Journal of Anesthesia & Clinical Research
Yatabe et al., J Anesthe Clinic Res 2012, 3:1
DOI: 10.4172/2155-6148.1000186
Research Article Open Access

Automating Blood Glucose Control

Tomoaki Yatabe[1]*, Kazuhiro Hanazaki[2] and Masataka Yokoyama[1]

[1]*Department of Anesthesiology and Critical Care Medicine, Kochi Medical School*
[2]*Department of Surgery, Kochi Medical School*

Abstract

Blood glucose control in ICUs and operation rooms has some issues. First, hypoglycemia worsens the neurological prognosis of ICU patients and should definitely be avoided. To avoid hypoglycemic attacks require extensive attention by hospital staff. The two biggest advantages of continuous monitoring are the avoidance of hypoglycemia and the reduced workload for ICU staff. However, to achievement of automating blood glucose control, closed loop continuous glucose monitoring is essential. In this review, topics of blood glucose management in ICUs and operation rooms are introduced and advantages and limitations of closed loop continuous glucose monitoring are discussed.

Keywords: Intensive care; Insulin; Continuous glucose monitoring; Closed loop system; Glucose variability; Artificial pancreas

Introduction

Since the 2001 report by Van den Berghe et al., there has been a dramatic increase in interest regarding glycemic control in intensive care unit (ICU) patients [1]. At present, intensive insulin therapy (IIT) is widely used in ICUs to keep blood glucose levels between 80–110 mg/dl. However, compared to conventional glycemic control methods, IIT is associated with a higher frequency of hypoglycemic attacks [2,3]. Thus the benefits of IIT are nullified by the increased occurrence of hypoglycemic attacks, which lead to adverse neurological after effects and complications [4,5]. In 2009, the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) research group reported that keeping blood glucose between 80–108 mg/dl using IIT was associated with a poorer prognosis than that associated with blood glucose between 144–180 mg/dl [6]. These results, however, do not discount the fact that glycemic control is important in ICU patients [7]. Hyperglycemia is also harmful, but neither does this reduce the importance of glycemic control. Hypoglycemic attacks and glycemic control both require extensive attention by hospital staff [8,9]. Thus resolving these issues is vital for improving glycemic control in the ICU. In this review, we provide an overview of the solutions and strategies associated with continuous glucose monitoring.

Targeted Blood Glucose Levels and Adverse Effects of Hyperglycemia

Prior to the discussion of continuous blood glucose monitoring, we have compiled a brief explanation of glycemic control and target blood glucose levels. Diabetes is common in patients who undergo surgery or require care in the ICU [10]. Regardless of whether the patient has diabetes, surgical stress, sepsis, or severe clinical conditions may increase insulin resistance or cause hyperglycemia due to decreased glucose uptake [10]. Hyperglycemia, particularly in the ICU, can develop due to catecholamines, steroids, or nutritional therapy [11]. Hyperglycemia is the main cause of complications such as vascular endothelial damage, impediment of neutrophil chemotactic activity, and increases in active oxygen levels [11,12]. Lastly, an increase in infectious disease has been shown to be particularly responsible for poor clinical outcomes in a significant number of patients. Therefore, the recommended target blood sugar level for glycemic control was set at 80–110 mg/dl; but since the NICE-SUGAR study the target has been 150–180 mg/dl [6,12,13]. However, there have been few articles on glycemic control during surgery compared the number of studies examining glycemic control in ICU patients. A clear consensus has not been achieved on target blood glucose levels or whether IIT should be used during surgery. Nevertheless, hyperglycemia is clearly linked to surgery-associated infections, and blood glucose levels above 180 mg/dl should therefore be avoided.

Issues of Glycemic Control

Glycemic control in ICUs and operation rooms have some issues. First, hypoglycemia worsens the neurological prognosis of ICU patients and should definitely be avoided [13,14]. However, during surgery when the patient is sedated or under anesthesia, it is difficult to determine the presence of hypoglycemia using methods other than measuring blood glucose levels. Using IIT, the frequency of hypoglycemia increases 5–20% and it becomes difficult to avoid severe hypoglycemic states [8]. In addition, the presence of infectious diseases such as sepsis further increases the frequency of hypoglycemia [15]. Second, should we recommend tight glycemic control irrespective of whether the patient is diabetic? It is not understood well. At present, the efficacy of IIT in patients with a history of diabetes has not been recognized, and there have even been reports linking it to a dangerous increase in mortality [16]. Therefore, we have to decide target blood glucose level in diabetes patient carefully. Third, blood glucose variability have received significant attention since Egi et al. reported in 2006 that keeping blood glucose variability to a minimum might contribute to improvement of patients outcome [17]. The standard deviation of blood glucose levels was measured among 7049 ICU patients, who were divided into survival and non-survival groups. The levels were 30.6 ± 23.4 mg/dl in the survival group and 41.4 ± 28.8 mg/dl in the non-survival group, which was a significant difference [17]. Acute glucose variability during

