

Continuous Postoperative Blood Glucose Monitoring and Control by Artificial Pancreas in Patients Having Pancreatic Resection

A Prospective Randomized Clinical Trial

Takehiro Okabayashi, MD; Isao Nishimori, MD; Koichi Yamashita, MD; Takeki Sugimoto, MD; Hiromichi Maeda, MD; Tomoaki Yatabe, MD; Takuhiro Kohsaki, MD; Michiya Kobayashi, MD; Kazuhiro Hanazaki, MD

Objective: To evaluate a closed-loop system providing continuous monitoring and strict control of perioperative blood glucose following pancreatic resection.

Design: Prospective, randomized clinical trial.

Patients: Thirty patients who had pancreatic resection for pancreatic neoplasm.

Interventions: Patients were prospectively randomized. Perioperative blood glucose levels were continuously monitored using an artificial endocrine pancreas (STG-22). Glucose levels were controlled using either the sliding scale method (sliding scale group, n=13) or the artificial pancreas (artificial pancreas group, n=17).

Main Outcome Measures: Incidence of severe hypoglycemia (<40 mg/dL) during the intensive care period following pancreatic resection in patients monitored with the artificial pancreas. The secondary outcome measure was the total amount of insulin required for glycemic control in the first 18 hours after pancreatic resection in each patient group.

Results: In the sliding scale group, postoperative blood glucose levels rose initially before reaching a plateau of approximately 200 mg/dL between 4 and 6 hours after pancreatectomy. The levels remained high for 18 hours postoperatively. In the artificial pancreas group, blood glucose levels reduced steadily, reaching the target zone (80-110 mg/dL) by 6 hours after surgery. The total insulin dose administered per patient during the first postoperative 18 hours was significantly higher in the artificial pancreas group (mean [SD], 107 [109] IU) than the sliding scale group (8 [6] IU; $P < .01$). Neither group showed hypoglycemia.

Conclusions: Perioperative use of an artificial endocrine pancreas to control pancreatogenic diabetes after pancreatic resection is an easy and effective way to maintain near-normal blood glucose levels. The artificial pancreas shows promise for use as insulin treatment for patients with pancreatogenic diabetes after pancreatic resection.

Arch Surg. 2009;144(10):933-937


POSTOPERATIVE HYPERGLYCEMIA is common in critically ill patients, including those without a history of diabetes mellitus.¹⁻³ Hyperglycemia induced by surgical stress often

operative morbidity and mortality.^{6,7} Maintaining blood glucose levels in the reference range during surgery might therefore reduce postoperative complications.⁸⁻¹¹ Hypoglycemia is a counterproblem during intensive insulin therapy in patients with high-risk surgery because there is no reliable technique to avoid hypoglycemia during intensive insulin therapy.^{6,7}

Diabetes associated with pancreatic resection is termed *pancreatogenic diabetes*. This complication necessitates high amounts of insulin to control postoperative blood glucose levels after pancreatic surgery.^{12,13} Whereas the hormonal abnormalities that follow pancreatic resection depend on the extent and type

Author Affiliations:

Departments of Surgery (Drs Okabayashi, Sugimoto, Maeda, Yatabe, and Hanazaki), Gastroenterology and Hepatology (Drs Nishimori and Kohsaki), Anesthesiology and Critical Care Medicine (Dr Yamashita), and Clinical Health and Medical Services, Kochi Medical School, Kochi, Japan (Dr Kobayashi).

 **CME available online at www.jamaarchivescme.com and questions on page 889**

dysregulates liver metabolism and immune function, resulting in impaired postoperative recovery.^{4,5} Several randomized controlled studies indicated that strict control of blood glucose with insulin in a surgical intensive care unit reduces post-

Insulin Therapy by Artificial Pancreas

Table 1. Sliding Scale Insulin Protocol

Blood Glucose Level, mg/dL	Human Insulin, IU ^a	Additional Action Requested
0-80	0	1 Ampule of D50, call physician
81-100	0	No action
101-150	0	No action
151-200	2	No action
201-250	4	No action
251-300	6	No action
301-350	8	No action
351-400	10	No action
>401	12	Call physician

SI conversion factor: To convert to millimoles per liter, multiply by 0.0555.

