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Review Article

Continuous Glucose Monitoring in the Cardiac ICU: Current Use and Future Directions

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Abstract: Perioperative glucose control is highly important, particularly for patients undergoing cardiac surgery. Variable glucose levels before, during and after cardiac surgery lead to increased post-operative complications and patient mortality. [1] Current methods for intensive monitoring and treating hyperglycemia in the Intensive Care Unit (ICU) usually involve hourly glucose monitoring and continuous intravenous insulin infusions. With the advent of more accurate subcutaneous glucose monitoring systems, the role of improved glucose control with newer systems deserves consideration for widespread adoption.

Keywords: Continuous Glucose Monitoring, ICU, Cardiac Surgery

1. Introduction

Suboptimal perioperative glucose control is associated with increased risk of complications in patients undergoing cardiac surgery. Hyperglycemia is associated with increased incidence of sternal wound infections, stroke, and renal complications. [1] As the prevalence of diabetes increases in the population, the prevalence of hyperglycemia-related cardiac surgical complications is growing and deserves consideration for prevention and optimization of treatment.

Intensive insulin control with continuous intravenous insulin infusions has become the standard of care for patients requiring insulin post-operatively, as it has been shown to both reduce mortality as well as decrease sternal wound infections. [2, 3] Intensive care unit (ICU) protocols currently use bedside glucometers to check glucose levels every 30-60 minutes in the immediate post-operative period and adjust insulin titrations accordingly. However, intravenous administration of regular insulin has a rapid onset of action and a plasma half-life of less than ten minutes, so the duration of a single dose has often cleared within 30-60 minutes. Therefore, the intervals of glucose monitoring may be missing hypo- or hyperglycemic events occurring between glucose tests. Hypoglycemia in the ICU in particular is dangerous as it may cause irreversible cerebral damage, while hyperglycemia can increase risks of atrial fibrillation, infections, acute kidney injury among other effects. [4] Furthermore, rapidly changing glucose levels are also dangerous and damaging; again something that is difficult to identify with intermittent testing of glucose levels. [5] This is further complicated by the fact that post-cardiac surgical patients in the ICU are sedated often for hours to days after surgery and unable to demonstrate symptoms of hypo- or hyperglycemia.

This review discusses other methods that are available to monitor and regulate glucose levels in perioperative patients. Continuous glucose monitoring (CGM) is defined as providing a glucose reading at least every 15 minutes. [6] Early systems of CGM were introduced by corporations such as Medtronic (Medtronic Diabetes, Northridge, CA) about 20 years ago and functioned by measuring subcutaneous glucose levels. Other early attempts for outpatient glucose readings included suctioning of interstitial fluid measurements in the arm, designed by Gluco Watch (Cygnus Inc, San Francisco, CA), but unfortunately were plagued by lag times and inaccuracy, causing the company to fold a decade ago. Similarly, the Free Style Navigator (Abbott, Abbott Park, IL), which measured glucose by subcutaneous interstitial fluid, earned early success in research trials but struggled with

Federal Drug Agency (FDA) approval that required significant redesign of their system. They finally gained approval (Free Style Libre Pro) and their product is now on the market.

All initial systems faced barriers with FDA approval due to inaccuracy, particularly during rapid glucose fluctuations and hypoglycemia. However, technology has continued to improve and continuous glucose monitoring is evolving as the standard of care in type 1 diabetes. Recent advances include communication between a CGM system and a continuous subcutaneous insulin infusion pump (or insulin pump) and the FDA approval of a partially closed-loop system (Medtronic 670G, which uses a CGM for glucose detection and delivers insulin for hyperglycemia and decreases insulin delivery for hypoglycemia, although still requires user input for boluses of insulin for carbohydrates) earlier this year. While there is a still a long way to go before a completely closed-loop system is safe, effective, and able to function without any user input, effective and available to the public, these major advancements may serve an important place outside of the realm of outpatient treatment of diabetes.

2. Types of Continuous Glucose Monitoring: Current Technology

Early studies of continuous glucose monitors in post-operative cardiac surgical patients demonstrated concerns of accuracy, despite safety, prohibiting widespread adoption. [7] Current recommendations for glucose meters in critically ill patients require 98% of glucose readings to be within a 12.5% reference range as a minimum standard. Mean absolute relative difference values (MARD), which measures the deviation from a gold-standard laboratory blood glucose assessment, are the best way to assess accuracy and >18% are considered poor, while <14% are considered acceptable. [6] One of the other issues which has markedly improved in recent years is lag time, which was previously often upwards of ten to fifteen minutes.

