Tight Glycemic Control in the Neonatal Intensive Care Unit – Proof of Concept Pilot Trials

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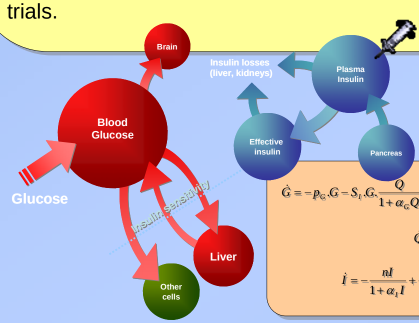
INTRODUCTION

Premature, low-birth-weight infants in the neonatal intensive care unit (NICU) can lose blood glucose homeostasis due to immaturity of endogenous regulatory systems and the stress of their condition. Hyperglycemia occurs in 40-80% of premature, low birthweight infants. This condition has been linked to worsened outcomes in preterm neonates, including an increased risk of further complications, such as sepsis, increased ventilator dependence, retinopathy of prematurity, hospital length of stay and mortality

Often, glucose restriction is used to control high blood glucose levels. However, this restriction also deprives the neonate of crucial energy required to promote growth. Continuous insulin infusion has thus been proposed as a solution to reduce plasma glucose concentrations and optimize nutrition in these small infants.

The pathogenesis of hyperglycemia in critically ill adults and preterm may differ. The mechanisms responsible for hyperglycemia in preterm infants are related to immaturity of the glucose regulatory system, in addition to clinical stress.

A model of the fundamental glucose regulatory dynamics in neonates can provide insight about the metabolic state of the patient. *In-silico* virtual trials were used to design optimal insulin therapy regimes for this vulnerable patient group, and piloted in 24-hour clinical trials.



$$\dot{G} = -p_G.G - S_I.G.\frac{Q}{1+\alpha_G Q} + \frac{P(t) + (P_{END} * m_{body}) - (CNS * m_{brain})}{(V_{G,frac}(t) * m_{body})}$$

$$\dot{Q} = -kQ + kI$$

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}(t)}{(V_{I,frac} * m_{body})} + e^{-(k_I u_{ex}(t))} I_B$$

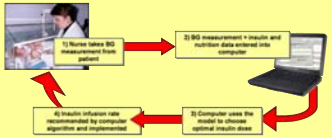
MODELS AND METHODS

A metabolic computer system model, clinically validated in adult intensive care patients and virtual trials using neonatal data, is used to provide tight control in very low birth weights infants.

Seven clinical trials up to 24 hours each were performed based on initial blood glucose over 10 mmol/L to initiate insulin.

Pilot trial cohort clinical details.

Patient	Gestational age at birth [weeks]	Age at start of trial [days]	Birth weight [g]	Insulin usage before trial [hours]
A	24.4	7	685	15.3
B	27.3	9	770	15.0
C	25.4	1	720	3.2
D	25.4	7	785	91.6
E	25.9	4	540	2.2
F	27.0	2	900	0.0
G	25.0	6	995	11.5



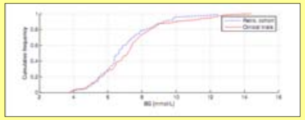
Controller implementation overview.

Insulin infusions were modulated to hit a pre-determined target based on measurements every 2-3 hours (max 12 measurements/day). The overall goal was to control blood glucose in a 4-7 mmol/L band. A stochastic model ensured the risk of blood glucose below 4 mmol/L was less than 5% for each intervention. Ethics approval was granted by the Upper South Regional Ethics Committee.

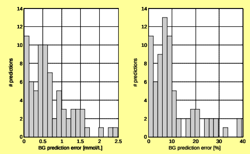
Overall cohort BG prediction error was 7.6% (0.54 mmol/L) during clinical trials. Distribution of BG prediction errors revealed 69% and 84% of BG measurements within ±10% and ±20% of forecasted concentration.

BG prediction accuracy and stochastic model prediction coverage.

