

ORIGINAL

Impact of newly developed, next-generation artificial endocrine pancreas

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Abstract : Background : Recent studies have shown that strict perioperative blood glucose management may reduce mortality and morbidity in critically ill adult patients. The purpose of this study was to assess the accuracy and efficacy of the intraoperative application of a newly developed, next-generation artificial endocrine pancreas (STG-55, Nikkiso Co., Ltd., Tokyo, Japan). **Methods :** Twenty patients scheduled to undergo surgery were enrolled in this study. The STG-55 is designed to be more user-friendly than its conventional counterpart (STG-22) while maintaining the latter's fundamental functions, such as a closed-loop system using algorithms for insulin and glucose infusion. After anesthetic induction, a 20G intravenous catheter was inserted into a peripheral forearm vein and connected to a continuous blood glucose monitor. The resultant 105 scores for paired blood glucose values were compared by Bland-Altman analysis. **Results :** Stable blood glucose values were maintained automatically, and there were no complications related to use of the STG-55. A close correlation ($r=0.96$) was observed between continuous glucose measurements using the STG-55 and conventional intermittent glucose measurements. The difficulty of manipulation using this system was decreased by improved preparation procedures. **Conclusion :** The glycemic control system using the STG-55 could provide an alternative way to achieve effective and safe perioperative glycemic control. *J. Med. Invest.* 62 : 41-44, February, 2015

Keywords : intensive insulin therapy, artificial endocrine pancreas, perioperative blood glucose management, continuous blood glucose monitoring, STG-55

INTRODUCTION

Hyperglycemia can exacerbate a number of perioperative problems, including cardiac, neurologic, and infectious complications (1). Strict perioperative glycemic control is effective for protecting against injury in many organs and reducing the incidence of infection, and is thus thought to lead to improved prognosis (2, 3). Establishment of a new perioperative blood glucose control method with the aid of an artificial endocrine pancreas (STG-22, Nikkiso Co., Ltd., Tokyo, Japan) (Figure 1, left) was previously reported (4-7). The purpose of this study was to assess the accuracy and efficacy of the intraoperative application of a newly developed, next-generation artificial endocrine pancreas (STG-55; Nikkiso Co., Ltd., Tokyo, Japan) (Figure 1, right).

METHODS

This investigation conformed to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee on Human Studies of Tokushima University Hospital, and written informed consent was obtained from each patient. Twenty patients scheduled to undergo surgery (four hepatectomies,



STG-22 STG-55

Figure 1. The conventional artificial endocrine pancreas (left : STG-22, Nikkiso Co., Ltd., Tokyo, Japan) and the newly developed next-generation artificial endocrine pancreas (right : STG-55, Nikkiso), a bedside-type artificial endocrine pancreas with a closed-loop system.

three liver transplantations, two pancreaticoduodenectomies, three pancreas head-tailpiece resections, and eight cardiovascular surgeries without cardiopulmonary bypass : six cases of off-pump coronary artery bypass grafting and two femoro-femoral artery

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bypasses) were enrolled in this study. Diagnoses of the patients were as follows : four hepatocellular carcinoma, two liver cirrhosis, one fulminant hepatitis, five pancreatic cancer, six angina pectoris, two arteriosclerosis obliterans). Patients' characteristics were as follows : age, 54-87 years ; height, 129.1-178.0 cm ; weight, 39.7-91.4 kg ; body mass index, 17.8-30.6 kg/m² ; gender (male/female), 13/7 ; previous diabetes mellitus, 4 patients ; and metabolic syndrome, 2 patients.

The newly developed artificial endocrine pancreas (STG-55) is designed to be more user-friendly than its conventional counterpart (STG-22) while maintaining the latter's fundamental functions, such as a closed-loop system using algorithms for insulin and glucose infusion. The device is equipped with a disposable and modular tubing circuit with an auto-priming function, a sensor set-up with automatic calibration and quick response, and a compact structure (Figure 2). It has been specifically modified to comply with surgical and ICU needs (8, 9). Table 1 shows the differences between STG-22 and STG-55. STG-55 has many new and beneficial features.

Rapidlab860 (Bayer Medical, Tokyo, Japan) was used for conventional blood glucose assessment. After anesthetic induction, a 20G intravenous catheter was inserted into a peripheral forearm vein and connected to the continuous blood glucose monitor.



