REVIEW ARTICLE

# Treating Hyperglycemia in the Critically Ill Child: Is there Enough Evidence?

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**Need and purpose of review:** Hyperglycemia is prevalent among critically ill pediatric patients. Previously thought to be an adaptive response to stress, hyperglycemia is now recognized to be associated with an adverse outcome. Correction of such hyperglycemia with insulin infusion has been shown to improve outcome but carries risk of hypoglycemia. This review addresses these issues related to treatment of hyperglycemia.

**Methods:** A Pubmed search was performed using the search strategy: (*hyperglycemia* OR *blood glucose* OR *insulin therapy*) AND (*critical illness* OR *critical care* OR *intensive care unit*). Randomized controlled trials, clinical trials, meta-analysis and observational studies (adult and pediatric) published in the last 10 years were included.

**Conclusion:** Blood sugar monitoring and correction of hyperglycemia while caring for critically ill children is crucial. A modest blood glucose target of <150 mg/dL is appropriate. Providing adequate nutrition along with training of the nursing personnel would prevent any adverse effect such as hypoglycemia.

**Key words:** *Critical illness, Hyperglycemia, Glucose, Insulin.*

With increasing facilities for intensive care becoming available in India, a large number of pediatricians are looking after critically ill children. The prevalence, consequences and management of hypoglycemia have been highlighted in pediatric literature but there is a lack of awareness regarding the prevalence and adverse effects of hyperglycemia among sick children.

During any acute illness, glucose regulation is lost and hyperglycemia develops due to insulin resistance and an absolute or relative insulin deficiency [1,2]. Counter regulatory hormones (growth hormone, glucagon, cortisol, catecholamines) and inflammatory cytokines promote lipolysis and proteolysis and thus gluconeogenesis. Hepatic insulin resistance prevails and there is abundant endogenous production of glucose inspite of elevated glucose levels. Insulin-stimulated uptake of glucose by peripheral tissues such as skeletal muscle, heart and adipose tissue is decreased. Immobility further impairs the exercise stimulated uptake of glucose in skeletal muscle.

Hyperglycemia, a frequent finding in the critically ill, was thought to be an adaptive response to stress and was not treated. Recently, it has been recognised to be a marker of poor outcome [3]. Among patients with trauma, stroke, myocardial infarction, and many other such acute illnesses, hyperglycemia has been shown to increase morbidity and mortality [4-7].

Hyperglycemia stimulates a cascade of pro-inflammatory events [1], is prothrombotic, and increases oxidative stress by lipid peroxidation. It promotes infection by decreasing neutrophil phagocytic activity and the oxidative burst of leukocytes. In laboratory studies, exacerbation of ischemic brain injury, myocardial cell apoptosis due to reactive oxygen species and adverse effects on pulmonary and

renal tissue due to free radical injury have been seen [7]. Insulin therapy seems to counter these harmful effects of hyperglycemia with potent anti-inflammatory effects [1]. Levels of mannose-binding lectin and C reactive protein are lowered by insulin [2]. Insulin lowers blood glucose, mainly by stimulation of skeletal muscle glucose uptake, but is unable to reverse the hepatic insulin resistance. Insulin is known to lower free fatty acids and normalise endothelial function as also being anabolic and cardio-protective.

### EVIDENCE IN CRITICALLY ILL ADULTS

In 2001,Van den Berghe, *et al*. [8] from Leuven, Belgium, randomized adult patients receiving mechanical ventilation in a surgical intensive care unit (ICU) to maintain blood glucose between 80 to 110 mg/dL using insulin infusion in the 'intensive insulin therapy' arm or between 180 to 200 mg/dL in the 'conventional therapy' arm. A 42% reduction in ICU mortality was seen with intensive insulin therapy; this was entirely attributable to reduction of deaths in patients staying in the ICU for more than five days. Intensive insulin therapy reduced episodes of septicaemia by 46%, new onset acute renal failure by 41%, median number of red cell transfusions by 50%, critical-illness polyneuropathy by 44% and also the duration of mechanical ventilation and intensive care

Several subsequent studies on this intervention; however, yielded conflicting results. The substantial benefits obtained in the Leuven study could not be consistently replicated and a higher incidence of hypoglycemia (blood glucose <40 mg/dL) was noted. In a mixed medical-surgical population of patients studied by Krinsley [9], a benefit was seen with reduction in hospital mortality, new onset renal failure, number of patients requiring red blood cell transfusions and length of ICU stay. No increase in episodes of hypoglycemia was seen. Van den Berghe, *et al*. [10] conducted a randomized, controlled study of tight glycemic control in a medical ICU in 1200 adult patients. While there was no decrease in hospital mortality with tight glycemic control, a significant reduction in new-onset renal failure, duration of mechanical ventilation, ICU and hospital stay were noted. Patients staying in the ICU for less than 3 days had a higher mortality with tight glycemic control while the reverse was true for those staying more than 3 days; a significantly higher incidence of hypoglycemia was seen in the study group (18.7% *vs* 3.1%). Treggiari, *et al*. [11] studied the outcome among 10,456 patients admitted to medical, surgical and trauma ICUs at a single centre over three consecutive time periods with differing glycemic control protocols; no protocol, target glucose 80 to 130 mg/dL and target glucose 80 to 110 mg/dL. There was no mortality benefit with tight glycemic control, rather an increase in mortality was noted in patients staying in the ICU for less than three days and the incidence of hypoglycemia increased fourfold. Conflicting results were obtained in two studies in the Asian population, with benefit from tight glycemic control demonstrated by Wang, *et al*. [12] and no benefit demonstrated by Arabi, *et al.* [13]. Two large multicentre studies were designed to resolve the conflicting results obtained in these single centre studies. In a multicentric study in Germany conducted across 18 multidisciplinary ICUs [14], tight glycemic control in patients with severe sepsis resulted in an increase in the rate of hypoglycemia to unacceptably high level (4.1% to 17%). The study was terminated after the first interim analysis for safety reasons. Similarly, a multicentric European study from 19 centers of 7 countries [15] documented a fourfold increase in the rate of hypoglycemia with intensive insulin therapy as against conventional therapy (9.8% *vs* 2.7%) with no mortality benefit.