Patient	Median BG prediction error (absolute) [%]	[mmol/L]	BG within IQR forecast range	BG within 5%-95% forecast range
A	19.20%	1.47	33%	83%
B	8.60%	0.52	31%	85%
C	7.60%	0.77	80%	90%
D	8.40%	0.53	33%	100%
E	6.40%	0.48	100%	100%
F	8.50%	0.72	50%	83%
G	5.90%	0.44	92%	100%
Whole cohort	**7.60%**	**0.54**	**62%**	**92%**

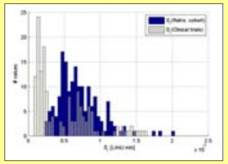


Distribution of BG between clinical trial patients (n=7) and matched 24-hour simulated trials on retrospective cohort (n=7).



BG prediction errors during trials (expressed as absolute concentration in left panel, and percentage of measured BG concentration in right panel).

Comparison with simulated trial results indicated level of control matched predictions, despite significantly insulin-resistant clinical cohort.



Distribution of insulin sensitivity between clinical trial patients (n=7) and matched 24-hour simulated trials on retrospective cohort (n=7).

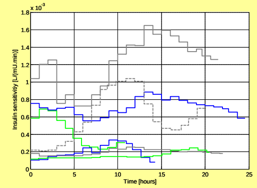
RESULTS: CLINICAL TRIALS

Normoglycemia in a 4-7 mmol/L band was achieved in all cases. Median initial blood glucose was 10.1 mmol/L (Range: 7.4 – 14.4 mmol/L). Over all trials median blood glucose was 6.9 (IQR: 5.6 – 7.9, 90%CI: 4.6 – 11.2) mmol/L over 74 measurements. The minimum blood glucose was 3.8 mmol/L.

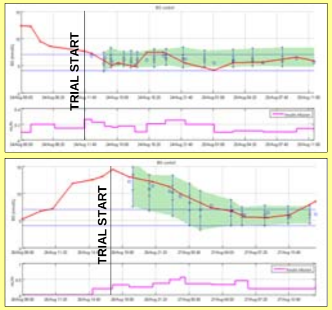
Clinical glycemic variables during trials. Infusion rates are computed as hourly averages. BG mean and standard deviation are computed using lognormal statistics. EBM = Expressed Breast Milk.

Patient	Median dextrose rate mg/kg/min	kcal.kg.day	Total EBM [mL]	Median insulin rate [U/kg/hr]	Geometric BG mean [mmol/L]	Geometric BG StDev [mmol/L]	Max. BG [mmol/L]	Min. BG [mmol/L]	Measurement period, hours	Median insulin sensitivity [L/(mU.min)]
A	7.1	40.6	0.0	0.025	7.7	1.04	8.7	6.9	2.1	0.45
B	9.4	54.4	5.0	0.040	6.7	1.16	12.3	4.1	1.7	1.25
C	4.1	23.3	0.0	0.068	8.7	1.19	14.4	5.2	1.7	0.14
D	9.6	55.0	3.0	0.052	6.5	1.08	8.0	5.0	2.5	0.7
E	6.8	39.1	11.0	0.116	9.0	1.12	12.6	6.5	2.1	0.2
F	8.2	47.5	4.5	0.069	7.0	1.23	14.5	3.8	1.7	0.5
G	9.4	54.3	2.0	0.191	8.7	1.17	14.7	5.3	1.9	0.14

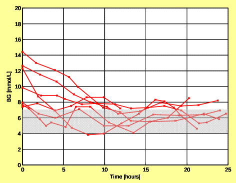
Within the relatively small study population, a 2.3x spread of dextrose infusion rates were used, and an 8.9x spread of insulin sensitivity was computed. In response, the controller used a 7.6x spread of median insulin infusion rates.



Model-fitted insulin sensitivity during trials. Each line represents the hourly evolution of patient sensitivity to exogenous insulin.

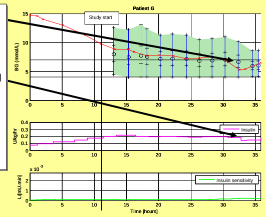


Clinical BG results for pilot trial patients 2 (top panel) and 3 (bottom panel). Green areas denote stochastic model 5%-95% BG prediction confidence interval.



Per-patient BG concentration during computerised insulin dosing. The shaded region represents the 4-7 mmol/L target band.

- Change in insulin sensitivity contained
- Insulin infusion rate adjusted
- More aggressive control may have created hypo event for this patient
- Controller tolerated period of higher BG to balance risk of changes in patient condition.



Stochastic model forecasts drove controller decisions for more insulin resistant and/or dynamic patients, preventing episodes of hypoglycaemia.

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