Insulin infusion for hyperglycaemia in very preterm infants appears safe with no effect on morbidity, mortality and long-term neurodevelopmental outcome

Alicia Heald¹, Mohamed E. Abdel-Latif¹,² & Alison L. Kent¹,²

¹Australian National University Medical School, Canberra, 2601, ACT, Australia and ²Department of Neonatology, Canberra Hospital, Woden, 2606, ACT, Australia

**Background/Objective:** Hyperglycaemia is common in very premature neonates and is associated with increased risk of intraventricular haemorrhage, necrotising enterocolitis, sepsis and death. Administration of insulin may risk hypoglycaemia and associated complications. To determine effects of insulin infusions in very premature infants on morbidity, mortality and long-term neurodevelopmental outcome. **Methods:** Retrospective audit of 97 infants delivered at <29 weeks gestation and admitted to The Canberra Hospital NICU. Data on insulin treatment, Blood Glucose Levels (BGLs) prior and during insulin therapy, episodes of significant hypoglycaemia and neurodevelopmental outcome at 12 months corrected age was collected. **Results:** 17 (17.5%) neonates received insulin. Episodes of hypoglycaemia were infrequent (1.3%, 95% CI 0.5 – 2.9). Multiple regression analysis showed that insulin treatment was not associated with an increased risk of retinopathy of prematurity (OR 3.6, 95% CI 0.4 – 32.3) or mortality (OR 1.2, 95% CI 0.29 – 5.0). No significant difference in 12 month neurodevelopmental or anthropometric outcomes was detected in infants who received insulin. **Conclusion:** Insulin infusions for hyperglycaemia appear to be safe with infrequent episodes of hypoglycaemia, no increased risk of morbidity or mortality and no adverse effect on long-term neurodevelopmental outcome.

**Keywords:** Hyperglycaemia, insulin, mortality, neonate, premature

**Introduction:** Hyperglycaemia contributes to significant morbidity and mortality in individuals of all ages, but can have particularly devastating effects on the health of preterm infants [1,2]. Occurring in 40–80% of extremely low birth-weight infants (weight ≤1000 g [1]), hyperglycaemia has been associated with retinopathy of prematurity (ROP), intra-ventricular haemorrhage (IVH), necrotising enterocolitis (NEC), sepsis and death [2–5]. There are suggestions that it also contributes to early growth failure and increased risk of diabetes in later life [2].

The pathophysiological mechanisms underlying hyperglycaemia in the preterm infant are complex and multifactorial. In the fetus, glucose is transported across the placenta via insulin-independent transporters, and the fetal liver does not produce glucose [2]. Placental glucose delivery stimulates fetal pancreatic insulin secretion, with 40% of glucose converted into glycogen or lipid for storage [2]. This process is particularly important in the third trimester, where glycogen stores are maximized to prepare for life outside of the uterus. In the preterm infant, limited glycogen and lipid stores contribute to early hypoglycaemia, exacerbated by difficulties with respiration, hypoxia and maintaining thermoregulation [2]. Hypoglycaemia is typically followed by rebound hyperglycaemia, due to both insulin resistance and relative insulin deficiency [2]. There is continued endogenous glucose production despite high levels of glucose and insulin, and hyperglycaemia is further compounded by exogenous dextrose infusions [2].

It is difficult to treat hyperglycaemia through reduction of glucose infusion alone, as this carries a significant risk of growth failure [2]. Insulin treatment is frequently necessary to establish euglycaemia in these infants, but the absence of evidence-based guidelines to guide appropriate and safe insulin therapy contributes to ongoing confusion amongst neonatologists. Lack of standardized definitions for normal blood glucose levels (BGL) further complicates this issue, though values ≤2.6 mmol/L and ≥10.0 mmol/L are largely accepted to describe hypo- and hyperglycaemia respectively [2,3,6]. Benefits of insulin therapy include decreased prevalence of hyperglycaemia, increased energy intake and improved growth [1], though risk of hypoglycaemia is always present, and the importance of tight blood glucose control is paramount.