A meta-analysis of twenty-nine randomized controlled studies with data for over 8000 adult patients comparing tight glucose control (blood sugar <150 mg/dL) using insulin infusion or usual glucose control, reported no difference in hospital mortality (21.6% *vs* 23.3%) [16]. Further stratifi-cation of results based on setting (medical, surgical, or medical-surgical) or degree of glucose control (very tight; blood glucose maintained ≤110mg/dL or moderately tight; ≤150 mg/dL) also revealed no difference in mortality. Tight glucose control was not associated with a decrease in the new need for dialysis but the risk of septicemia decreased signi-ficantly [10.9% *vs* 13.4%; RR, 0.76 (95% CI: 0.59-0.97]. Hypoglycemia was significantly higher in the group receiving tight glucose control as compared to usual care [13.7% *vs* 2.5%; RR: 5.13:95% CI: 4.09-6.43].

The NICE-SUGAR trial [17], a multcentric study across three countries recruiting 6104 adult patients expected to require ≥3 days of treatment in the ICU, was published subsequently. Patients were randomized to either intensive glucose control, with a glucose target of 81 to 110 mg/dL or conventional glucose control, with target ≤180 mg/dL and the mortality at 90 days was compared. Contrary to the earlier studies, an increase in the 90 days' mortality with intensive glucose control as compared to conventional control (27.5% *vs* 24.9%; OR, 1.14; 95% CI: 1.02-1.28; *P*=0.02) was found. There was no difference in the length of hospital or ICU stay, duration of mechanical ventilation or renal replacement, new-onset organ failures, red cell transfusions or positive blood cultures. Hypoglycemia was significantly more frequent in the intensive glucose control as compared to the conventional control (6.8% *vs* 0.5%; *P*<0.001). A meta-analysis including the NICE-SUGAR trial [18], again showed that intensive insulin therapy conferred no mortality benefit to critically ill patients. Intensive glucose control resulted in a mortality benefit among patients from a surgical ICU (RR 0.63, 95% CI 0.44-0.91) while the same was not true in other ICU settings. The target glucose level did not influence either mortality or the risk of hypoglycemia. Among the 14 trials that reported hypoglycemia, the pooled risk of hypoglycemia was several times higher with intensive insulin therapy (RR 6.0, 95% CI 4.5-8.0).

Several methodological differences can explain the strikingly different results obtained in the NICE-SUGAR trial [17] as compared to the Leuven study by Van den Berghe, *et al*. [8]. The glucose target in the control groups in the latter study was higher (180 -200 mg/dL) in comparison to <180 mg/dL in the NICE-SUGAR trial. Most patients in the control group of the NICE-SUGAR trial too received insulin to maintain blood glucose as glucose control had become a standard of care. Other differences include techniques of blood sugar measurement and insulin infusion, relatively large doses of parenteral glucose (200-300 g/day) and predominantly surgical patients from a single centre in the Leuven study. Also, the NICE-SUGAR trial used a different outcome measure, *i.e.,* mortality at 90 days while other studies included ICU and/or hospital mortality.

Some investigators have highlighted the role of variability of blood glucose levels in critically ill patients as an independent predictor of mortality. In a study including 7049 patients, Egi, *et al*. [19] reported that glucose variability was more significantly associated with mortality than hyperglycemia. Among patients with sepsis, Ali, *et al*. [20] found that glucose variability was independently associa-ted with hospital mortality. In a retrospective analysis, Bagshaw, *et al*. [21] demonstrated that both hypoglycemia and glucose variability independently increase the risk of mortality among ICU patients. Hermanides, *et al*. [22] demonstrated that low glucose variability is protective, even when mean glucose levels remain elevated. The hypothesis put forward is that intensive insulin therapy, while tightly controlling blood glucose level within a narrow range, actually decreases the variability of blood sugar levels, thus improving the outcome. This could further explain the differences in the outcome in the Leuven study as against the other subsequent randomized controlled studies.