***Corresponding author:** Tomoaki Yatabe, Department of Anesthesiology and Critical Care Medicine, Kochi Medical School, Kohasu Oko-cho Nankoku city, Kochi, Japan 783-8505, Tel: +81-88-880-2471; Fax: +81-88-880-2475; E-mail: yatabe@kochi-u.ac.jp

Received December 01, 2011; **Accepted** January 22, 2012; **Published** January 24, 2012

Citation: Yatabe T, Hanazaki K, Yokoyama M (2012) Automating Blood Glucose Control. J Anesthe Clinic Res 3:186. doi:10.4172/2155-6148.1000186

glucose swings exhibited a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia [18]. These oxidative stresses leaded to several undesirable effects such as endothelium damages [18]. Controlling blood glucose variability is now considered an important component of blood glucose management.

Efficacy of Continuous Blood Monitoring

As can be seen from the above, proper ICU glycemic control should involve completely avoiding hypoglycemic events, restricting blood glucose fluctuations, and maintaining blood glucose levels under 180 mg/dl. However, to avoid hypoglycemia and carry out proper glycemic control, frequent blood glucose measurements are necessary. Exactly how frequent these measurements should be taken is not clear, but Surviving Sepsis Campaign Guidelines 2008 (SSCG 2008) recommended that until blood glucose levels and insulin infusion rates are stabilized, measurements should be performed every 1–2 hours, after which they should be taken at 4-hour intervals [19]. Thus patients could require as many as 24 measurements in one day, significantly increasing the workload of ICU staff. The two biggest advantages of continuous monitoring are the avoidance of hypoglycemia and the reduced workload for ICU staff.

Types of Continuous Blood Glucose Monitoring

Continuous glucose monitoring systems are broadly classified into 2 categories based on where measurements are taken: systems in which sensors are placed in subcutaneous tissue, and those in which measurements are taken form arterial or venous blood. In patients with type 1 diabetes, several different devices are being used to prevent hypoglycemia and improve the accuracy of blood glucose monitoring. These devices measure glucose concentration in the interstitial fluid using sensors placed in the subcutaneous tissue [20]. However, these devices measure glucose levels in interstitial fluid, not blood, and thus involve problems such as a time lag of about 20 minutes, and the need to wait several hours for stabilization before measurements can begin [9]. Moreover, in the ICU or during surgery, there is often instability of peripheral circulation, and edema due to fluid imbalance is common. These situations are even more pronounced in critically ill patients for whom glycemic control is most important. Under these circumstances, declines in measurement accuracy are cause for concern [21]. Therefore, in such situations the most current technique is to use a special catheter to continuously draw blood. Several devices that can be placed directly in blood vessels or draw blood with a catheter to continuously measure glucose levels are currently in development [20]. Continuous glucose monitoring devices include those that take measurements every few minutes. Researchers have questioned whether truly continuous glucose monitoring is necessary, but reports have suggested that delays of even 12 minutes in glucose measurement are a factor in hypoglycemia [22]. Moreover, in hepatic ischemia reperfusion during hepatectomy or major vascular surgery involving hepatic circulatory arrest, blood glucose levels can increase 50–100 mg/dl within 5 minutes of hepatic ischemic reperfusion [23-25]. Therefore, real-time continuous glucose monitoring is considered the best option. Below we introduce a fully automated glucose control device, the STG-22, and its next generation model STG-55 (Nikkiso, Tokyo, Japan) (Figure 1).

An Overview of the STG Series [26,27]

The artificial pancreas STG-22 continuously draws small amounts of blood at a rate of about 2 ml per hour. Blood glucose is measured via a reaction between the blood and a glucose oxidase membrane. The STG-22 can also carry out automatic glycemic control using a built-in algorithm if blood glucose levels for the start of insulin or glucose administration are set. The STG-22 determines the required dosage of insulin or glucose based on current glucose levels, difference from the target level, and blood glucose fluctuations every minute. In accordance with the infusion rate, insulin or glucose can be automatically injected via the device's pump. For example, if insulin injection is set to begin at 110 mg/dl, and glucose injection is set to begin at 80 mg/dl, insulin injection starts if blood glucose exceeds 110 mg/dl and is stopped if it drops below 110 mg/dl; neither insulin nor glucose is injected when blood glucose is between 80-110 mg/dl; and glucose is automatically injected at levels below 80 mg/dl. There are no restrictions on glucose administration for total parenteral nutrition or enteral nutrition. In other words, flexible limits can be set for blood glucose, such as the 80–110 mg/dl target recommended by Van den Berghe et al. or the 144–180 mg/dl NICE-SUGAR standard. In systems that continually draw blood from the veins, clot formation may cause catheter occlusion, but the STG-22 contains a fixed amount of heparin on the tip of the catheter, thereby preventing thrombotic occlusion that would interrupt glucose measurements.