The aims of this retrospective audit were: (1) to determine whether insulin infusion for neonatal hyperglycaemia was associated with significant hypoglycaemia, defined as a blood glucose level of ≤2.0 mmol/L; and (2) to assess whether insulin treatment for hyperglycaemia is associated with any adverse effects on morbidity, mortality or long-term neurodevelopmental outcome at 12 months corrected age.

**Methods**

The electronic medical records of neonates delivered at <29 weeks gestation and admitted to The Canberra Hospital Neonatal Intensive Care Unit (TCH NICU) were reviewed from January
Intraventricular haemorrhage Grade III or IVa 9 (11.4) 4 (23.5) 0.237
Hypotension 19 (23.8) 12 (70.6) <0.001
Patent ductus arteriosus 47 (58.8) 12 (70.6) 0.526
Time to full feeds, days 19.0 (12.0–30.8) 25.0 (18.8–51.8) 0.099
Duration of oxygen supplement, days 16.0 (0–36.0) 21.5 (4.5–69.0) 0.214
Duration of ventilation and CPAP, days 26.7 (13.2–45.6) 23.8 (10.9–58.9) 0.733
CRIB-II score 9.0 (7.0–10.0) 12.0 (10.0–13.5) <0.001
Gestational age, weeks 27.0 (26.0–28.0) 26.0 (25.0–26.5) 0.002
Birth weight, grams 1065.0 (900.0–1200.0) 810.0 (695.0–898.0) <0.001
Hospital mortality 12 (15.0) 8 (47.1) 0.006
Antenatal steroids 61 (76.3) 14 (82.4) 0.775
Patent ductus arteriosus 47 (58.8) 12 (70.6) 0.526
Hypotension 19 (23.8) 12 (70.6) <0.001
Necrotising enterocolitis 18/76 (23.7) 5/12 (41.7) 0.286
Intraventricular haemorrhage Grade III or IVa 9 (11.4) 4 (23.5) 0.237
ROP Grade 3 or 4a 4/57 (7.0) 3/7 (42.9) 0.026
Length of hospital stay, days 49.5 (25–71.8) 23.0 (11.0–102.0) 0.488
Hospital mortality 12 (15.0) 8 (47.1) 0.006

Data are presented as number (%) or median (interquartile range).

Abbreviations: CLD indicates chronic lung disease; CRIB II, clinical risk index for babies II; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

*Denominator is number of infants examined.

Follow-up assessment and tools
All surviving children were offered an assessment at 12 months of age, corrected for prematurity. These children were assessed by the developmental assessment team at Canberra Hospital. The assessment involved examining four domains: (1) developmental, (2) neurological, (3) vision and (4) hearing. The developmental assessment used the Griffiths Mental Developmental Scales (GMDS [7]) which our unit used in 2006 and then changed in 2007 to the Bayley Scales of Infant Development-II (BSID-II [8]).

Neurological assessment included an evaluation of muscle tone, primitive reflexes, automatic reactions and volitional movement [9]. Cerebral palsy was diagnosed if the child had non-progressive motor impairment characterized by abnormal muscle tone and a decreased range or decreased control of movements, accompanied by neurological signs [10].

Definitions
The CRIB-II was calculated according to published method [11]. Small for gestational age was defined as a birth weight less than 10th percentile for gender and gestation. Chronic lung disease (CLD) is defined as the need for supplementary oxygen and/or ventilatory support at 36 weeks postconceptual age [12]. IVH grading is based on Papile classification [13] and NEC is staged using the modified Bell Staging Criteria [14]. All premature neonates admitted to TCH NICU were assessed by an ophthalmologist for ROP, and the International Classification of ROP was used to assign a Stage of I–IV to positive cases [15].

Moderate/severe functional disability was defined as one or more of the following: developmental delay (<2 SD below the mean for adjusted age determined by the GMDS or BSID-II), cerebral palsy (unable to walk without aids), bilateral blindness (visual acuity <6/60 in better eye), or bilateral deafness (requiring bilateral hearing aids or cochlear implants [16–18]).

