Editorial

Glycaemic control in the critically ill

Critically ill patients often demonstrate hyperglycaemia due to a variety of mechanisms which include insulin resistance, relative insulin deficiency, impaired glucose metabolism, medications such as corticosteroids, and enteral and parenteral hyperalimentation. Apart from being a marker of severity of illness, several studies have demonstrated that this acute hyperglycaemia, also referred to as 'stress hyperglycaemia' worsens outcome.[1]

Based on the above, in 2001, Van den Berghe and colleagues[2] from Leuven, Belgium, hypothesized that maintaining 'normal' glucose levels with insulin in such patients would reduce mortality and morbidity. They conducted a prospective, randomized, controlled study involving 1548 adults who were admitted to a surgical intensive care unit (ICU) and were on mechanical ventilation. Blood glucose was maintained at 80–110 mg/dl using insulin infusion in patients in the 'intensive insulin' arm, while in the 'conventional' arm blood glucose was maintained at 180–200 mg/dl (insulin used only if blood glucose >215 mg/dl), irrespective of the pre-existing status of diabetes. A dramatic reduction in the ICU mortality from 8% in the conventional treatment group to 4.6% in the intensive treatment group, a reduction of 42%, was noted. Interestingly, the reduction in mortality occurred exclusively in patients whose ICU stay was >5 days (10.6% in the intensive treatment group compared with 20.2% in the conventional treatment group). The maximum reduction was in deaths due to multiorgan failure with a proven septic focus. Further, the in-hospital mortality was reduced by 34%, with reduction in morbidity due to blood stream infections by 46%, renal replacement in acute renal failure by 41%, median number of red cell transfusions by 50% and critical illness polyneuropathy by 44%. The duration of mechanical ventilation and ICU stay was also reduced.

As a result of the multiple benefits demonstrated, the results were accepted by many professional bodies and implemented widely.[3] This was adopted in various ICU settings worldwide as a result of incorporation into guidelines such as the 'surviving sepsis guidelines'.[4] The adherence to 'tight glycaemic control' with insulin has since become a benchmark for measuring the quality of ICU care.

Maintaining such 'tight glucose control' involves a substantial increase in nursing activity and also requires a degree of expertise and decision-making to adjust the insulin infusion. Hence, the implementation of this guideline in ICUs in the Indian context is fraught with difficulties due to the poor nurse-to-patient ratio, non-availability of point-of-care blood glucose measurement, increased cost of therapy and, above all, lack of expertise among the nursing staff. Under these circumstances, the risk of hypoglycaemia would increase enormously as the expertise of the nursing staff is crucial to prevent hypoglycaemia.

Subsequent studies on glycaemic control in ICU patients done in different settings yielded conflicting results.[5–8] Not only was it difficult to obtain similar substantially better results, reports of disturbingly high rates of hypoglycaemia were evident in some studies. Van den Berghe *et al*., in a study similar to the first one,[2] but conducted in a medical ICU,[5] could not demonstrate mortality benefits with tight glucose control with insulin but were able to show benefits with regard to new-onset renal failure,

duration of mechanical ventilation, ICU stay and hospital stay. Patients staying in the ICU for >3 days had a lower mortality while the mortality was higher for those staying <3 days. A substantially higher rate of hypoglycaemia (blood glucose <40 mg/dl) (3.1% *v*. 18.7%) was also seen. In the study conducted by Treggiari *et al*.,[8] there was no benefit in mortality with tight glucose control; rather, an increased mortality was seen in patients requiring <3 days of ICU stay. Again, a substantial increase in the rate of hypoglycaemia occurred. A multicentre, randomized study conducted in 18 multidisciplinary ICUs reported by Brunkhorst *et al*.[9] was terminated after the first safety analysis due to an unacceptably high rate of hypoglycaemia (2.1% in the conventional therapy group *v*. 12.1% in the intensive therapy group). In a large multicentre European study by Devos *et al*.,[10] the rate of hypoglycaemia was 3-fold higher in the conventional therapy group compared with the intensive insulin therapy group (9.8% *v*. 2.7%, p<0.0001) with no benefit in mortality. A meta-analysis on this topic[11] included 34 randomized controlled trials with data for over 8000 adult patients. This showed no benefit of tight glucose control in reducing hospital mortality. Further stratifying the analysis based on the ICU setting (medical, surgical or mixed) and glucose goal ('very tight', i.e. <110 mg/dl *v*. 'moderately tight', i.e. <150 mg/dl) did not change these findings. Tight glucose control significantly reduced the risk of septicaemia (10.9% *v*. 13.4%; relative risk [RR] 0.76; 95% CI 0.59–0.97) compared with conventional care, while there was no effect on new need for dialysis. Hypoglycaemia was significantly higher in the group receiving tight glucose control (13.7% *v*. 2.5%; RR 5.13; 95% CI 4.09–6.43).

The largest study on this topic till date, the NICE-SUGAR trial,[12] an international, randomized trial, included 6104 patients, and compared the mortality at 90 days among ICU patients randomized to maintain blood glucose at 81–108 mg/dl (intensive glucose control) against those with a blood glucose ≤180 mg/dl (conventional glucose control). Surprisingly, an absolute increase in the 90-day mortality was noted with intensive glucose control as against conventional glucose control (27.5% *v*. 24.9%; OR 1.14, p=0.02) with a significant increase in the number of deaths due to cardiovascular causes among the former. Also, severe hypoglycaemia occurred more often in the intensive control group (6.8% *v*. 0.5%; OR 14.7; 95% CI 9.0–25.9). No difference was noted in length of ICU or hospital stay, duration of mechanical ventilation, new-onset organ failures or the rates of positive blood cultures or red cell transfusions.

Methodological differences could explain the differences in results obtained in the Leuven study[2] *vis-à-vis* the NICE-SUGAR trial. Relatively large doses of parenteral glucose (200–300 g/day) were used in the former, while most current ICUs use enteral calories to feed patients. At the time of the Leuven study, it was not routine to treat hyperglycaemia unless it exceeded the renal threshold and hence insulin was used in the control group only if blood glucose was >215 mg/dl as against a target blood glucose range of <180 mg/dl in the control group of the NICE-SUGAR trial; thus, almost all patients in the control group too received insulin. While the Leuven study was a single-centre study with predominantly surgical patients, the NICE-SUGAR trial was an international study that included patients in medical and surgical ICUs. Also, the NICE-SUGAR trial compared the 90-day mortality; an outcome measure which had not been used previously.

Hyperglycaemia has been recognized as a marker of adverse outcome in children too.[13] Only one prospective, randomized, controlled study has been conducted in children in the paediatric ICU[14] in Leuven, Belgium. This reported a shortened paediatric ICU stay in the group assigned to a target blood glucose of 50–80 mg/dl in infants and 70–100 mg/dl in children compared to those with a target blood glucose <215 mg/dl (conventional group). However, hypoglycaemia occurred more often in this group as compared to the conventional control group (25% *v*. 1%).

It seems that the benefits from decreasing blood glucose to 'normal' levels in critically ill patients using insulin infusions have been over-rated. Hyperglycaemia is clearly harmful but it may be a marker of more severe illness rather than a target for therapy. Hypoglycaemia is not benign and the long term consequences, especially

its effects on long term neurological outcome, are not known. Trying to correct all physiological derangements to normal levels do not always yield the best outcomes. For example, accepting higher $PaCO_2$ values during mechanical ventilation of acute respiratory distress syndrome (ARDS) prevents lung injury. It is prudent to aim for modest blood glucose levels of 140–180 mg/dl in patients in the ICU, rather than target 'normal' glucose levels.

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