Figure 1: Outward appearance of the STG-22 (left) and STG-55 (right).

Benefits of the STG-22

The benefits of the STG-22 in glycemic control are as follows:

High accuracy of blood glucose measurement

Blood glucose measurements obtained by the STG-22 were compared to those taken with a blood gas analyzer ABL800FLEX (Radiometer, Copenhagen, Denmark) in scenarios easily affected by dilution from transfusion or bleeding, such as hepatectomy or cardiovascular surgery; and the perioperative period when there are large fluctuations in peripheral circulation [26] (Figure 2). No influence from bleeding or dilution was detected, and the results of both methods showed a strong correlation. Further, highly accurate results were obtained in ICU patients [28].

Prevention of hypoglycemia

Hypoglycemia is the biggest problem in blood glucose control. Our institution began using the STG-22 in 2006 and used the closed-loop method of glycemic control in more than 200 patients, with zero cases of hypoglycemia [27]. Thus the STG-22 can be used to avoid

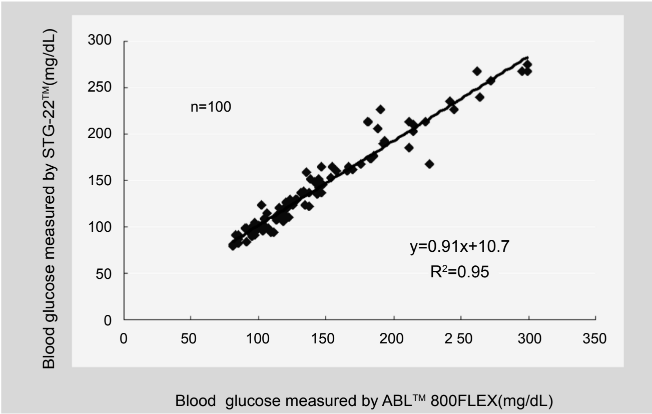

Figure 2: Accuracy of the STG-22.

hypoglycemia. In addition, the device constantly displays blood glucose readings, which eliminates one source of worry for ICU staff.

Reduced workload for ICU staff

Conventional glucose control methods such as sliding scale require frequent blood glucose measurement, which is a burden for ICU staff. In cases involving blood glucose fluctuations, measurements are required every 30 minutes, and IIT requires measurements at intervals of 1–2 h. After measuring blood glucose, insulin often needs to be injected; or in continuous insulin administration, more-frequent adjustments to the infusion rate are required. Nurses dealing with the care of critically ill patients in the ICU are constantly under tension and stress [29]. Under these situations, a lot of stress is caused to ICU nurses because of the frequent measurements of blood glucose levels and the repetitive handling of insulin, which is likely to cause incidents [30]. Although computer-assisted insulin infusion protocols have been used increasingly in recent years, changes in insulin and monitoring of blood glucose levels remains an essential task. In this respect, the STG-22 is better able to reduce staff workloads than the conventional sliding-scale method of glucose control [30]. By using an artificial pancreas, the amount of labor spent per patient was reduced by about 20 min, and stress was substantially relieved. Because this allows nurses to devote more time and concentration on other care-giving tasks, it may contribute to the improvement of the overall quality of care and to the reduction of the risk of occurrence of other incidents [30].

Glucose control with minimal glucose variability

Blood glucose variability have been linked to prognosis [17,31]. The STG-22 is capable of reducing blood glucose bariablity, allowing a standard deviation of 19.9 ± 10.9 mg/dl [27]. In addition, this system does not require blood glucose measurement by the ICU staff. In other studies [17,32], the standard deviation of blood glucose in survivors and non-survivors were reported to be 30.6–33.3 mg/dl and 41.4–42.1 mg/dl, respectively. Thus, the blood glucose variability associated with the use of STG-22 was lower than the above-mentioned values. Notably, STG-22 achieved SD reduction in patients without causing hypoglycemia [27].

