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Editorial

Strict Glycemic Control: The Demise of another Good Strategy?

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Introduction

Problems of hyperglycemia in ICU patients!

It is beyond any dispute that diabetes/increased blood glucose levels in the hospitalized patients, especially in ICU/critically ill patients, is one of the most important cause of morbidity and mortality [1,2]. In fact that in itself maybe one of the major causes of hospital admissions (15% of 3.5 million total hospitalization), both for medical as well as surgical reasons. It also is the most common reason of maximum number of hospital days. (20% of all hospital days out of about 14 million hospital days).

Hyperglycemia puts the patients at high risk for bacterial infection during surgery or anesthesia or minor procedures like catheter placements and intravenous access, especially central lines, for impaired tissue and organ perfusion and as a result, delayed wound healing.

It also leads to

1. Neutrophil dysfunctions such as impaired chemotaxis, phagocytosis, adherence, etc.
2. Compliment inhibition
3. Glucose stimulating the process of inflammation as well as acting as a rich culture medium (glucose rich edema fluid) [3].

Strict (Tight) Glycemic Control (SGC/TGC) can be defined as:

Maintenance of the blood glucose level in the range of 80-110 mg /dl. with help of dose variable and Intensive Insulin Therapy (IIT). Since its introduction, there have been conflicting reports of its efficacy and complications. This resulted in slow but steady neglect of this very good strategy leading to its almost complete demise.

It all started with a very interesting, path-breaking study by Van den Berghe., *et al.* [4], in 2001, which claimed that in twelve months period of time, in the patients enrolled in the study (N = 1548), with intensive insulin therapy (IIT) when the blood glucose levels were maintained < 110 mg/ dl, there was drastic reduction in mortality in critically ill patients. The conventional group had 1.74 times more mortality while IIT patients had 34% reduction in mortality, 46% reduction in sepsis, 41% reduction in dialysis, 50% reduction in the blood transfusion & 44% reduction in polyneuropathy.

This was followed by few encouraging studies by Lazar., *et al.* [5], Juvela., *et al.* [6] & Krinsley., *et al.* [7], which were supporting the use of IIT or strict/tight control of glucose improving the outcomes. Then Van den Berghe., *et al.* [8] came back again in 2006, this time with IIT in medical ICU with the idea of understanding its impact. Here they could not convincingly prove significant reduction in-hospital mortality (40% in conventional treatment vs. 37.7% in IIT group, p = 0.33). The saving grace was significant reduction in morbidity by prevention of new kidney injury, earlier ventilator weaning, so logically earlier ICU and hospital discharge. This led to serious introspection, debates and further trials.

The study done by Treggiari., *et al*. on 10000 patients in a level I, care unit extending for over four years was very enlightening [10]. The authors used 3 glycemic control protocols to monitor the outcome: mainly the mortality both in ICU as well as in the hospital.

A. No control protocol (no glucose limits)
B. Target glucose of 80-130 mg per dl.
C. Standard (Tight Glucose Control) of 80-110 mg per dl.

The results were striking. In all the 3 groups, the use of insulin was increased by 9%, 25%, and 42% respectively. But what was contradictory to the previous thinking was that, there was overall higher mortality in group c, the patients receiving TGC (Odds Ratio 1.15) especially in patients with ICU stay of 3 or lesser days. As would be expected nearly 4 times increase in the incidence of hypoglycemia from group A through B to C.

While these findings were being assessed and assimilated, a newer study emerged, where authors had studied in another trauma center, over 2000 adults with 2 protocols

A. Pre TGC (80-200 mg per dl)
B. Post TGC (80-110 mg per dl)

The most important finding was that the mortality was significantly higher in pre TGC period (21.5%) as compared to that of post TGC period (14.7%) [11].

Also the point to be noted of Van den Berghe., *et al*. trial was that the randomly assigned intensive insulin therapy (IIT) group received insulin infusion tailored to control blood glucose levels in the range 80-110 mg/dl, whereas the conventional treatment group received insulin only when glucose levels exceeded 200 mg/dl and in that event were maintained in a target range of 180-200 mg/dl. The statistical analysis indicated that that control of blood glucose levels rather than insulin administration itself explained observed clinical benefits [9].

The final straw which actually broke the proverbial camel's back was,

NICE-SUGAR study (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation study)[12], which was published in 2009, where in 38 tertiary hospitals and 4 community hospitals, 6030 patients evaluable in the period of 5 years (December 2004-November 2008) were studied. Again the groups were intensive vs. conventional i.e. 81 to 108 mg per dl vs. < 180 mg per dl glucose levels were the targets. Here the patients were randomized but not blinded. The mean age was 60 years with equal distribution by gender and Apache II scoring of 21 in each group. The outcome majors were:

A. 90-day mortality
B. Duration of mechanical ventilation, renal replacement therapy, length of stay in ICU/hospital and cause of death.
C. 28-day all-cause mortality, incidence of organ system failure, transfusion requirements and new positive blood cultures.

The results were very revealing:

1. Mortality at 90 days was 27.5% in IIT group vs. 24.9% in conventional group (CT),
2. (Odds Ratio-O.R. 1.14, p = 0.02)
3. Mortality at 28 days was 22.3% in IIT group vs. 20.8% in CT (O.R. 1.09, p = 0.17)
4. Location of death in ICU
    A. 65.9% in IIT vs. 66.3% in CT
    B. In-hospital 26.9% IIT vs. 26.2% CT

There was absolutely no difference in the length of the ICU stay of 6 days, hospital stay of 17 days or on-ventilator stay of 6.6 days in both the groups on the top of that hypoglycemia (glucose levels < 40 mg per dl) was found in 6.8% patients in IIT as compared to 0.5% in CT with Odds Ratio (O.R.) of 14.7.