Statistical analysis
All analyses were done using Predictive Analytics SoftWare (PASW) Statistics (version 18.0.2; SPSS: An IBM Company, Chicago, Illinois, USA, 2010). Data are presented as number (%) or median (interquartile range, IQR). Mann–Whitney, χ² and Fisher Exact tests were used as appropriate. Multivariate analysis was performed by means of multiple logistic regression using stepwise elimination based on likelihood ratio [19,20] to control for severity of illness using Clinical Risk Index for Babies (CRIB-II) score. The level of statistical significance for all analyses was set at p < 0.05 using two-tailed comparisons.

This study was approved by the ACT Human Research Ethics Committee under the NHMRC guidelines for clinical audit.

Results
Ninety-seven infants were included in the study. The median birth weight and gestational age were 1030 g and 27 weeks, respectively. 17 (17.5%) infants had hyperglycaemia managed with an insulin infusion. Neonates receiving insulin were less mature with lower birth weight. Their CRIB-II score was significantly higher than infants who did not receive insulin (Table I). Of the 77 survivors 64 had eye examination results available. In a multiple logistic regression analysis, insulin treatment had no impact on mortality (OR 1.197, 95% CI 0.287–4.989, p = 0.805) and ROP (OR 3.605, 95% CI 0.403–32.283) (Table II).

The median length of insulin treatment was 41 h (IQR 19–172). There were 6/449 (1.3%, 95% CI 0.5–2.9) significant hypoglycaemic episodes during insulin treatment. These six episodes occurred in two of the 17 (12%) neonates. The first neonate was...
Table II. Multivariate analysis of clinical features predictive of mortality (Panel A) and retinopathy of prematurity (Panel B).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>β coefficient (SE)</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panel A:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin treatment</td>
<td>0.180 (0.728)</td>
<td>1.197 (0.287–4.989)</td>
<td>0.805</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1.347 (0.625)</td>
<td>3.847 (1.130–13.099)</td>
<td>0.031</td>
</tr>
<tr>
<td>CRIB-II score</td>
<td>0.411 (0.134)</td>
<td>1.508 (1.161–1.959)</td>
<td>0.002</td>
</tr>
<tr>
<td>Panel B:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin treatment</td>
<td>1.282 (1.118)</td>
<td>3.605 (0.403–32.283)</td>
<td>0.252</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0.023 (1.110)</td>
<td>1.023 (0.116–9.014)</td>
<td>0.983</td>
</tr>
<tr>
<td>CRIB-II score</td>
<td>0.644 (0.237)</td>
<td>1.905 (1.198–3.030)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

CRIB-II indicates clinical risk index for babies II.

Table III. Neurodevelopmental and anthropometric outcomes of neonates requiring and not requiring insulin at 12 months of age, corrected for prematurity.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No insulin (N = 64)</th>
<th>Insulin (N = 9)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GQ/MDI &lt;–2 SD</td>
<td>1 (1.6)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>CP requiring walking aids</td>
<td>4 (6.3)</td>
<td>1 (11.1)</td>
<td>0.492</td>
</tr>
<tr>
<td>Bilateral blindness</td>
<td>0</td>
<td>1 (11.1)</td>
<td>0.123</td>
</tr>
<tr>
<td>Bilateral hearing loss</td>
<td>0</td>
<td>1 (11.1)</td>
<td>0.123</td>
</tr>
<tr>
<td>Weight &lt;10th percentile</td>
<td>23 (35.9)</td>
<td>5 (55.6)</td>
<td>0.291</td>
</tr>
<tr>
<td>Height &lt;10th percentile</td>
<td>9 (14.1)</td>
<td>2 (22.2)</td>
<td>0.617</td>
</tr>
<tr>
<td>HC &lt;10th percentile</td>
<td>8 (12.5)</td>
<td>2 (22.2)</td>
<td>0.601</td>
</tr>
</tbody>
</table>

Data are presented as n (%).

