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


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.

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.

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

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.

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.

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 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.

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

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