Concept
Target: Acute phase
(Operation room & ICU)

- Simple handling
- Short preparation time
- Down sizing & slimming



Figure 2. STG-55 (Nikkiso), equipped with a disposable and modular tubing circuit with an auto-priming function, automatic calibration with quick response in the sensor set-up, and a compact structure.

Table 1 : Comparison between STG-22 and STG-55

	Conventional artificial pancreas, STG-22	Next-generation artificial pancreas, STG-55
Size (mm)	505 (W) × 565 (D) × 1335 (H)	375 (W) × 425 (D) × 1350 (H)
Weight (kg)	62	36
Preparation on the previous day	Necessary for sensor aging	Not necessary
Battery	Not installed	Installed
Consumables	Reusable partially	Single use within 24 hours
Priming function	Not installed	Installed
Data display/output	External printer/cable	Liquid crystal display/USB
Time of preparation (hours)	3-12	1-1.5

A radial arterial catheter was also inserted to obtain samples for blood glucose determination. The blood glucose determination was carried out approximately once an hour for a stable condition. The resultant 105 scores for paired blood glucose values obtained with continuous glucose measurements (STG-55) and with conventional intermittent glucose measurements (Rapidlab 860) were compared.

The accuracy of continuous glucose measurements (STG-55) and that of conventional intermittent glucose measurements (Rapidlab 860) were compared by a Bland-Altman plot (10). In addition, the values obtained using the two methods were subjected to correlation analysis. StatView version 5.0 (SAS institute Inc., Cary, NC) was used for the statistical analysis, and $P < 0.05$ was considered to be statistically significant.

RESULTS

Stable blood glucose values were maintained automatically, and there were no complications related to use of the STG-55. A close correlation ($r=0.96$) was observed between continuous glucose measurements by the STG-55 and conventional intermittent glucose measurements (Rapidlab 860) (Figure 3, left). Significant agreement was also observed when the differences between the two measurements were plotted against their mean values (Figure 3, right).

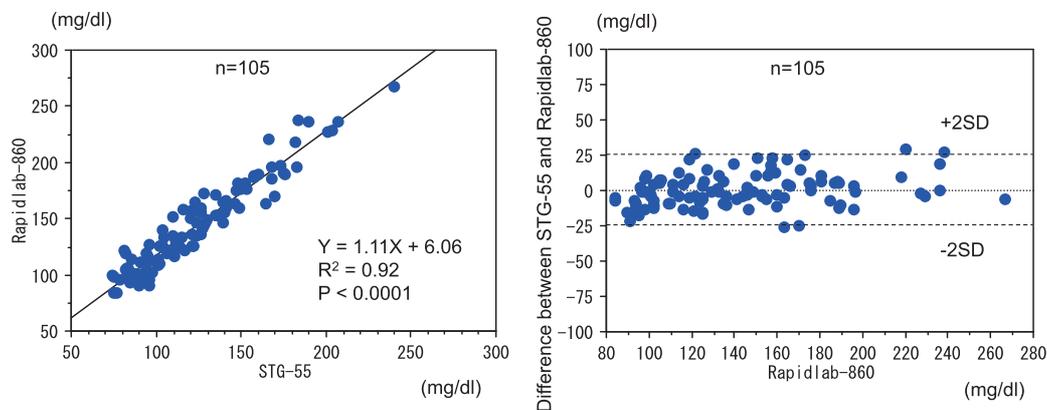


Figure 3. Accuracy of continuous blood glucose monitoring during surgery. Left : Correlations between continuous glucose measurements (STG-55) and conventional intermittent glucose measurements (Rapidlab 860). Right : Differences between the two measurements plotted against their mean (Bland-Altman plot of continuous glucose measurements (STG-55) and conventional intermittent glucose measurements (Rapidlab 860)).

The difficulty of manipulation using this system was decreased by improved preparation procedures. In all patients, there was no hypoglycemia during the perioperative period. Figure 4 shows a typical example of intraoperative blood glucose changes (a 64-year-old male patient undergoing pancreaticoduodenectomy). Continuous monitoring and control of blood glucose were successfully attained with the aid of the artificial endocrine pancreas (STG-55). A suitable blood glucose level was ensured by appropriate insulin administration.