^aSubcutaneous dose of rapid human insulin to be given.

of surgery, the early resolution of pancreatogenic diabetes enables tight postoperative glycemic control after pancreatic surgery. This study evaluated the closed-loop STG-22 system (Nikkiso Inc, Tokyo, Japan), a type of artificial pancreas, for the continuous monitoring and control of postoperative blood glucose in patients having pancreatic resection. We also investigated hyperglycemia induced by the associated surgical stress in these patients.

METHODS

PATIENTS

This study recruited 32 patients having elective pancreatic resection for pancreatic disease. Exclusion criteria were weight loss greater than 10% during the previous 6 months, signs of distant metastasis, and respiratory, renal, or heart disease. Patients provided written informed consent prior to enrollment. The study was approved by the local ethics committee and carried out in accordance with the Declaration of Helsinki. All studies were performed at Kochi Medical School from April 2007 to December 2007.

Perioperative blood glucose concentration was continuously monitored using the STG-22 system. We prospectively divided patients into 2 groups: one in which glucose levels were controlled using a manual injection of insulin, according to the commonly used sliding scale (SS group, $n=15$),^{14,15} and another that received programmed infusions of insulin determined by the control algorithm of the artificial pancreas (AP group, $n=17$).

INSULIN THERAPY AT SURGICAL INTENSIVE CARE UNIT

Sliding Scale Method

The 15 patients assigned to the SS group had continuous monitoring of blood glucose by the artificial pancreas and routine checking by nursing staff every 2 hours. In this group, blood glucose levels were controlled by the subcutaneous injection of regular human insulin; the dose was determined by the commonly used sliding scale, and the target blood glucose level to avoid hypoglycemia was 150 to 200 mg/dL (to convert to millimoles per liter, multiply by 0.0555), as shown in **Table 1**.^{14,15}

The Nikkiso Company developed the STG-22 unit in 1984 as an artificial endocrine pancreas. Peripheral blood for glucose monitoring was sampled continuously at 2 mL/h during the first postoperative 18 hours in the surgical intensive care unit. The STG-22 is a reliable and accurate device to measure blood glucose concentration, compared with the ABL800 FLEX machine (Radiometer Medical ApS, Brønshøj, Denmark) recommended by the National Committee for Clinical Laboratory.¹⁶ This closed-loop glycemic control system maintains stable blood glucose concentrations by the automatic infusion of regular insulin or glucose into the circulation.^{17,18}

Because hyperglycemia induced by surgical stress increased postoperative morbidity and mortality, it is recommended that tight glycemic control with intensive insulin therapy be performed in patients having major surgery.⁴⁻⁷ However, hypoglycemia induced by intensive insulin therapy is often also encountered in patients following high-risk surgery because there is no reliable technique for avoiding this condition during intensive insulin therapy.^{7,8} Recently, it has been reported that the development of accurate, continuous blood glucose monitoring devices, preferably closed-loop systems, for computer-assisted blood glucose control in the intensive care unit will help avoid hypoglycemia.¹⁹ In this study, we used the artificial pancreas machinery.

OUTCOME MEASURES

The main outcome measure of this study was the incidence of severe hypoglycemia (<40 mg/dL) during the intensive care period following pancreatic resection in patients monitored using the STG-22 artificial pancreas.²⁰ The secondary outcome was the total amount of insulin required for glycemic control in the first 18 hours after pancreatic resection in each patient group.

STATISTICAL ANALYSIS

Continuous variables are presented as mean (SD). Dichotomous variables are presented as number and percentage. $P < .05$ was considered significant. Data were analyzed using the t test (2-tailed), with dichotomous variables analyzed by the χ^2 test (2-tailed) or Fisher exact test (2-tailed). All analyses were performed using SPSS (SPSS Inc, Chicago, Illinois).

RESULTS

DEMOGRAPHIC AND OPERATIVE DATA

Thirty-two patients were initially enrolled and randomized (**Figure 1**). Two patients in the SS group with pancreatic carcinoma with peritoneal dissemination were excluded, leaving 13 patients in the SS group and 17 in the AP group for the final analysis. There was no significant difference between the 2 groups in clinical characteristics including nutritional status, serum amylase, and fasting blood glucose levels (**Table 2**). Pancreatectomy was done as a curative procedure in all patients who had pancreatic resection. Age, sex, and history of diabetes mellitus were equally distributed between groups. Surgical procedures were distributed as follows: 15 had pancreaticoduodenectomy; 11, pancreaticosplenectomy; 2, middle pancreatectomy; and 2, total pancreatectomy. Operation time and estimated blood loss volume were also not significantly different between groups (Table 2).

