INTRODUCTION

Hyperglycemia occurs in 40–80% of very premature, low birthweight infants. The pathogenesis of hyperglycemia in critically ill adults and preterm infants may differ. The mechanisms responsible for hyperglycemia in preterm infants are related to immaturity of the glucose regulatory system, in addition to clinical stress.

This condition has been linked to worsened outcomes, including increased incidence of sepsis, increased ventilator dependence, retinopathy of prematurity, hospital length of stay and mortality

Often, glucose restriction is used to control high blood glucose levels, but this can deprive 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.

However, great heterogeneity is the hallmark of neonatal glucose metabolism. Thus, the emerging use of insulin carries a significant risk of hypoglycemia due to patient response variations to insulin over time.

An adaptive model of the fundamental glucose regulatory dynamics in neonates can track an infant’s sensitivity to exogenous insulin in real-time. Targeted control forecasts the range of likely future glucose levels to select the optimal insulin rate, adapting control to the infant’s current metabolic state.

SIMULATION STUDIES

Simulation studies performed using insulin sensitivity profiles generated from 25 retrospective episodes of insulin. Controller refined in-silico before clinical implementation.

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

Improved control in simulation with up to 65% - 82% more measurements inside target 4 – 7 mmol/L BG range indicated on both per-patient (left) and whole-cohort (below) scales.

Insulin sensitivity exhibits greater inter-patient variance in neonates versus adults. Therefore, optimal control requires adaptive methods in this population.

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 weight infants. Median model BG fit error is 2.4% on retrospective data and forecast errors are 5.2% to 13.6% for 1 to 4 hour BG predictions.

Insulin infusions were modulated using an iterative bisection algorithm to match forecasted BG to a pre-determined target based on measurements every 2-3 hours (max 12 measurements/day).

Stochastic forecasting models quantify the expected variation of insulin sensitivity based on retrospective patient data. BG system equations are solved using successive values of forecasted insulin sensitivity using to yield forecast BG range.

CLINICAL TRIALS

Seven clinical trials up to 24 hours each were performed based on initial blood glucose over 10 mmol/L to initiate insulin. Over all trials median BG was 6.9 (IQR: 5.6 – 7.9, 90%CI: 4.6 – 11.2) mmol/L over 74 measurements. Minimum BG was 3.8 mmol/L.

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.

Overall cohort BG target error was 7.8% (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 value.