Glucose Homeostasis in the Intensive Care: The end of a Cycle

Abstract:

Over the last decade there has been extensive literature and debate about blood glucose control in adults and children undergoing intensive care. The concept of tight glycaemic management began in adults and subsequently trickled down to paediatric patients. Hyperglycaemia is known to correlate with the degree of organ failure and death. The central question is whether hyperglycaemia is simply a marker of illness severity or a contributory factor in the patientâ s illness. This is of fundamental importance in that it determines whether one should intervene or defer insulin treatment. The other issue is whether treatment with insulin is beneficial or harmful in this ICU setting. Possible explanations for the adverse effects of high glucose include pro-inflammatory responses. It was postulated that lethal perfusion injury to vital organs could be reduced by the prevention of hyperglycaemia with insulin. It was clear that randomised trials were needed to determine the best course of action.

A study in 2001 in adult ICU patients reported that insulin therapy to control blood glucose resulted in reduced morbidity and mortality [1]. The greatest reduction was in multiple organ failure deaths due to proven sepsis. During the 2000s clinical guidelines were produced which set out narrow glycaemic control. It became accepted that high blood glucose concentrations were disadvantageous to patients and should be treated. Guidelines and protocols were generated to support this approach. This remained the perceived wisdom in adult ICUs for the following 6 years.

A prospective randomised control in children found that that tight glycaemic control had short term beneficial effects [2]. However the measure was not widely adopted in ICU children because of the concerns about hypoglycaemia. In the study hypoglycaemia occurred in 25% of the children in the intervention group compared with 1% in the control group.

Things changed significantly with the publication of the NICE- Sugar Study [3] in 2009. Adults who were expected to require treatment in the intensive care unit on 3 or more consecutive days were randomly assigned to undergo intensive blood glucose control (target range 4.5 to 6.0 mmol/l) or conventional blood glucose control (10.0 mmol). The primary end point was death from any cause within 90 days after randomization. Intensive glucose control increased mortality among the patients. The number needed to harm was 38. Also the rate of hypoglycaemia was significantly greater in the intervention group. These findings were different to the perceived wisdom on the matter. Targeted glucose control with insulin was now regarded as inadvisable.

In a more recent study Agus et al [4] report that children assigned to tight glucose control following cardiac surgery. In this group of children the incidence of blood glucose greater than 7 mmol/l was 90%. A total of 444 children were assigned to insulin therapy and compared with 490 children who received standard care. The children who received targeted glucose control did not have a decreased rate of healthcare associated infections. The outcome in both limbs of the trial were similar.

We appear to have come full circle. The early promise of better outcomes with targeted lower blood sugar levels has not been fulfilled. Kavanagh [5] states that the door is closed on the routine normalisation of plasma glucose in ill adults and children. However studies on glucose homeostasis need to continue.
The sequence of events surrounding glucose control in the ICU setting raises a number of questions about research findings and how we adopt them into clinical practice. Following the initial study in 2001 blood glucose levels became a key quality measure in ICU management. Expert consensus endorsed tight glucose control. This recommendation was incorporated into the clinical guidelines in many ICUs. Tight glucose became a quality metric and was widely introduced in the US. There were reports of doctors being criticised for not adhering to the new approach. Ultimately the programme for aggressive glucose control in ICU patients was challenged by the NICE-Sugar Study. It would appear that the initial studies and their findings were over-interpreted. The biological plausibility of hyperglycaemia causing infection may not have been sufficiently challenged. At any rate tight glycaemic control does not confer advantage and may in effect be harmful. It exposes a fundamental flaw on quality is defined and metrics are applied.

Groopman and Hartzband [6] have commented that rigid rules to broadly standardise care for all patients will often break down. Flexibility is essential when applying evidence from clinical trials. A good doctor exerting sound clinical judgement must always be given the clinical latitude as to what is the preferred course of action for the individual patient. What is best for a patient will at times deviate from the current guideline. It is a worry that quality metrics may make a doctor feel compelled to follow a particular course of action against his best judgement. This is an important point also in this country. There multiple sources of guidelines both nationally and internationally being produced at frequent intervals. Their quality is variable and most of them have not been subjected to sufficient scrutiny. When a clinician finds a guideline to be at variance with his clinical experience he must challenge it at the outset.
There must be a balance between the new findings from trials, the introduction of guidelines and a physicianâ s decision making.

JFA Murphy
Editor

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Comments: