

Persistent hyperglycemia in a neonate: Is it a complication of therapeutic hypothermia?

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The aim of this report is to present a newborn with persistent hyperglycemia requiring insulin therapy as a possible complication of therapeutic hypothermia. A term appropriate for gestational age (AGA) female infant, was born by emergency cesarean section due to abruption of placenta and was resuscitated and intubated in the delivery room. Whole body cooling was initiated according to standard cooling criteria. The patient's blood glucose increased up to 250 mg/dl on a glucose perfusion rate of 6 mg/kg/min after the second day of cooling. Insulin therapy was started due to persistent hyperglycemia and continued for 17 days. As it has been reported in adults after therapeutic cooling, persistent hyperglycemia attributed to hypothermia can also complicate therapeutic hypothermia in neonates.

Key words: asphyxia, hyperglycemia, hypothermia, newborn.

Hypoxic-ischemic encephalopathy remains a serious condition that causes significant mortality and long-term morbidity. Therapeutic hypothermia is an established standard of care in the treatment of hypoxic-ischemic encephalopathy. Furthermore, hypothermia has a significant profile of potential adverse effects, including metabolic, cardiovascular, pulmonary, coagulation, and immunologic complications. Fewer side effects of hypothermia such as arrhythmia, thrombocytopenia, and subcutaneous fat necrosis have been reported¹. It is crucial to recognize, prevent and treat various adverse events of this treatment.

We present a term newborn baby who fulfilled the criteria for therapeutic cooling and developed insulin-requiring hyperglycemia during and after therapeutic hypothermia.

Case Report

A 2,525 g, female AGA baby was born at 38 weeks by emergency cesarean section due to abruption of the placenta. Apgar scores were 0, 0, and 4 at the 1st, 5th, and 10th minutes, respectively. At birth, the infant was hypotonic,

cyanotic, and had bradycardia. Her cord blood gas analysis (pH 6.7, HCO₃ 6.3 mmol/L, BE -19 mmol/L) showed severe metabolic acidosis. After 15 minutes of resuscitation including intubation, she was transferred to the neonatal intensive care unit. Whole body cooling was initiated according to our units hypothermia protocol [Gestational age \geq 36 weeks and \leq 6 hours of age and Apgar score \leq 5 at 10 minutes after birth or continued need for resuscitation 10 minutes after birth or pH $<$ 7.00 or base deficit \geq 16 mmol/L on umbilical cord or arterial or capillary blood sample obtained within 60 minutes after birth and moderate or severe encephalopathy on clinical examination and abnormal background activity of at least 30 minutes duration or seizures on amplitude integrated electroencephalogram] which was adapted from the TOBY study². According to the modified Sarnat criteria the baby was diagnosed with moderate encephalopathy. Cooling was started in two hours after delivery with a target rectal temperature of 34°C. Phenobarbital was started due to the epileptic activity observed on amplitude-integrated electroencephalography.

Cooling was continued for 72 hours, and the baby was rewarmed gradually ($0.5^{\circ}\text{C}/\text{hour}$) afterwards until the desired rectal temperature (36.5°C) was reached. She was moderately hypotensive and required inotropic agents for the first days of life. Furosemide infusion was started because of low urinary output due to acute renal injury caused by asphyxia. The total daily fluid amount was restricted in addition to allopurinol as the patient's uric acid level increased to 14.1 mg/dl due to renal failure. The patient's capillary blood sugar increased up and continued to be over 250 mg/dl with a glucose infusion rate of 6 mg/kg/min after the second hour of hypothermia treatment; therefore, glucose infusion rate was initially reduced to 4 mg/kg/min at the sixth hour of life. Glucosuria accompanied hyperglycemia but neither ketonuria nor acidosis was observed. As the patient's high glucose levels remained (persistent levels of blood glucose level $>250\text{ mg/dl}$, up to 380 mg/dl) insulin infusion was started at postnatal 36 hours, and continued for 17 days (Fig. 1). Insulin was given by infusion ($0.01\text{-}0.02\text{ U/kg/hour}$) for the first five days and continued by intermittent subcutaneous insulin treatment for the following 12 days. Meanwhile, the patient's insulin and C peptide levels were $4.27\text{ }\mu\text{IU/ml}$ (normal range: $3.28\text{+/-}2.04\text{ }\mu\text{IU/ml}$) and 1.59 ng/ml (normal range: $0.8\text{-}3.1\text{ ng/ml}$) respectively, when the blood glucose level was 350 mg/dl .

Alpha-1 antitripsin, lipase and amylase levels were found to be normal, revealing a normal

exocrine pancreas function. Sepsis screening, including TORCH-S group infections were found to be negative. The abdominal ultrasound was normal including the pancreas. The patient's mother's glycemic status was found to be normal and she did not use any medications during pregnancy.

Insulin was gradually decreased and stopped at the 17th day of life as the patient's glucose levels were within normal limits. She was extubated on the 10th day of life and was discharged on day 25, fully orally fed. At discharge her neurological examination revealed mild axial hypotonia and weak head control.

Written informed consent was obtained from the patient's parent for the publication of this report.

