose gel is inexpensive and easy to administer, which potentially makes it a useful treatment in resource poor countries where neonatal and childhood hypoglycaemia are linked with increased morbidity and mortality (Anderson, Shakya et al. 1993; Kochar, Thanvi et al. 1998). There are no special requirements for storage of the gel; it remains stable for at least three months at room temperature without bacterial growth. Sublingual sugar has been shown to treat hypoglycaemia as well as intravenous dextrose for hypoglycaemic children with malaria. However, if the children swallowed the sugar it was necessary to repeat the sugar treatment and it was difficult for the clinical team to assess if the sugar had been swallowed (Barennes, Valea et al. 2005). Dextrose gel via the buccal mucosa may provide a useful alternative in similar circumstances.

9.5.3 Further investigations following from the Sugar Babies Study

9.5.3.1 Parental perceptions

There are few reports in the literature providing guidance for investigators and ethics committees about clinical trials in babies soon after birth. Investigators are often reluctant to undertake research in babies because of concerns surrounding informed consent and the potential to increase stress for parents (Stenson, Becher et al. 2004). This is particularly true in randomised controlled trials, where a baby has an equal chance of receiving a treatment or not. However, there are reports showing babies benefit from being in randomised controlled trials when compared with those eligible and not enrolled (Lantos 1999; Schmidt, Gillie et al. 1999), and others have reported that the parents of extremely preterm babies were supportive of participation in multiple studies (Morley, Lau et al. 2005). Therefore, a secondary outcome of the Sugar Babies Study was to determine the mothers’
experience of having a late-preterm or term baby in this trial soon after birth. We contacted the mother by phone two weeks after the birth of the baby and completed a brief questionnaire which included questions about their experience and mode of feeding their baby. The findings from this part of our study are yet to be published. However, our initial findings show mothers valued being able to contribute to the Sugar Babies Study. They reported that the consistent advice and close attention to feeding and care of their baby was helpful and supportive, and made the hospitalisation a more positive experience.

9.6 Conclusion

Neonatal hypoglycaemia is important because it is common and the only preventable cause of neurological damage in the newborn period. However, there remains a paucity of evidence about the severity, duration, or frequency of hypoglycaemia required before neurological integrity is impaired. We were unable to demonstrate subtle changes in cot-side aEEG monitoring related to glucose concentrations that would assist the clinicians to identify babies at risk.

We have shown that neonatal hypoglycaemia is common in babies identified as being at risk, and continuous interstitial glucose monitoring appears to be a useful way to measure glucose concentrations in these babies. However, continuous glucose monitoring detected many more episodes of low glucose concentrations than intermittent blood glucose measurements, and the significance of these episodes remains unclear.

Our survey within Australia and New Zealand demonstrated that the majority of clinicians were treating babies with a blood glucose concentration <2.6 mmol/L but many were unsure about the best treatment. Our randomised controlled trial showed that dextrose gel is an effective, non-invasive treatment for hypoglycaemia in late-preterm and term hypoglycaemic babies.

Together, the studies reported in this thesis have substantially increased our understanding of neonatal hypoglycaemia, its detection, and management. Our findings are likely in the near future to change clinical practice in the management of this common and important condition in the newborn.

9.7 References


