What, Why and How of Blood glucose monitoring in critically ill patients

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INTRODUCTION

Blood glucose (BG) monitoring is a vital component of critical care management. Diabetes is an important risk factor for developing severe disease necessitating intensive care unit (ICU) admission. Additionally, any acute illness may increase the risk of derangement of BG levels. These fluctuations may happen irrespective of the diabetes status of the patient and may affect their ICU course and outcomes. Several factors have been identified that increase the risk of developing hyperglycaemia and hypoglycaemia in ICU patients (table 1)[1-5]. The use of multiple medications, underlying comorbidities and organ dysfunctions, and rapidly changing patient conditions make BG control challenging in critically ill patients. Even the commonly used capillary blood sampling for BG monitoring may be unreliable in these patients[6].

Furthermore, there needs to be more clarity regarding glycaemic indices and targets to be employed for optimising outcomes in critically ill patients. Targeting tight glucose control, which was earlier recommended, has not shown any mortality benefit but may increase the risk of hypoglycemia by five times[7]. It also requires frequent blood sampling and regulation of insulin dose, which may increase the workload of healthcare workers (HCWs) and add to the cost of care. Hence, recent guidelines recommend more liberal BG targets to avoid the risk of hypoglycemia[8,9]. In addition to the commonly employed indices like hyperglycaemia and hypoglycaemia, glycaemic variability (GV) and time in target range (TITR) are recently recognized components of

dysglycaemia which may affect patient outcomes[10-12]. However, the exact targets for these indices still need to be well established, making their clinical utility questionable.

ARTERIAL VS CAPILLARY MONITORING

BG management requires frequent blood sampling and insulin dose adjustments. BG monitoring in critically ill patients by plasma-based central laboratory methods using venous or arterial samples is considered standard. However, due to the long turnaround time and convenience associated with a point of care testing (POCT), currently, glucometers and arterial blood gas (ABG) analysers are being frequently used. Bedside capillary blood glucose monitoring (CBGM) arguably remains the most commonly employed method, even in critically ill patients. However, its accuracy may be affected in patients with subcutaneous oedema, shock, and hypoxemia, which commonly affect ICU patients[4]. This may lead to highly variable results and higher bias (overestimation) for fingerstick sampling than arterial or venous BG monitoring, which can significantly affect clinical decision-making[13]. Hence, arterial blood is preferred but requires repeated arterial punctures or an invasive arterial line (table 2). The correlation between arterial and capillary glucose levels is also significantly affected in patients with shock requiring vasopressors, with a proportion of disagreement ranging from 1.4 to 27.1% [14,15].

Over the years, there has been remarkable progress in the technologies used for bedside glucometers. Based on the glucose oxidase method, the initial generation of glucometers was affected by low and high haematocrit, blood pH, and even some medications[16]. The more recent glucose dehydrogenase-based glucometers are largely unaffected by high PaO2 and other interferences

but had a serious flaw of being highly inaccurate in patients on peritoneal dialysis whose dialysate contains Icodextrin, because of its hydrolysis to maltose, causing pseudo-hyperglycaemia[17]. The accuracy and precision of the newer generation of glucometers have improved significantly. They have largely overcome the fallacies of their predecessors to acceptable clinical levels, especially if arterial or venous blood is used for analysis. Recent data suggest that these devices may achieve more than 97% correlation with the reference standard when testing venous and arterial samples. These systems have demonstrated acceptable clinical performance with high specificity, sensitivity, and low risk of potential insulin-dosing errors[18].

It can be inferred that arterial blood should be preferred over capillary blood for glucose monitoring, irrespective of the method used, provided standards of calibration are being followed. Although capillary glucose serves well in hospitalised patients, caution should be exercised in patients with shock[14], insulin infusion[15], vasopressors[14,19], coma[20], and even critically ill adult patients[6]. A large meta-analysis with 21 studies showed that BG readings taken from arterial samples were significantly more accurate than those taken from the capillary samples. Again, compared to glucometer readings, readings taken from ABG analysers were more accurate, especially in the hypoglycaemic range[6]. Despite venous samples tested in the laboratory remaining the gold standard, POCT using arterial samples analysed using ABG analysers may provide an accurate estimation of the BG levels with the advantage of rapid turnaround times and may provide more clinically relevant and actionable information.

CONTINUOUS GLUCOSE MONITORING

Continuous glucose monitoring (CGM) devices have evolved from retrospective analysers validated in outpatient services and can even be utilised in

hospitalised patients to optimise glucose control. These devices have been associated with better control of short-time fluctuations in BG levels, reduced glycated haemoglobin (HbA1c) values, reduced risk of severe hypoglycaemia, improved glycaemic control, increased treatment satisfaction, and may also reduce healthcare costs[21,22]. Numerous CGM devices are commercially available, which are approved for in-hospital use. These devices are classified as non-invasive (transdermal), minimally invasive (subcutaneous) and invasive (intra-vascular).

