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EFFECT OF INSULIN ON THE METABOLIC AND NEUROENDOCRINE STRESS RESPONSES TO CRITICAL ILLNESS IN CHILDREN

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Background/aims: Neuroimmunoendocrine and metabolic dysfunctions are present in critical illness. We investigated whether insulin could reverse or limit these changes.

Methods: Open-label randomized controlled physiology study of the effects of insulin during critical illness. 31 children with multiple organ dysfunction syndrome were recruited: 13 children received continuous insulin infusion (0.1Unit/Kg/hr) and glucose was added if required to maintain glucose levels between 4.5 and 7.0mmol/L. Blood samples for neuroimmunoendocrine and metabolic evaluation were obtained before randomization, and 24 and 72hours later. A growth hormone(GH) oscillation profile was obtained during the first night.

Results: At baseline both groups were similar. There was also no absolute difference in between the groups, at any time, in GH, IGF-1 and IGFBP-3. GH had higher relative increase in children receiving insulin, which suggests worsened GH resistance. By day 2, insulin decreased IGFBP-1 levels. At the same time insulin decreased free fatty acid levels, which was accompanied by increased LDL cholesterol and relative increase in HDL levels. Total cholesterol and triglycerides were unchanged. TNF-alpha and interleukin(IL)-1beta decreased in both groups, whereas IL-6 levels were significantly reduced significantly in children receiving insulin.

Conclusions: Insulin does not reverse most of the neuroendocrine changes induced by stress of critical illness. However, it does appear to improve lipid metabolism (preserved LDL and HDL cholesterol) and down-regulate inflammation (decreased IL-6). These findings suggest that insulin in critical illness acts as a modulator of lipid dysfunction, which suggests new targets for future investigations.

Figure 1. Insulin effect on neuroendocrine, metabolic and inflammatory stress responses. There was no absolute difference in GH, IGF-1 and IGFBP-3 levels between groups at any time (A, B, C), but insulin decreased IGFBP-1 levels on day 2 (D). Insulin also decreased FFA (E) levels, which was accompanied by an increase in LDL cholesterol (F) and a percentage increase in HDL levels on day 2 (G). TNF-alpha decreased in both groups, but IL-6 levels reduced significantly only in children receiving insulin.

[Figure 1]

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INTENSIVE INSULIN THERAPY AND BRIEF HYPOGLYCEMIA DO NOT INCREASE MARKERS OF NEUROLOGICAL INJURY IN CRITICALLY ILL CHILDREN

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Background and aims: Targeting normoglycemia with intensive insulin therapy (IIT) improved short-term outcome of pediatric intensive care unit (PICU) patients, but concomitantly increased the incidence of hypoglycemia. Both hyperglycemia and hypoglycemia may adversely affect the developing brain in children. We studied the impact of targeting normoglycemia with IIT on circulating markers of brain injury in critically ill children.

Methods: This was a pre-planned analysis of critically ill pediatric patients included in a randomized controlled study on IIT. Patients were assigned to IIT targeting normal-for-age fasting blood glucose levels throughout intensive care or insulin infusion only to prevent excessive hyperglycemia. Serum S100B and neuron-specific enolase (NSE), biomarkers of astrocytic and neuronal damage, respectively, were measured on fixed days (n=700) and in a "nested case-control" design before and after hypoglycemia (n=126).

Results: Admission levels of S100B and NSE differed according to diagnosis and illness severity ($P < 0.0001$). IIT did not affect the time course of these markers. Patients experiencing hypoglycemia during intensive care had higher S100B and NSE from admission onwards than those without hypoglycemia. In the nested case-control study, both markers decreased after hypoglycemia ($P = 0.001$ and $P = 0.009$), unlike in the “controls” on matched days.

Conclusions: IIT in PICU did not evoke neurological damage detectable by circulating S100B and NSE, despite increased incidence of hypoglycemia. Elevated markers in patients with hypoglycemia were not caused by hypoglycemia itself, but rather reflect an increased risk of hypoglycemia in the most severely ill. This risk is difficult to capture by the classical illness severity scores.

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PREDICTING DEATH DESPITE THERAPEUTIC HYPOTHERMIA IN INFANTS WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE)

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To avoid offering false hope to parents it is important to identify potentially untreatable cases of HIE for whom cooling may not be of benefit. **Objective:** To determine pre-cooling attributes that could predict death in infants with HIE despite cooling.

Methods: 85 infants of ≥ 36 weeks' gestation who received cooling for HIE were reviewed. Logistic regression analysis was performed using pre-cooling clinical/ laboratory variables with HIE related death during first 9 months of life as primary outcome.

Results: Thirteen (15%) of 85 infants with HIE died during 9-18 months follow up despite cooling. In all, 27 of 85 infants were asystolic at birth but only 12 of these infants had Apgar of zero at both 5 and 10 minutes. Univariate analysis identified Apgar of zero at 5 minutes and at 10 minutes, $\text{pH} < 6.7$, base deficit > 22 mmol/L, and absent spontaneous movement as being significant but on multivariate analysis, only Apgar score of zero at 10 minutes ($p < 0.001$, OR 51.7, 95% CI 9.9 - 269.5) remained significantly associated with primary outcome. Of 12 infants who were asystolic at and beyond 10 minutes of life, 9

died from HIE, 2 had spastic quadriplegia at 18-24 months, and one had extensive encephalomalacia on brain MRI.

Conclusions: Among all pre-cooling variables, only 10 minute Apgar score is independently associated with death despite cooling. Furthermore, infants who remain asystolic at 10 minutes and beyond are unlikely to survive despite cooling, and the rare survivor is likely to survive with severe disability.

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EARLY DIAGNOSIS OF POSTOPERATIVE COMPLICATIONS AFTER LIVER TRANSPLANTS IN CHILDREN

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Introduction: The UMCG is the only medical centre in the Netherlands that has performed liver transplants on children since 1982. In the last few years a lot has improved in the treatment thereof.

At this current moment approximately 15 children are being transplanted each year. The survival rate has improved by 50%.

During these admissions pitfalls may occur that can lead to postoperative complications!

Aim: To give insight on the means used to recognize post operative complications in early stages in children after liver transplants.

Methods: Protocols have been developed in which post operative parameters concerning monitoring, blood results and radiology imaging have been described. Nurse observation and interpretation parameters are of further essential significance. These are mainly directed towards prevention of infections, timely detubation, and keeping up with the fluid balance and temperature of the patient. Adjacent to that, the in research phase TEG-study, offers important information about the coagulation.

Results: Working according to protocol makes it possible to perceive and intercept complications in early stages. Moreover we aim at thrombosis, infections and liver failure. In pediatric care parents are indissolubly attached to their child. This makes