

Hyperglycemic control in the ICU

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Margaret Mulligan

BA, BSN, RN

Based in Cleveland, Ohio (USA)

Margaret Mulligan is a writer and registered nurse with experience in heart/lung transplant and critical care.

Tight glycemic control (TGC) in the intensive care unit is essential to comprehensive clinical management.

However, TGC that is too aggressive in the wrong patient populations (particularly non-diabetics) can result in hypoglycemia, which brings with it a set of sequelae that can increase morbidity and mortality.

It is also important to determine which blood glucose sources and devices will allow clinicians to make quick decisions on TGC based on accurate data. The discussion is ongoing.

There is little controversy surrounding the idea that glucose control for patients in the intensive care unit (ICU) is an essential component of good clinical management.

However, there is a great deal of comment and even confusion as to how much glycemic control is too much, as well as which types of patients would either benefit or worse, be harmed by such control.

The dilemma facing clinicians is multifaceted. Glucose levels must be measured and acted upon. The question then arises, what should be done about an elevated glucose level?

If one goes too far with insulin therapy in particular, one may induce hypoglycemia, which has its own serious implications with regard to morbidity and mortality.

There is also the concern that the measurement itself may not be accurate enough to plan an effective and safe intervention.

How did we get here?

The seminal study that began the current round of tight glycemic control (TGC) protocols is widely acknowledged to be the work of van den Berghe *et al* [1] who studied TGC in a surgical ICU in Leuven, Belgium.

This 2001 analysis launched a worldwide revolution in the way glucose was managed in ICUs, despite the fact

that the Leuven study was done at a single institution and thus far, no one has reliably been able to reproduce their findings [2]. Even van den Berghe's team could not replicate their findings completely when they conducted a similar study in a medical ICU in 2006 [3].

As a result, anyone who has worked in an ICU over the past 5 to 10 years might be forgiven for thinking that the idea of aggressive TGC for everyone – diabetic or not – is a natural outgrowth of a clear march of scientific progress.

It makes good sense, given the known morbidities and mortality associated with hyperglycemia. However, as Alter and Deines note, *"until 2001, inpatient glycemic management focused solely on the diabetic patient with few reported studies that discussed hyperglycemic management of the nondiabetic patient."* [4]

They do point out however, that there were a few studies concentrating on patients who did not have diabetes. This is because of the known sequelae associated with hyperglycemia.

Additionally, *"it was thought that hyperglycemia may be an adaptive response to injury necessary for survival and not necessarily a prognostic indicator of morbidity or mortality."* [4]

That said, hyperglycemia is not benign, and it has consistently been observed that hyperglycemia, whether secondary to diabetes or stress-induced (in the non-diabetic) is seen in critically ill patients [5].

Survival after the appearance of hyperglycemia is of particular concern in the non-diabetic patient [5]. Hyperglycemia appears in up to 80 % of critical care patients who suffer from acute illness [4]. Hyperglycemia can also manifest when patients are given parenteral nutrition and infusions of dextrose [4].

These types of data were the impetus for van den Berghe and colleagues, who point out that in addition to hyperglycemia, patients in the ICU also suffer from insulin resistance, even if they are not diabetic.

In their 2001 study, the researchers looked at what could be done to manage and treat hyperglycemia in the ICU [1]. They performed a randomized, prospective, controlled study with patients in their unit (surgical intensive care) who were on mechanical ventilation.

They randomized 1,548 patients to receive either *"intensive insulin therapy"* (IIT) or *"conventional treatment"* (CT). Under the IIT protocol, patients' blood glucose levels were to be maintained between 80 and 110 mg/dL (4.4 and 6.1 mmol/L); under the CT protocol, patients were to receive insulin infusions if the blood glucose level rose above 215 mg/dL (11.0 mmol/L) with maintenance levels between 180 and 200 mg/dL (10 and 11.1 mmol/L).

At 12 months, the researchers found that IIT had reduced mortality to 4.6 %, compared to 8 % for CT ($p < 0.04$). A caveat, however: the benefit was seen in patients who were in the intensive care unit for more than 5 days (10.6 % with IIT versus 20.2 with CT, $p = 0.005$).

They also note, *"the greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus."* [1] So it would seem that aggressive treatment of hyperglycemia is a worthy goal – for some patients, but not necessarily for all.

And while it is a worthy goal, it does not come without risks. The most notable risk is uncontrolled hypoglycemia, which has its own sequelae. This outcome is what gave pause to clinicians who unsuccessfully sought to replicate van den Berghe and colleagues' results.