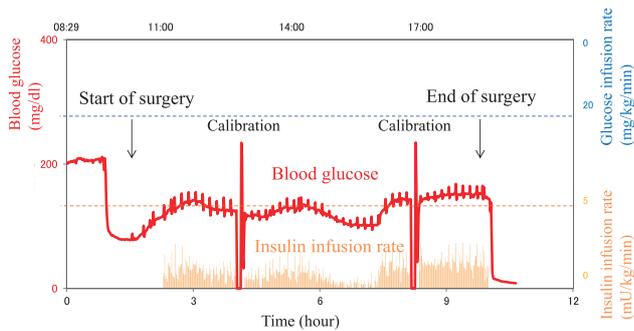


Figure 4. Glycemic control in a typical case using artificial endocrine pancreas (a 64-year-old male patient during pancreaticoduodenectomy). The target glucose level range was set at 80-150 mg/dl. The insulin infusion rate increased according to the increase in glucose concentration.

DISCUSSION

Hyperglycemia induced by surgical stress often causes dysregulation of liver metabolism and immune function, resulting in impaired post-operative recovery. Several mechanisms have been proposed to explain the adverse effects of hyperglycemia. It was found that persistent hyperglycemia resulted in functional decline of neutrophils. Infection is thus the critical problem resulting from hyperglycemia in the acute phase of the post-operative period. Additionally, hyperglycemia can exacerbate a number of perioperative problems, including cardiac and neurologic complications (1). On the other hand, hypoglycemia may also cause severe neurologic complications dependent on its duration and absolute value of plasma glucose. Furthermore, recent studies have shown that reducing the variability of blood glucose concentration may play an important role in glucose management (11). Anesthesiologists must avoid severe hypo- or hyperglycemia during surgery.

However, it has also been shown that intensive insulin treatment is sometimes difficult to perform when using sliding-scale manual insulin injection because hypo/hyperglycemia often occurs in spite of frequent blood glucose testing. It has therefore been suggested that continuous blood glucose monitoring would be beneficial for maintaining target blood glucose levels.

The usefulness of a closed-loop system (artificial endocrine pancreas) to achieve strict glycemic control during surgery was reported (12-14). The artificial endocrine pancreas (STG-22) provides continuous blood glucose monitoring through a dual lumen catheter blood sampling technique, a high-quality roller pump (multichannel pump), and a glucose sensor electrode with a glucose oxidase membrane. Before starting blood glucose monitoring, two-point calibration was performed using a standard solution for internal calibration (glucose concentration: 0 mg/dl) and a standard glucose solution (200 mg/dl). During blood glucose monitoring, internal calibration using the standard solution for internal calibration was performed automatically every 4 h. After calibration of the equipment, blood was sampled continuously from

a peripheral vein at a rate of 2 ml/h and continuously diluted with a heparinized isotonic solution. The diluted blood was further diluted with an isotonic buffer solution of phosphoric acid, pH 7.4, after which the glucose sensor electrode was exposed to the sampled blood. The multichannel pump and the glucose sensor electrode both had an accuracy of $\pm 5\%$. The accuracy and reliability of this system during and after surgery have been confirmed (15, 16). In this study, the results using STG-55 were similar to those obtained with the conventional artificial pancreas (STG-22).

In December 2007, our clinical team at Tokushima University Hospital initiated a clinical trial to evaluate the efficacy of the artificial pancreas for intra-operative patients. Two Nikkiso STG-22 artificial pancreas systems were put into clinical use at Tokushima University Hospital for intra- and post-operative glucose control. The usefulness of a closed-loop system providing continuous monitoring and strict control of perioperative blood glucose in patients during several surgeries was also reported (4-7).

However, improved preparation procedures are needed to reduce the difficulty of manipulation using this system. Such a new device has to be simple to use and easily adaptable to various clinical situations, including emergency medicine. This newly developed artificial pancreas was approved by the Ministry of Health, Labour and Welfare of Japan in late 2009. This next-generation artificial endocrine pancreas, equipped with a disposable and modular tubing circuit with an auto-priming function, automatic calibration with quick response in sensor set-up, and a compact structure, is also available (8, 9). The most beneficial point seems to be the improved glucose sensor. This glucose sensor is newly developed for single use in order to avoid long preparation. It is now compact and can reduce the preparation time, including the performance of sensor aging and the assembly of disposable tubing parts. The conventional artificial pancreas (STG-22) requires 3-12 hours of operation before starting the glucose sensor, so it should ideally be started the day before surgery. In contrast, the new sensor in the STG-55 only requires 5 minutes of warm-up before use.