### EVIDENCE IN CRITICALLY ILL CHILDREN

Hyperglycemia has been recognized to be harmful in critically ill pediatric patients too [7], and a poor prognostic marker in children with head injury and gun shot wounds of the brain **(Web Table)**. Srinivasan, *et al*. [7] in a retrospective study, reported that hyperglycemia at 24 hours was present in 54% of the patients and was associated with a 3.5 fold higher mortality risk. A longer duration of hyperglycemia and a higher peak blood glucose value during PICU stay were associated with an adverse outcome; both these were independently associated with mortality on multi-variate logistic regression. Overall, 8% of children had hypoglycemia, irrespective of insulin infusion and the latter did not increase the risk of hypogly-cemia. Another retrospective study by Faustino and Apkon in 942 non-diabetic children admitted in a PICU reported that maximum glucose concentration within 24 hours of >150 mg/dL and highest blood glucose concentration within 10 days of admission >120 mg/dL correlated with the risk of in-hospital mortality [23]. However, being retrospective, these studies had inherent limitations.

Some studies have documented the prevalence of hyperglycemia in specific disease states [24-26]. In a prospective study on children with septic shock, Branco, *et al.* [26] found that a peak blood glucose value of ≥178 mg/dL was found to be the best discriminatory blood glucose level associated with a significantly higher risk of death in children with sepsis.

Another dimension of deranged glucose regulation in critically ill children, variablility in glucose level and its adverse effect on outcome was elucidated in further studies [27,28]. In a retrospective study by Wintergrest, *et al*. [27], glucose variability was calculated as an index based on consecutive glucose values and reflected the fluctuations in glucose values. Higher glucose variability was associated with a significantly higher hospital length of stay and mortality. Hirshberg, *et al*. [28] also found that hyperglycemia and glucose variability were significantly associated with mortality, increased hospital length of stay and risk of nosocomial infections. No glucose control protocol was in vogue when these studies were conducted. Unfortunately, these studies do not give any data regarding the nutrition, steroids, vasoactive infusions etc. used, which might have affected glucose levels.

Though strict glycemic control has been accepted easily as a standard of care among adults, the same is not true for pediatric patients. A survey among the pediatric intensivists in the UK [29], and a pros-pective study from the PICUs of Australia and New Zealand [30] showed neither uniform glucose con-trol regimes nor consensus regarding levels of hyper-glycemia requiring therapy.

Preissig, *et al*. [31] instituted a protocol to control hyperglycemia in a PICU. Blood glucose was main-tained between 80 to 140 mg/dL using insulin infu-sion as and when necessary. On an average, 51% of the children were hyperglycemic, most developed this on day 2 of PICU admission and a mean of 5.4 hours were required to correct the hyperglycemia with insulin infusion. This study highlighted that it was feasible and safe to institute glycemic control in critically ill children without any significant increase in the episodes of hypoglycemia.

The single randomized controlled study of targeting age-adjusted normoglycemia using insulin infusion in pediatric patients was published by Vlasselaers, *et al.* [32]. 700 children admitted to the PICU at Leuven were randomly assigned to either intensive insulin group (target glucose 50-80 mg/dL in infants and 70-100 mg/dL in children) or conventional group (insulin to prevent blood glucose >215 mg/dL). This intervention resulted in a shorter stay in the PICU, an attenuated inflammatory response as indicated by C-reactive protein level on day 5 compared to baseline ($P$=0.07) and a lower mortality (3% *vs* 6%, $P$=0.038) with intensive insulin approach. However, a higher incidence of hypoglycemia occurred in the patients in the intensive insulin group (25%) as compared to the conventional group (1%).

In view of the high prevalence of hyperglycemia in critically ill children, and lack of good quality data supporting its treatment, large randomized controlled studies are required to evaluate efficacy and safety of insulin in the management of critically sick children. The results of at least three large randomized controlled trials of strict glycemic control in pediatric patients are eagerly awaited [33-35].

## EPILOGUE

Those caring for sick children should be aware of the high prevalence and dangers of hyperglycemia. Accepting hyperglycemia as an adaptive response to critical illness and treating it only when it crosses the renal threshold is not justified. Treating hyperglycemia with insulin infusion as one of the many arms of modern day 'intensive care' seems necessary. However, the glucose target should be modest. Targeting blood glucose levels in the 'normal' range; i.e., <110 mg/dL is difficult, increases nursing activity significantly [36] and is fraught with the risk of hypoglycemia. It is more appropriate to target a level of 110-150 mg/dL [37,38]. With this range of blood glucose, the ill effects of hyperglycemia are overcome while avoiding the dangers and difficulty of achieving normoglycemia. In view of paucity of such studies in the developing world with a high prevalence of malnutrition, extrapolation of Western literature should be done with caution. Each PICU should implement locally appropriate protocols of blood glucose control while providing adequate

**KEY MESSAGES**

- Hyperglycemia is common in critically ill children and is associated with a poor outcome.
- Treating hyperglycemia with insulin infusion, taking care to avoid hypoglycemia, improves outcome.

nutrition. Training of the nursing staff to implement a protocol of frequent monitoring of blood glucose at the bedside and fine adjustment of insulin infusion is crucial to prevent not only hypoglycemia but also excessive variations in the glucose level, which may be as harmful.

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