Despite the dramatic improvements in glycemic control initially achieved by van den Berghe *et al* [1], other clinicians eventually raised questions about their study results and methods.

For example, Bellomo and Egi [2], in an editorial for Mayo Clinic Proceedings, enumerated key issues with the 2001 study. Among other things, they say the study was not blinded (possible bias); most patients had undergone cardiac surgery (raising the question, could the findings

be applied to other patients?); and patients received IV glucose, which they say is not generally done.

Bellomo and Egi also point out that a single-center study is not sufficient to create Level I evidence to guide practice. Their suggestion to clinicians? *"One simple message: Wait for the results of the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation) trial."* [2] The NICE-SUGAR trial [6] results were released last year.

The trial was a multi-center, multinational trial conducted at 42 hospitals in Australia, New Zealand and Canada. In the trial, more than 6,100 patients were randomized to either CT or IIT. In this trial, CT was defined as maintaining glucose at <180 mg/dL [6].

Even though the IIT group had a lower rate of reported hypoglycemia than had ever been found in any studies to date, the IIT group had an increased mortality rate 90 days after randomization.

Hypoglycemia, then, is an important side effect, if you will, of aggressive glycemia control in the ICU. It can cause hypotension, vasodilation, nitric oxide release and a decreased stress response by the body [2].

This may lead one to believe that perhaps clinicians should not measure and act on elevated blood glucose levels. Nothing could be further from the truth, say Bellomo and Egi.

"We think it is important to emphasize that the findings of NICE-SUGAR do not justify neglecting glycemic control...in the ICU, a glucose level of 243 mg/dL is just as undesirable as a glucose level of 80 mg/dL." [2]

Recommendations

The American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) released a consensus statement on inpatient glycemic control last year [7].

They point out that there is a *"growing national movement viewing the management of inpatient hyperglycemia as a quality-of-care measure."* [7] The organizations had released guidelines and statements previously; however, the continued confusion over just what level of glycemic control is adequate and safe prompted the AACE and ADA to update their guidelines and position statement.

The expert panel asked a number of questions, paraphrased here [7]:

1. Does improving glycemic control improve clinical outcomes in hyperglycemia?
2. What targets are appropriate for different patient populations?
3. What treatment options will result in optimal glycemic targets that are safe and effective in specific situations?
4. Is inpatient hyperglycemic management a safety issue?
5. What systems will ensure that we will achieve our desired outcomes?
6. Is inpatient hyperglycemia treatment cost-effective?
7. What are the best strategies to transition to outpatient care?
8. Areas for future research.

Essentially, the AACE/ADA currently advises that *"until further information becomes available, it is prudent to continue to emphasize the importance of glycemic control in hospitalized patients with critical and noncritical illness while aiming at targets that are less stringent than 80 to 110 mg/dL."* [7]

They go on to advise that once insulin therapy is initiated for the critically ill patient (threshold is 180 mg/dL) glucose levels should be maintained between 140 and 180 mg/dL, with *"greater benefit... at the lower end of this range."*

They also acknowledge that *"somewhat lower glucose targets may be appropriate in selected patients, however targets of less than 110 mg/dL are not recommended."*

Measuring and metrics

Once a clinician has some idea of where and when to treat, the question of how best to consistently measure blood glucose is not far from the mind. The AACE/ADA advisors make this point when they tell clinicians,

"Hospitals attempting to improve the quality of their glycemic control and clinical investigators who analyze glycemic management require standardized glucose measures for assessment of baseline performance and the effect of any intervention." [7] In their recommendations, they urge caution when "interpreting results of POC glucose meters in patients with anemia, polycythemia, hypoperfusion, or use of some medications." [7]

Once these confounding factors are taken into consideration, the question, "what is an appropriate blood glucose measurement?" would seem to be relatively straightforward. The devil, however, is in the details.

The measure can be "mean blood glucose"; or it could be "patient-day" measures. Need more? How about "median blood glucose" or "number of measures in a predefined target range" or even "frequency of blood glucose measurements", not to mention "time needed to reach blood glucose targets" and "time spent in predefined blood glucose protocol"? [8]

One can see that just deciding what to record and measure can be problematic. After that, one must decide how the metrics will be reliably and consistently measured, i.e. from where will blood be drawn?

Within ICUs, the source of blood used for measurement of blood glucose levels can be inconsistent. Measurements are often obtained interchangeably [9], rotating among fingersticks, indwelling venous catheters and arterial lines (via blood gas samples).