Demerits of the STG-22

The STG-22 system has the following disadvantages:

Interruption of glycemic control due to poor blood removal

The STG-22 measures blood glucose levels by drawing blood via a peripheral venous catheter. Therefore, blood sampling may be interrupted due to certain blood vessel conditions, and there are cases where the device cannot be used due to inability to secure peripheral veins [27]. To address this issue, a device capable of taking measurements from a central venous catheter is needed.

Problems of cost and device preparation

The STG-22 device is expensive, and there additional costs involving consumables and maintenance [8]. However, previous study described that the total hospital actual costs, including the costs of using the STG-22 system, for the original surgical admission of patients in the STG-22 group ($16,407) were significantly lower than those for patients in the sliding scale group ($21,879; P= 0.047) [32]. The main reason of this result was that incidence of surgical site infection in the STG-22 group was significantly lower than that in the sliding scale group [32]. In addition, we have reported that the cost simulations of our hospital's 5-bed ICU suggested that this device may allow cost cuts of 14,000 US dollars per year in personnel expenses related to nurses [30]. The next-generation STG-55 has a more affordable main device and is smaller in size. However, at present this system can only be used in Japan [20].

This has been a brief summary of how the STG series can be used to automate glycemic control in the ICU and during surgery. Van den Berghe has pointed out the need for a closed loop continuous glucose monitoring system [32]. Automating glycemic control makes it possible to avoid hypoglycemia, reduce labor, and reduce blood glucose variability. The STG series introduced here allows for vastly improved, although not perfect, glycemic control (Table 1). Further innovations will allow glycemic control to begin as soon as the switch is turned on and without interruption of blood sampling.

Factor	Optimal
Sample blood from...	peripheral vein and/or central venous (hybrid type is best)
First calibration	within a few minutes
Daily calibration	minimum for guaranteeing accuracy (within 4 times per day)
Frequency of measurement	continuously, real time
Closed-loop control	necessary for automation
Others	small size not so expensive

Table 1: Optimal continuous glucose monitor in perioperative period.

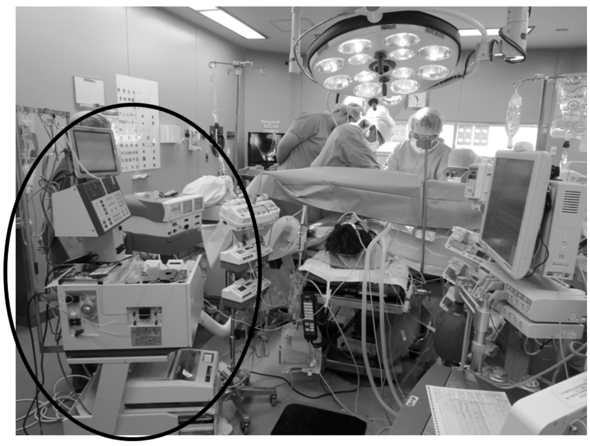

Figure 3: The STG-22 (black circle) in an operation room.

Conclusion

Recently, we can use continuous blood glucose monitoring devices in ICU and operation room (Figure 3). Furthermore, device with closed loop system such as the STG series provided us automating glucose control. However, these technologies are not perfect. Therefore, it is hoped that manufacturers will develop a novel optimal closed loop continuous glucose monitoring in the future.