The real-time analysers have a subcutaneous cannula with a biosensor to analyse glucose from interstitial fluid, which is then relayed wirelessly by the attached transmitter to the monitors[23]. Even though the initial trials with CGM devices showed a reduction in hypoglycaemic events compared to the intensive insulin protocols measuring glucose samples frequently, these devices failed to reduce the GV[24,25].

The newer systems have shown a fair correlation in direct comparison with each other and capillary measurements in non-critically ill diabetic patients[26]. However, the data from critically ill patients still needed to be included. Early results from testing in critically ill COVID-19 patients have been encouraging, and these devices have been shown to have good accuracy, increase TITR, and reduce GV[27,28]. The latest generation of continuous subcutaneous flash glucose monitoring (FGM) system (FreeStyle Libre) has been shown to have high test-retest reliability and acceptable accuracy even in critically ill patients[29,30].

Although evidence is still evolving, some drawbacks exist (table 3). There is usually a time lag between blood and interstitial fluid to equilibrate, which hinders accurate real-time sampling[31]. Other issues worth considering are variable biosensor life, frequent calibration, and limited working range (BG

levels between 40 to 400 mg/dl). Their efficacy has still not been evaluated in patients with severe oedema due to hypoalbuminemia and hepatic failure. The correlation between blood and interstitial fluid might be altered and inaccurate[23]. Additionally, the presence of hypoxemia and shock may also affect their accuracy.

These shortcomings can be overcome by using intravenous CGM systems, which are more accurate, making frequent monitoring possible in critical patients without putting extra load on nursing staff time. In addition, these devices can also be integrated with closed-loop systems providing an automated insulin delivery to improve BG management[32]. However, their application is also associated with a high incidence of sensor failure, loss of venous integrity, and logistic issues[33]. Besides this, finding a suitable vein may also be an issue in critically ill patients[34].

The evidence base supporting the clinical effectiveness and efficiency of these systems in ICU patients is still limited. Their impact on clinically relevant outcomes like ICU mortality and length of stay (LOS) in hospitals and ICU remains unknown[35]. Moreover, validation of these systems in various ICU populations may lead to their widespread use, considering the advantages of avoiding hypoglycaemia, hyperglycaemia, and GV and reducing nursing loads with less need for finger pricks. Even though these devices may not be beneficial to all critically ill patients, they may benefit some specific ICU patients like those on intravenous insulin or corticosteroids, end-stage organ dysfunction (renal or liver), post-operative neurosurgery patients or those with traumatic brain injury and post-organ transplant patients[36-38]. CGM is effective and safe in critically ill COVID-19 patients and may significantly reduce the need for bedside BG testing; thus, it is recommended to use CGM in these patients to reduce nursing exposure [39].

GLYCAEMIC INDICES

Traditionally, *glycaemic control* has been defined as the highest and lowest target BG levels to prevent hypoglycaemia and hyperglycaemia. In recent years, studies have evaluated other aspects of dysglycaemia and their association with clinical outcomes in critically ill patients. Variability of these indices is a predictor of worse patient outcomes, independent of the frequency and severity of hypoglycaemia and hyperglycaemia[40,41]. Even though the current glycaemic management guidelines do not recommend any specific target for many of these indices, based on the current data, some suggestions may be made to optimise glycaemic control in critically ill patients (table 4)[8,41-45].

Blood glucose targets

Safe BG levels have been challenging to define in critically ill patients. Till recent years glucose control in ICUs has swayed between tight glycaemic control (avoiding hyperglycaemia) to liberal glucose control (avoiding hypoglycaemia) in different case mix populations[46,47].

The American Diabetes Association (ADA) recommends that a BG level below 180 mg/dl is acceptable for ICU patients[8]. In patients with sepsis, the recent version of surviving sepsis guidelines recommend targeting BG levels between 140-180 mg/dl and initiating intravenous insulin therapy if BG levels are above 180 mg/dl for two consecutive readings[9]. They further recommend measuring BG levels every 1-2 hours, especially in the first 24 hours after admission.

Glycaemic variability

The GV can be defined as the measurement of fluctuations of blood glucose over a given interval of variable time. Markers of GV like standard deviation, coefficient of variation, mean amplitude of glycaemic excursion (MAGE), and

one time-weighted index, the glycaemic lability index (GLI), are significantly associated with a higher risk of infections and mortality in medical-surgical ICU patients, even though the mean blood glucose failed to show any association. Additionally, the patients in the upper quartile of GLI had the strongest association with infections (odds ratio, OR 5.044, P = 0.004.)[41]. Even after correcting for hypoglycaemia, GV has been reported to be an independent predictor of worse patient outcomes. GV is a precursor of hypoglycaemia, as the risk of hypoglycaemia is 3.2 times higher in patients with increased GV[48].

Time in target range

Time in target range (TITR) is the percentage of time where the BG stays in the predefined glycaemic range, calculated per patient per day and expressed as a percentage of time spent. Glucotrol was one of the earliest randomised control trials (RCT) to show that TITR above 50% was independently associated with improved survival rates in critically ill patients irrespective of whether tight (80–110mg/dL) or liberal (140–180mg/dL) glycaemic control was applied[49]. In another study, when three thresholds of TITR of 30%, 50%, and 70% were compared in 784 medical surgical patients, it was reported that there was significantly reduced organ failure with TITR of 50%. A TITR above 70% also significantly improved survival rates[42]. Similarly, improved outcomes in terms of reduced sternal wound infection and LOS on invasive mechanical ventilation (IMV) and ICU have been reported in cardiac surgery patients who could achieve TITR above 80%[22]. The exact cut-offs remain to be defined as different studies have suggested TITR, from 50-80%, to improve patient outcomes[22,42].

Glycaemic gap

A glycaemic gap is calculated by subtracting HbA1C-derived average glucose (ADAG) = ([28.7 × HbA1c]-46.7) from plasma glucose at admission. In a cohort

of 200 patients with type 2 diabetes mellitus admitted to ICUs, the glycaemic gap was found to be a predictor of multi-organ dysfunction syndrome (MODS), acute respiratory distress syndrome (ARDS), shock, upper gastrointestinal bleeding, and acute renal failure (ARF). A glycaemic gap of 25.89 mg/dL was predictive for mortality, MODS, and ARF[43]. Similarly, in a retrospective analysis of patients with community-acquired pneumonia, an elevated glycaemic gap of 40 mg/dl had an OR of 3.84 for the incidence of a composite of adverse outcomes, which included length of invasive mechanical ventilation, and LOS in the ICU and hospital[50].

Glycaemic lability

Glycaemic lability (GL) is a measure of GV which records the change in glucose level over weeks calculated from all recorded glucose values. In a multicentric study, GL and time-weighted average BG were calculated and analysed, compared to patients with GLI below median 40 [mmol/L]2/h/week, patients with GLI above this median had a significantly longer ICU stay and a higher ICU and hospital mortality. There was no significant association between GLI and mortality when comparing patients with and without diabetes and baseline HbA1c values. It was found that high GV, as determined by the GLI, was associated with increased hospital mortality independent of average BG, age, diabetes status, HbA1c, hypoglycaemia, and illness severity[44].

Stress hyperglycaemia ratio

Stress hyperglycaemia ratio (SHR) is defined as the ratio of plasma glucose to average glucose derived by HbA1C [(1.59 × HbA1c)–2.59], where HbA1c is used to estimate average glucose concentration over the prior three months. It accounts for acute stress-induced hyperglycaemia and long-standing glycaemic control. GLI and SHR are indices which account for premorbid

glycaemic control. Preliminary reports suggest that SHR may be a better marker of patient outcomes than hyperglycaemia[51]. In specific patient populations, SHR predicts haemorrhagic conversion in acute ischemic stroke and poor outcomes in acute coronary syndrome[52,53]. In diabetic patients with sepsis, a high SHR (> 1.14) is predictive of mortality[45]. While the exact cut-off value for SHR remains unclear, different SHR definitions have been used in the literature[54].

SHR1 = fasting glucose (mmol/L)/glycated haemoglobin (HbA1c) (%)

SHR2 = fasting glucose (mmol/L)/ [(1.59 × HbA1c)-2.59]

SHR3 = admission blood glucose (mmol/L)/ [(1.59 × HbA1c)-2.59]

SHR1 and SHR2 have been shown to be independently associated with worse clinical outcomes in patients with ischemic stroke after intravenous thrombolysis. Furthermore, SHR1 has been shown to have a better predictive performance for outcomes than other SHR definitions[54].

Diabetic status and glycaemic targets

The effect of acute and chronic hyperglycaemia on modifying glycaemic targets to optimise glycaemic control in critical patients has yet to be studied in detail. The results from a study by Krinsley and Preiser suggest that TITR greater than 80% for a BG target between 70 to 140 mg/dL was strongly associated with increased survival in critically ill patients without diabetes mellitus. However, such a relationship was not found in the case of diabetic patients[55]. Lanspa et al. reported that a TITR greater than 80% was associated with reduced mortality in non-diabetic patients and those with well-controlled premorbid diabetes (judged by admission HbA1c). However, no such association could be shown in patients with poorly controlled diabetes[56].