Medtronic is one of the largest companies involved in the development of subcutaneous sensor technology. Their product line has evolved through various real-time sensors from an initial MARD of 19.7% down to 13.7% in the more recent Enlite sensor. [8, 9] Medtronic's newest sensor, the Guardian G3, which is used in their recently-released closed-loop system, has reported significantly higher accuracy; however results from large studies evaluating this are still pending. Similarly, Dexcom (Dexcom Inc., San Diego, CA), another company dedicated to glucose sensor technology, created an initial sensor with a MARD of >20%, but have improved their system to the point that their more recent iterations of the Dexcom G4 and G5 have been shown to have MARDs of 14% or better. [9] Table 1 lists many of the continuous glucose monitoring systems in use. Other types of continuous glucose monitoring systems for inpatient use have been developed, including intravenous and intra-arterial systems. However, concerns over complications including thrombus formation and increased infection risk have prevented them from being adopted in frequent use. These systems are beyond the scope of this review.

Table 1. *Continuous Glucose Monitoring Systems.*

	Sensor life	Accuracy (MARD)	Calibration time	Compatibility with other devices	Comments
Medtronic Enlite	6 days	13.9%*	2 hours, calibrate q12 hours	530G insulin pump	First to shut-off for hypoglycemia
Medtronic Guardian Sensor 3	7 days	9.4%**	40 min – 2 hours, calibrate q12 hours	670G closed-loop, iPhone receiver	First closed-loop system
Guardian REAL-time, Medtronic	6 days	14.0-23.7***	2 hours, calibrate q12 hours	None	
CGMS System Gold, Medtronic	3 days	17.6-23.0***	2 hours, calibrate q12 hours (q6 recommended)	None	Glucose values not displayed real-time, must be downloaded
Dexcom SEVEN	7 days	26%	2 hours, calibrate q12 hours	None	
Dexcom G4	7 days	14%	2 hours, calibrate q12 hours	Animas	
Dexcom G5	7 days		2 hours, calibrate q12 hours	iPhone receiver	
FreeStyle Libre Pro, Abbott	14 days		None	None	Recent FDA approval
FreeStyle Navigator, Abbott	5 days	9.6-15.6***	10 hours, recalibrate at 12, 24, and 72 hours	None	Never received FDA approval

* -[8], ** - [23], *** - [24]

2.1. Glucose Management in the ICU

Critical illness is known to increase morbidity and mortality. Furthermore, hyperglycemia commonly occurs in critical illness, whether patients have pre-existing diabetes or not, and has been shown to be associated with worse outcomes, including increased risk of infections and poor wound-healing. [10] An important study evaluating glucose control in patients with diabetes at admission demonstrated that intensive insulin treatment improves patient outcomes. [11] While glucose control in the ICU is now accepted to be important to improving outcomes, the optimal levels to target for control have been hotly debated in recent decades. Early studies compared patients with lower glucose levels as a target (generally <110-120 mg/dL) to conventional goals of 200 mg/dL or greater. In 2001, a randomized control trial demonstrated that intensive insulin therapy with goals of glucose levels <110 mg/dL decreased renal failure, infection

rate, and improved mortality, leading to the initial adoption of aiming for tight glycemic control. [12]

However, the landmark NICE-SUGAR trial published in the New England Journal of Medicine in 2009 suggested that tight glycemic control is in fact more dangerous than conventional control in ICU patients, as suggested by a higher mortality rate. This challenged previous notions of the importance of tight glycemic control, particularly in the ICU. The patients in the intensive group had glucose goals of 81-108 mg/dL, while the conventional control group aimed for glucose levels <180 mg/dL. Of note, this conventional group goal of 180 mg/dL is lower than many previous studies aiming for <200 mg/dL. The higher mortality in the intensive group was suggested to be due to higher levels of hypoglycemia. However, it is important to accept these results with the knowledge that only 37% of patients in each group were operative, and other data suggests operative patients do better with tighter glycemic control. [12] Furthermore, only 20% of the subjects in either group had diabetes and of those, <30% in either group had previously used insulin. [13]

Since the release of the NICE-SUGAR trial, the application of looser glycemic control goals has been controversial, particularly in specific populations and as technology has progressed to allow continuous glucose monitoring. [5] Further studies of operative and specifically cardiac surgical patients have come up with tighter glucose goals for post-operative cardiac surgical patients, although strong randomized control trials with newer, more accurate devices and in cardiac patients are lacking.