References

1. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, et al. (2001) Intensive insulin therapy in the critically ill patients. N Engl J Med 345: 1359–1367.
2. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, et al. (2008) Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 358: 125–139.
3. Preiser JC, Devos P, Ruiz-Santana S, Mélot C, Annane D, et al. (2009) A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med 35: 1738-1748.
4. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, et al. (2009) Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 180: 821-827.
5. Mraovic B (2009) Analysis: Continuous glucose monitoring during intensive insulin therapy. J Diabetes Sci Technol 3: 960-963.
6. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. (2009) Intensive versus conventional glucose control in critically ill patients. N Engl J Med 360: 1283-1297.
7. Bellomo R, Egi M (2009) What is a NICE-SUGAR for patients in the intensive care unit? Mayo Clin Proc 84: 400-402.
8. Hanazaki K, Maeda H, Okabayashi T (2010) Tight perioperative glycemic control using an artificial endocrine pancreas. Surg Today 40: 1-7.
9. Jacobs B, Phan K, Bertheau L, Dogbey G, Schwartz F, et al. (2010) Continuous glucose monitoring system in a rural intensive care unit: a pilot study evaluating accuracy and acceptance. J Diabetes Sci Technol 4: 636-644.
10. Rice MJ, Pitkin AD, Coursin DB (2010) Glucose measurement in the operating room: more complicated than it seems. Anesth Analg 110: 1056-1065.
11. Kovalaske MA, Gandhi GY (2009) Glycemic control in the medical intensive care unit. J Diabetes Sci Technol 3: 1330-1341.
12. Lipshutz AK, Gropper MA (2009) Perioperative glycemic control: an evidence-based review. Anesthesiology 110: 408-421.
13. Maerz LL, Akhtar S (2011) Perioperative glycemic management in 2011: paradigm shifts. Curr Opin Crit Care 17: 370-375.
14. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, et al. (2010) Hypoglycemia and outcome in critically ill patients. Mayo Clin Proc 85: 217-224.
15. Vriesendorp TM, van Santen S, DeVries JH, de Jonge E, Rosendaal FR, et al. (2006) Predisposing factors for hypoglycemia in the intensive care unit. Crit Care Med 34: 96-101.
16. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, et al. (2011) The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. Crit Care Med 39:105-111.
17. Egi M, Bellomo R, Stachowski E, French CJ, Hart G (2006) Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology 105: 244-252.
18. Monnier L, Mas E, Ginet C, Michel F, Villon L, et al. (2006) Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 295: 1681-1687.
19. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, et al. (2008) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 36: 296-327.
20. Joseph JI, Hipszer B, Mraovic B, Chervoneva I, Joseph M, et al. (2009) Clinical need for continuous glucose monitoring in the hospital. J Diabetes Sci Technol 3: 1309-1318.
21. Rabiee A, Andreasik RN, Abu-Hamdah R, Galiatsatos BS, Khouri Z, et al. (2009) Numerical and clinical accuracy of a continuous glucose monitoring system during intravenous insulin therapy in the surgical and burn intensive care units. J Diabetes Sci Technol 3: 951-959.
22. Juneja R, Roudebush CP, Nasraway SA, Golas AA, Jacobi J, et al. (2009) Computerized intensive insulin dosing can mitigate hypoglycemia and achieve tight glycemic control when glucose measurement is performed frequently and on time. Crit Care 13: R163
23. Yatabe T, Yokoyama T, Yamashita K, Okabayashi T, Hanazaki K (2009) Increase in blood glucose with the start of the reperfusion after large vessel surgery. Anesth Analg 109: 684.
24. Maeda H, Okabayashi T, Nishimori I, Yamashita K, Sugimoto T, et al. (2010) Hyperglycemia during hepatic resection: continuous monitoring of blood glucose concentration. Am J Surg 199: 8-13.
25. Yatabe T, Kitagawa H, Kawano T, Munekage M, Okabayashi T, et al. (2011) Continuous monitoring of glucose levels in the hepatic vein and systemic circulation during the Pringle maneuver in beagles. J Artif Organs 14: 232-237.
26. Yamashita K, Okabayashi T, Yokoyama T, Yatabe T, Maeda H, et al. (2008) The accuracy of a continuous blood glucose monitor during surgery. Anesth Analg 106: 160-163.
27. Yatabe T, Yamazaki R, Kitagawa H, Okabayashi T, Yamashita K, et al. (2011) The evaluation of the ability of closed-loop glycemic control device to maintain the blood glucose concentration in intensive care unit patients. Crit Care Med 39: 575-578.
28. Yamashita K, Okabayashi T, Yokoyama T, Yatabe T, Maeda H, et al. (2009) Accuracy and reliability of continuous blood glucose monitor in post-surgical patients. Acta Anaesthesiol Scand 53: 66-71.
29. Valentin A, Capuzzo M, Guidet B, Moreno R, Metnitz B, et al. (2009) Research Group on Quality Improvement of the European Society of Intensive Care Medicine (ESICM); Sentinel Events Evaluation (SEE) Study Investigators. Errors in administration of parenteral drugs in intensive care units. multinational prospective study. BMJ 338: b814.
30. Mibu K, Yatabe T, Hanazaki K (2011) Blood glucose control using an artificial pancreas reduces the workload of ICU nurses. J Artif Organs (in press).
31. Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, et al. (2010) Glucose variability is associated with intensive care unit mortality. Crit Care Med 38: 838-842.
32. Meyfroidt G, Keenan DM, Wang X, Wouters PJ, Veldhuis JD, et al. (2010) Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. Crit Care Med 38: 1021-1029.
33. Okabayashi T, Nishimori I, Maeda H, Yamashita K, Yatabe T, et al. (2009) Effect of intensive insulin therapy using a closed-loop glycemic control system in hepatic resection patients: a prospective randomized clinical trial. Diabetes Care 32: 1425-1427.
34. Van den Berghe G (2008) Insulin therapy in the intensive care unit should be targeted to maintain blood glucose between 4.4 mmol/l and 6.1 mmol/l. Diabetologia 51: 911–915.