Cook et al [9] looked at this phenomenon, examining the level of agreement between values obtained via point-of-care (POC) methods (fingerstick and central venous catheters (CVCs)) and laboratory analysis.

They found that laboratory values for blood glucose (drawn from the catheter) were significantly different from the POC values obtained directly from the catheter at the bedside or from a fingerstick.

Glucose values differed by 20 % mg/dL or more for 15 % of the patients for catheter samples and for 21 % of fingerstick samples. POC values for fingerstick and catheter samples did not differ ($p = 0.98$).

The authors say that hematocrit levels significantly explained the difference between the values seen using the lab versus the POC methods ($R^2 = 0.288$, $p < 0.001$ for the catheter; $R^2 = 0.280$, $p = 0.02$ for the fingerstick).

They conclude that using commonly available POC devices "when precise glucose values are needed may lead to faulty treatment." [9] This is not necessarily the fault of the POC devices, they explain, "Because most POC glucose meters have an adjustment to correct glucose values, to align with laboratory measures, use of CVC blood with a POC device could introduce additional measurement error." [9]

The study comprised 67 patients, tested over a 5-month period. Glucose values ranged between 62 and 218 mg/dL.

Hematocrit values ranged between 22 and 46.2 %. The researchers simultaneously obtained CVC and fingerstick blood samples to determine whether the two could be used interchangeably when comparing results to laboratory values. They could not. Further, they caution,

"most POC devices were never intended to be used for treatment situations in which precise measurement of glucose is required; the devices were designed for monitoring trends in glucose levels." [9]

What do results like these portend for TGC? As Alter and Deines explain, "TGC hinges on the blood glucose result, with the expectation that it is as accurate and precise as possible." [2] It also has to be fast.

Part of the appeal of the POC method is that presumably it allows clinicians to make treatment decisions quickly. However, as has been explained, speed may sacrifice accuracy. What to do? Alter and Deines ask this question as well, *"are POC units sufficiently accurate and precise to support intensive insulin regimens in the ICU?"* [2]

They point out that not only is there no uniformity in methods to evaluate TGC, *"almost every manner of specimen type and source (arterial, venous) has been used."* There have been studies as well using blood gas analyzers, POC handhelds, and so on; plus, researchers do not often describe or control for these variables [2].

Alter and Deines agree that POC results are not interchangeable with laboratory results [2], noting that lab results are 11 % higher than POC results due to *"differences in the aqueous components of cellular versus noncellular compartments of blood."*

The result, they say, is a difference in the amount of diffused glucose in the various liquid environments, thus skewing results. The resulting calibration factor of 11 % is set for a hematocrit of 45 %, they explain [2].

They conclude that while POC testing may not be the most effective method of blood glucose testing for TGC, *"one possible solution would be to decide which modality of testing is to be used (for a unit) and adhere to it."* [2]

Petersen *et al* [10] also examined POC testing and TGC. They concluded that arterial or venous whole blood can be used to monitor blood glucose in the medical ICU; however, they do not recommend capillary blood sampling for this purpose.

They followed 84 patients on TGC. They compared glucose levels for the glucose meter (arterial/venous/capillary), blood gas (arterial/venous), and central clinical laboratory (serum/plasma from arterial/venous samples).

Mean glucose levels of all arterial/venous/fingerstick samples using the glucose meter demonstrated a positive bias of 0.7-0.9 mmol/L (12.6-16.2 mg/dL) ($p < 0.001$)

relative to central laboratory venous plasma. There was also a smaller positive (0.1-0.3 mmol/L or 1.8-5.4 mg/dL, $p < 0.05$) bias for arterial/venous blood gas samples and laboratory arterial serum/plasma glucose samples.

They say that arterial or venous POC glucose results would not have affected clinical care; however, with fingersticks, a high bias could have significantly affected clinical care [10].

Implications for clinicians

The clinician must be aware that POC glucose testing meters can be useful to track trends or to indicate somewhat *"normal"* ranges but they may not be the best modality to make decisions on treatment in a TGC protocol [11].

Some studies have also indicated that while hyperglycemia is a serious sequela in the critical care setting, it may be more serious for the non-diabetic patient, for whom it may confer increased mortality (compared to the diabetic patient) [11].

It is also important to not only look at the absolute blood glucose level, it is important to execute a protocol that will reduce blood glucose variability [11, 12], which has been associated with higher crude and adjusted mortality in the ICU than hypoglycemia or no hyperglycemia [12].

Conclusion

Tight glycemic control (TGC) in the intensive care unit is essential to comprehensive clinical management.

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