In another study, a lower hospital mortality rate was observed in patients with higher (>7%) preadmission levels of HbA1c and higher time-weighted average

glucose concentration in critically ill patients. This suggests that patients with chronic hyperglycaemia may benefit from more liberal glucose control and tolerate a higher BG level[57]. However, such claims need to be better evaluated in large-scale trials before they are applied in routine clinical practice.

ROLE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence (AI) based applications and devices have been in clinical use to manage non-critically ill diabetic patients for a long. These devices have been used in patient-centred care to make an early diagnosis, predict complications, and even engage patients to ensure treatment adherence. There has been a heightened interest in AI applications for critically ill patients in the last few years. Even though there is insufficient evidence for its routine use, AI is increasingly utilised and can potentially change the future of critical care glucose management (table 5)[58].

In ICU, frequent blood sampling and insulin dose adjustments are required to maintain glycaemic control, increasing nursing workload and chances of error. AI has the potential to improve glycaemic control while reducing nursing workload and errors. The LOGIC-1 and LOGIC-2 RCTs showed that software-guided algorithms could achieve better glycaemic control than nurses-guided protocols without increasing the risk of hypoglycaemia[59,60].

AI-based insulin bolus calculators and advisory systems like MD-Logic controllers are commercially available and have been shown to provide better glycaemic control and reduce nocturnal hypoglycaemic events[61]. Software-based algorithms have been used to regulate insulin infusion based on the patient's glucose levels. Model predictive controls (MPCs) use algorithms based on patient parameters like their age and diabetes status, along with the dose of dextrose administered and the insulin sensitivity, which can predict the

patient's response to hyperglycaemia and insulin therapy and adjust the insulin dose accordingly. These algorithms can improve the accuracy of predicting hyperglycaemia, reduce the need for repeated blood sampling, and provide highly individualised insulin therapy[62,63].

CGM devices (Dexcom G6™) have been integrated with automated insulin suspension using AI algorithms (Basal-IQ™ technology). AI-based algorithms can predict when the BG levels may fall below the predefined levels and alter the insulin infusion accordingly[64]. These CGM-regulated insulin infusion systems (CRIS) have effectively reduced hypoglycaemia episodes [65].

AI-based artificial pancreas (AP) has been shown to provide comprehensive glycaemic control by effectively controlling BG levels, reducing wide glucose excursions, reducing episodes of hypoglycaemia and hyperglycaemia, and increasing the percentage of TITR. Even in critically ill patients, AP achieved stable glucose control and reduced GV while reducing the episodes of hypoglycaemia or hyperglycaemia and the need for frequent sampling, thereby reducing the nursing workload[66-68]. Whether the use of AP can improve clinical outcomes and has, a favourable cost-benefit ratio still needs to be evaluated.

In addition to predicting long-term or chronic complications, AI may also be instrumental in predicting acute life-threatening complications like acute myocardial infarction in patients with diabetes[69]. AI using a convolutional neural network has been shown to be highly accurate in predicting mortality in critically ill diabetes patients with an area under the curve of 0.97[70,71]. However, these models need to be compared to more widely used and validated models for mortality prediction in ICU patients.

AI applications may improve patient care and outcomes and improve glycaemic control while reducing nursing workload. As AI-based devices may enable us to

monitor and institute therapy remotely, they may be particularly useful in managing highly infectious diseases like COVID-19. However, AI is still in the early stages of development. Moreover, AI-based applications still need to be thoroughly evaluated and validated in critically ill patients. In addition, the need for more regulations, recommendations, and guidelines for using AI limit its applicability. Safety, liability, and reliability issues pertaining to AI application need to be better assessed before it is integrated into the existing healthcare infrastructure and becomes acceptable at a larger scale.

CONCLUSIONS

ICU patients are a unique population with dynamic clinical conditions and therapeutic needs. High physiological stress, inflammatory cytokines, varying nutritional intake, and fluctuating organ functions make glycaemic control challenging in these patients. Guidelines may aid us in providing a generalised approach to glycaemic control, but there may be a need for a more personalised approach to reducing the harmful effects of dysglycaemia. The newer glycaemic indices like GV and TITR may allow us to achieve patient-centred care with better glycaemic control. However, their exact targets and impact on patient outcomes need to be better evaluated before they are routinely recommended. The use of AI-based applications may provide a more comprehensive solution in the future, but presently close monitoring and early detection and management of complications constitute the mainstay of glucose management.