What went wrong?

In their over enthusiasm to implement the IIT/ SGC/TGC, the researchers, clinicians went overboard with their own half-baked protocols. A very interesting review [13] tries to answer few very important and pertinent queries like

a. How safe is the intensive insulin treatment (IIT), with various glycemic targets from risk of hypoglycemia?
b. How tightly blood glucose must be controlled for this approach to be effective?
c. What role does the accuracy of blood glucose measurement play in affecting the study of this method?

One has to understand basic flaw in the design of TGC and that is:

With every eventuality, be it hyperglycemia, hypoglycemia or any variability in glucose levels, the targets/goals, risks and benefits of treatment including TGC protocol (IIT), might be different. With the standardization of blood glucose monitoring and improved accuracy, the risk of overdosing of insulin would be reduced, leading to less chance of hypoglycemia and hyperglycemia. Because if you look at the various methods of glucose measurement, from handheld devices, also called as Point Of Care Testing (POCT), paper or plastic sticks which use a drop of blood and Blood gas analyzers/other analyzers in the central labs. The values of these methods may have inherently based fallacies/ variations.

The handheld devices (POCTs) have not been found to be without their own significant variations and errors. So they even put forward very glaring variability especially in the terms of type of the sample. Accordingly it has been documented that Fasting Blood Glucose levels in the venous sample are 5 -10% lower than that in arterial sample. While capillary sample may be 5 – 15% higher, when those compared with venous sample.

Factors which can be considered as confounding

1. Accuracy and reproducibility of POCT
2. User Expertise
3. Types of devices
4. Anemia causes false evaluation of glucose levels. Anemia is one of the commonest findings in critically ill patients.
5. As already mentioned, arterial plasma, serum, capillary, venous samples give different results.
6. Findings may improve outcome, but is variable and inadequate.
7. Which insulin to be given: The onsets, peak and duration of action of various preparations varies: careful selection is essential.

How to overcome?

In a systematic analysis of various serial trials Shultz., *et al*. [14] have compared the outcomes of Van den Berghe's Leuven studies with those of serial studies from various hospitals from different countries, in order to pinpoint the root cause of the failures of SGC [15-18]. To summarize their observations:

The Leuven IIT trials were successful and effective because:

A. The SGC was applied by the insulin infusion via central venous line and administered using very precise syringe infusion pumps
B. Subtle dose adjustments, made by ICU nurses, using guidelines to keep blood glucose to lower normal limit (81-110 mg per dl) and also' high level of intuitive decision making' [19].
C. The blood glucose level measurement in arterial blood was carried out at strict time interval points using accurate blood gas analyzers.
D. The measurements were carried out at an intermediate time interval points if required.
E. Patients were always in a non-fasting state at all times.

We have to now judge on the basis of these observations, the later date trials reports and assessments. The glaring fallacies are:

1. Instead of syringe infusion pumps, volumetric infusion pumps were used.
2. Level of knowledge, training about guidelines and involvement of the ICU nurses was disputed.
3. In addition the decision making, training was related to only prevention and correction of hypoglycemia.
4. Fallacies of blood glucose level measurements also play a major factor. The use of capillary blood samples as an indicator of glycemic control is little inferior, so are the assessment of the glucose levels in the absence of accurate glucose analyzers.
5. Last but not the least, rather most important key factor in the success of Leuven trials is: The pure, simple plan and high level of intuitive decision making, skill and motivation on the part of ICU nurses and actual absence of highly explicit rules required in closed loop systems, computer-based decision support systems and paper-based systems required in sliding scales.

This discussion about what went goes and will go wrong can go on endlessly especially when discussing improperly and inadequately designed and executed randomized trials involving SGC/TGC. One has to, without an iota of doubt accept that hyperglycemia is deleterious to the critically ill patients [20-22,7]. In the light of adequate evidence to suggest that lowering of blood glucose levels have the potential to prevent injury in already compromised organs in the patients.

So while planning our own strategies to achieve these targets, one has to keep in mind:

1. Perfect planning of design of the trial.
2. Precise methodology to achieve optimal/achievable target levels of blood glucose.
3. Critical check of methods and equipment used to measure and control the glucose.
4. Try to extrapolate all the available evidence from various RCTs to their own circumstances and infrastructure.
5. Evolving newer strategies/protocol of maintaining good glycemic control (GGC):
    A. Continuous variable rate of intravenous insulin drip especially in patients undergoing major surgery or remaining NPO for prolonged duration, myocardial infarction, diabetic keto-acidosis or patience on chronic steroid administration.
    B. Devising SPRINT (Specialized Regulative Insulin Nutrition Table) protocols [23].

Conclusion

Hyperglycemia in hospitalized, especially critically ill patients is undoubtedly harmful. Adequate glycemic control has been proven to be beneficial by multiple SGC, TGC trials carried out by various workers. Some confounding evidence of supposed deleterious effects of SGC/TGC has caused lot of confabulations and dilemmas leading to almost near demise of a good therapeutic strategy.

One has to be very circumspect, have clear understanding of their own infrastructural and logistical short-comings while planning and implementing SGC/TGC protocols. It would be prudent to do thorough stock checking and defining our own target limits of SGC/TGC before embarking on this promising but tricky journey.

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