2.2. Challenges

While the advent of new technology poses exciting opportunities for optimizing inpatient glycemic control, many challenges still exist for increasing utilization of this technology. The forerunning concern is accuracy, which has been shown to be lacking in CGMs particularly during hypoglycemia. [14] On the other hand, concerns about accuracy of interstitial glucose levels in critically ill patients have largely been alleviated by studies demonstrating accuracy was largely unaffected by electrolyte and acid-base imbalances. [15] Furthermore, variability between measurement sites has been analyzed as not significantly different, which is an important consideration in cardiac patients who have multiple lines, tubes and other access sites, limiting available insertion sites. [16] Most importantly, however, is the advent of newer, more accurate CGM systems which have yet to be studied in randomized control trials in post-operative patients.

Technical concerns also present a hurdle for ICU patients. The technology used to measure interstitial glucose used by the majority of CGMs is affected by substance interference, most notably acetaminophen, but also dopamine, mannitol, heparin, ascorbic, uric and salicylic acid; many of which are commonly used in post-operative cardiac surgical care. [17] Acetaminophen is hydrolyzed and converted into indophenol, which can be followed at 600nm and has been shown to be directly affected proportional to the amount of acetaminophen present. [18] Additional risks specific to intravenous CGMS include concerns of thrombus or biofilm formation, occlusion, and catheter-related infections, rendering them less reasonable options for patients at high risk with other indwelling tubes, catheters and devices.

Another challenge is interpretation of various clinical trials when comparing patients with pre-existing diabetes to those who are experiencing hyperglycemia as a post-surgical systemic stress response as a new phenomenon. While patients with type 1 diabetes as well as patients with type 2 diabetes dependent on large doses of insulin infusions are the most appropriate candidates for CGM use in the ICU setting, patients with more robust intrinsic mechanisms may require different technology and/or different treatment algorithms with different optimal glucose targets for best outcomes. [19] Some have argued for baseline HbA1c levels as a means to determine relative hypoglycemia levels in the inpatient setting, which may be a way of differentiating treatment goals. [20]

Other challenges include cost and adaptation to new technology. The cost of technology remains an ongoing barrier. Intravenous insulin infusions and point-of-care glucose testing (POCT) require significantly less cost than that of a sensor and receiver initially, however over time these costs may balance or even be reduced. Furthermore, training is required for the nurses and aides who will be working with the instruments on a daily basis, as well as for the physicians to interpret and optimize their use of the technology. However, it has been shown that nursing workload as well as daily patient costs are decreased (12 Euro/day) with the use of CGM. [21] Adaptation to new technology is often a slow learning curve, as many health care providers are set in their ways and resistant to new tools unless a major benefit is clear to them. However, retrospectively looking at other technologies that are now standards of care demonstrate various invasive tools such as Swann-Ganz catheters, arterial blood pressure monitoring lines and others have become part of the everyday ICU technology. Additionally, data by Kosiborod et al. found critical care professionals reported CGMs as easy to use after only two patient experiences. [22] Furthermore, continuous glucose monitors are less-invasive by sampling subcutaneous tissue and are therefore at much lower risk of inciting an infection than are these other invasive monitoring lines. Finally, CGMs also decrease blood loss over a long hospitalization and therefore may limit iatrogenic anemia.

3. Conclusions

Adaptation of continuous glucose monitoring in a cardiac ICU setting poses multiple hurdles to overcome, however after surpassing the learning curve, the ease of use and frequency of data provided has the potential to revolutionize post-operative glycemic control and its complications related to cardiac surgery. Challenges related to optimal treatment algorithms remain, although CGMs may play a valuable role in helping define these algorithms for best outcomes. As sensors become more accurate and user-friendly, ushering them into ICU settings will become easier, likely reducing

nursing workload and potentially decreasing costs.

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