Discussion

As widespread implementation of therapeutic hypothermia occurs, regional guidelines and pathways have been increasingly established and early concerns about the safety of therapeutic hypothermia are subsiding as a body of experience accrues within the neonatal community.⁷

However, although randomized trials and meta-analyses reassure that significant side effects of cooling are few and mild, they are not powered to detect rare events that may become apparent when therapeutic hypothermia is implemented on a wider scale and within routine practice³. In addition, the evaluation

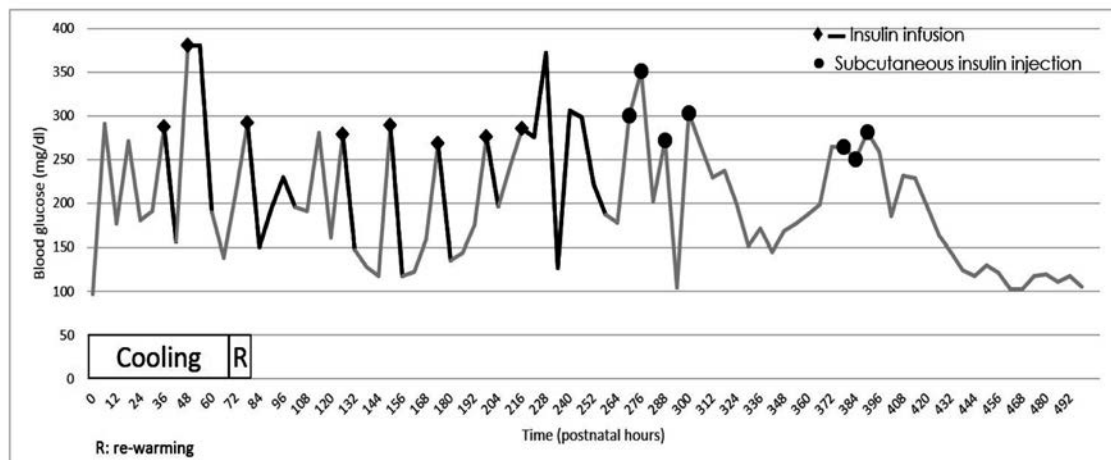


Fig. 1. Blood glucose levels and insulin treatments during and after hypothermia treatment.

of all possible adverse events is rarely the scope of randomized trials. National registers encourage reporting individual cases including the rare side effects of cooling, to audit practice and outcomes^{4,5}.

In this report we present an infant who underwent therapeutic hypothermia for intrapartum asphyxia who developed insulin-requiring hyperglycemia during and after cooling. Neonatal hyperglycemia is one of the most common metabolic abnormalities encountered in critically ill newborns. The causes of neonatal hyperglycemia are variable. Generally, hyperglycemia represents a mixture of excessive glucose production by the infant, too much infused exogenous glucose, and a reduced capacity for glucose utilization, which could be related to the insulin deficiency and/or insulin resistance⁶. Her insulin and C-peptide levels were indicating insulin deficiency, since she had insulin levels of lower normal range despite high blood glucose levels. Neonatal hyperglycemia can be directly related to some illnesses, particularly septicemia and all forms of stress⁶. Our case was evaluated for the possible causes of hyperglycemia. Sepsis screening was negative in our case.

One of the most common causes of hyperglycemia is increased circulating stress-reactive hormones such as epinephrine and norepinephrine⁷. Circulating concentrations of epinephrine and norepinephrine also increase during infusion of dopamine and dobutamine by as much as two to six fold, either by enhanced endogenous secretion or reduced clearance (saturation of binding receptors)⁸. The baby was started on dopamine infusion at a rate of 5 $\mu\text{g}/\text{kg}/\text{min}$ due to hypotension soon after birth for 24 hours. As hyperglycemia persisted after stopping the drug, high blood glucose levels were not related to dopamine infusion.

Hyperglycemia due to severe hypothermia (18-25°C) has been reported from animal studies in previous years^{9,10}. Several mechanisms have been proposed to explain hyperglycemia encountered during hypothermia, both in animal and human trials.⁹⁻¹¹ It has been shown that hypothermia leads to a lowering of the metabolic rate and includes changes in energy metabolism and decreases ATP demand resulting with inefficient glucose utilization.¹¹ Helman et al.¹⁰ have previously documented 80% decrease

in the insulin concentration of portal blood draining the pancreas in the hypothermic rat. In the study they showed that hyperglycemia was the result of rapid glycogenolysis (assuming reduced total peripheral glucose up take) and hypoinsulinemia. Torlinska et al.¹² also showed that the decrease in specific insulin binding in hypothermia is due to a decrease in the number of insulin receptors in the liver plasma membranes. It is possible, therefore, that perturbations in insulin release and action may potentiate the abnormalities of glucose metabolism during hypothermia. In our case we observed low insulin levels despite high blood glucose levels, and this finding supported the mechanism that pancreatic insulin release was inhibited during cooling.

Although higher temperatures (33°C) are used during hypothermia treatment after out-of-hospital cardiac arrest in adults, hyperglycemia has been reported as an adverse effect¹³.

Thomas et al.¹⁴ reported in their series hyperglycemia among adverse effects of therapeutic hypothermia in three out of twenty babies. A randomized controlled trial also comparing selective head cooling (34.5°C to 35.0°C) with the control group for whom rectal temperature was maintained at 36.0°C to 37.5°C reported no difference regarding hyperglycemia between the groups. In this study the duration of hyperglycemia and the need for insulin was not addressed¹⁵.

In conclusion, altered carbohydrate metabolism during hypothermia is accompanied by reduced secretion of insulin. Although rare, persistent and prolonged hyperglycemia severe enough to require insulin treatment can be observed during and after therapeutic hypothermia in neonates. Tight control of glucose levels may decrease mortality and morbidity in these patients.

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