Discussion

Extremely low birth-weight infants are at risk of hyperglycaemia due to their prematurity and need for exogenous dextrose supplementation for growth. Results of this study are consistent with previous studies with 17.5% of infants in this cohort receiving insulin treatment for hyperglycaemia [1,3,21]. However, importantly hypoglycaemic events were few and insulin treatment was not associated with an increased risk of morbidity or mortality. Although on initial analysis mortality was significantly higher in those managed with insulin, in a multiple regression analysis this risk was no longer evident with the major risk factor being the CRIB-II score. The CRIB-II score includes the gestation and birth weight (which were significantly lower in the insulin group) along with illness severity and once these factors are included insulin loses its relationship to mortality.

This study is the first to examine long-term neurodevelopmental and anthropometric outcomes of neonates requiring insulin around birth. No statistically significant difference was detected at 12 months corrected age between neonates who received insulin and those who did not, which provides further support for the ongoing safe use of insulin for the treatment of hyperglycaemia in very preterm infants.

This study is limited by the smaller number of infants received insulin than in other studies, but is strengthened by the long-term data available. The retrospective nature of this audit reduces its power and it may be limited by several biases, including clinician bias. Although several confounders were considered, others may have influenced the results. Despite these limitations, this study identified similar correlations reported in other studies. Our study confirms the high incidence of hyperglycaemia in very premature infants, and that insulin use is not associated with an increased risk of mortality [6]. The percentage of neonates experiencing hypoglycaemia was less in our study compared to others [1,6]. This audit found that only the CRIB-II score was predictive of mortality in this group. Unlike other studies, we did not find that hypotension was predictive of mortality [22,23].

Infants in this study received insulin for a median of 2 days, which is significantly shorter than the median 18 and 14 days of infusion recorded in similar studies [21,24]. Use of insulin in very premature infants was not predictive of mortality in this study, nor was gestational age. Other studies have shown similar results, with mild-moderate hyperglycaemia and early gestation not linked with an increased mortality risk in these infants [4,25].

Importantly the incidence of hypoglycaemic episodes in this study was low (1.3%) and lower than previously reported [1,6]. Hypoglycaemia can be deleterious for neonates and carries a risk of long-term neurodevelopmental sequelae [26], hence maintenance of euglycaemia is crucial. Collins et al. reported that infusion of insulin with a microliter pump successfully prevented large fluctuations in plasma glucose concentrations associated with intermittent insulin dosing [21]. Despite this improvement, frequent BGL monitoring is still required, and individual requirements differ widely between neonates [21]. The use of a BGL sliding scale complements an infusion pump, and the combination of both leads to fewer episodes of hypoglycaemia, as in our study.

In this study, the CRIB-II score was the only significant predictor of mortality (p = 0.002). Hypotension (p = 0.031) and insulin treatment (p = 0.805) were not predictive of mortality, though a positive correlation between hyperglycaemia and mortality has previously been reported [4,25]. These findings...
suggest that insulin treatment in this group of neonates is safe and given the potential benefits on improved growth should be considered when persistent hyperglycaemia is encountered.

Several studies have investigated the effects of tight versus conventional blood glucose control in critically ill adults and children [27–30]. In the adult population, conflicting results have reported that tight glucose control can be associated with increased [27], decreased [28], or no change in mortality [29,30]. Such variability in reporting no doubt leads to confusion among practitioners involved in the care of critically ill patients with hyperglycaemia. Fewer studies have been conducted in critically ill children, however, a recent randomized-controlled trial found that in children admitted to the paediatric intensive care unit (PICU), tight glucose control resulted in better short-term outcomes compared to conventional glucose control [31]. These results may indicate that critically ill children respond differently to hyperglycaemia and insulin treatment than critically ill adults. Similar studies have not been conducted in critically ill neonates. Consensus in respect to normal and abnormal blood glucose values in premature neonates is required before a study on glucose control in neonates could be commenced. In light of the findings for children in PICU [31], investigation of the potential benefits of tight versus conventional glucose control in reducing morbidity and mortality in critically ill neonates is warranted.

Conclusions

Insulin infusions for hyperglycaemia in extremely premature neonates appear to be safe with very infrequent episodes of hypo-glycaemia and no increased risk of morbidity and mortality. Long-term neurodevelopmental outcome does not appear to be affected by insulin use for hyperglycaemia in the early neonatal period.

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Declaration of Interest:
The authors declare no conflict of interest.

References

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