In December 2011, the next-generation model of this artificial endocrine pancreas, the STG-55 (Nikkiso), was put into clinical use at our hospital. We are using this device for patients with unstable intraoperative blood glucose control, including diabetic patients and those with insulinoma, or those who had undergone a total pancreatectomy or liver transplantation, hepatectomy, or cardiovascular surgery. The blood glucose levels of these patients fluctuated significantly during surgery, and were very difficult to control when using intermittent glucose measurements and manual insulin injections. By using this device, stable blood glucose values were maintained automatically (Figure 4), and there were no complications related to the use of this device.

In conclusion, we believe that it is necessary to establish a strict glycemic control strategy because, in view of the global increase in diabetes, it is expected that good glycemic control in surgical and emergency settings will become more and more important. Artificial endocrine pancreas (STG-55) could be a powerful tool to achieve safe and strict glycemic control by accurate and continuous blood glucose monitoring, and closed-loop glycemic control systems. Establishment of a new perioperative blood glucose control method with the aid of an artificial endocrine pancreas is urgently needed.

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CONFLICT OF INTEREST

None

REFERENCES

1. Kawahito S, Kitahata H, Oshita S : Problems associated with glucose toxicity : role of hyperglycemia-induced oxidative stress. *World J Gastroenterol* 15 : 4137-4142, 2009
2. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R : Intensive insulin therapy in critically ill patients. *N Eng J Med* 345 : 1359-1367, 2001
3. Van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P : Outcome benefit of intensive insulin therapy in the critically ill : insulin dose versus glycemic control. *Crit Care Med* 31 : 359-366, 2003
4. Kawahito S, Kitahata H, Kitagawa T, Oshita S : Intensive insulin therapy during cardiovascular surgery. *J Med Invest* 57 : 191-204, 2010
5. Okada T, Kawahito S, Mita N, Matsuhisa M, Kitahata H, Shimada M, Oshita S : Usefulness of continuous blood glucose monitoring and control for patients undergoing liver transplantation. *J Med Invest* 60 : 205-212, 2013
6. Kawahito S, Higuchi S, Mita N, Kitagawa T, Kitahata H : Novel blood sampling method of an artificial endocrine pancreas via the cardiopulmonary bypass circuit. *J Artif Organs* 16 : 508-509, 2013
7. Hirose K, Kawahito S, Mita N, Takaishi K, Kawahara T, Soga T, Katayama T, Imura S, Morine Y, Ikemoto T, Shimada M, Matsuhisa M, Kitahata H : Usefulness of artificial endocrine pancreas during resection of insulinoma. *J Med Invest* 61 : 421-425, 2014
8. Tsukamoto Y, Okabayashi T, Hanazaki K : Progressive artificial endocrine pancreas : the era of novel perioperative blood glucose control for surgery. *Surg Today* 41 : 1344-1351, 2011
9. Tsukamoto Y, Kinoshita Y, Kitagawa H, Munekage M, Munekage E, Takezaki Y, Yatabe T, Yamashita K, Yamazaki R, Okabayashi T, Tarumi M, Kobayashi M, Mishina S, Hanazaki K : Evaluation of a novel artificial pancreas : closed loop glycemic control system with continuous blood glucose monitoring. *Artif Organs* 37 : E67-E73, 2013
10. Bland JM, Altman DG : Agreed statistics : measurement method comparison. *Anesthesiology* 116 : 182-185, 2012
11. Egi M, Bellomo R, Stachowski E, French CJ, Hart G : Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology* 105 : 244-252, 2006
12. Hanazaki K, Nosé Y, Brunnicardi FC : Artificial endocrine pancreas. *J Am Coll Surg* 193 : 310-322, 2001
13. Kono T, Hanazaki K, Yazawa K, Ashizawa S, Fisher WE, Wang XP, Nosé Y, Brunnicardi FC : Pancreatic polypeptide administration reduces insulin requirements of artificial pancreas in pancreatectomized dogs. *Artificial Organs* 29 : 83-87, 2005
14. Hanazaki K, Maeda H, Okabayashi T : Tight perioperative glycemic control using an artificial endocrine pancreas. *Surg Today* 40 : 1-7, 2010
15. Yamashita K, Okabayashi T, Yokoyama T, Yatabe T, Maeda H, Manabe M, Hanazaki K : The accuracy of a continuous blood glucose monitor during surgery. *Anesth Analg* 106 : 160-163, 2008
16. Yamashita K, Okabayashi T, Yokoyama T, Yatabe T, Maeda H, Manabe M, Hanazaki K : Accuracy and reliability of continuous blood glucose monitor in post-surgical patients. *Acta Anaesthesiol Scand* 53 : 66-71, 2009