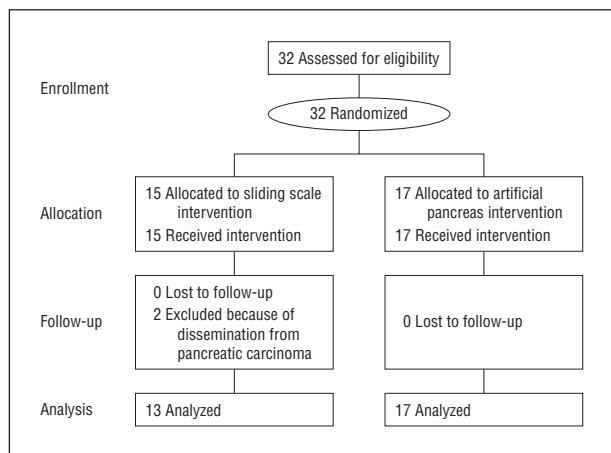


Figure 1. Randomization of patients having pancreatic resection.

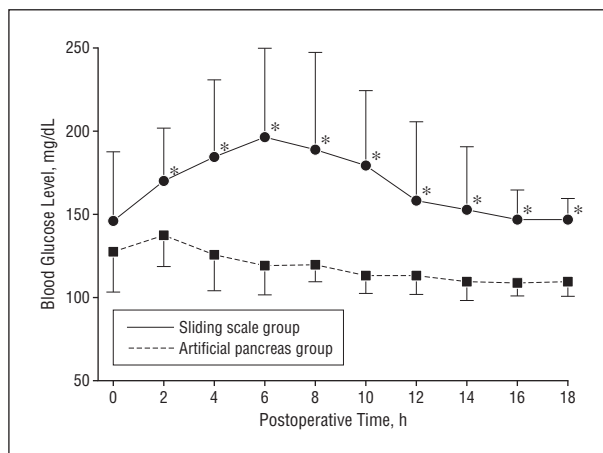


Figure 2. Postoperative blood glucose levels in the sliding scale (n=13) and artificial pancreas (n=17) groups during the first 18 hours after pancreatic resection. * $P < .05$.

Table 2. Baseline Characteristics of Patients Who Had Pancreatectomy

Variables	Mean (SD) by Group		P Value
	Sliding Scale (n=13)	Artificial Pancreas (n=17)	
Age, y	63.2 (7.5)	61.9 (13.6)	.76
Sex, male:female	6:7	12:5	.33
Body mass index ^a	21.5 (4.3)	21.1 (4.1)	.79
Blood chemistry, reference range			
Total protein, 6.5-8.0 g/dL	7.1 (0.7)	7.2 (0.5)	.61
Albumin, 3.8-5.1 g/dL	4.2 (0.4)	4.4 (0.4)	.23
Amylase, 40-115 U/L	96 (85)	95 (53)	.96
Fasting blood glucose, 70-110 mg/dL	126 (39)	127 (51)	.99
Hemoglobin A _{1c} , 4.3%-5.8%	6.3 (1.6)	6.0 (1.0)	.69
Previous diabetes mellitus, yes/no	6/7	9/10	.77
Operative procedure			.86
Pancreaticoduodenectomy	6	9	
Pancreaticosplenectomy	6	5	
Middle pancreatectomy	1	1	
Total pancreatectomy	0	2	
Operation time, min	325 (183)	427 (193)	.16
Estimated blood loss, mL	534 (639)	708 (603)	.45

SI conversion factors: To convert total protein and albumin to grams per liter, multiply by 10.0; amylase to microkatal per liter, 0.01667; blood glucose to millimoles per liter, 0.0555; and hemoglobin A_{1c} to proportion of total hemoglobin, 0.01.

^aCalculated as weight in kilograms divided by height in meters squared.

OPERATIVE MORTALITY AT 30 DAYS

Operative mortality 30 days after pancreatic resection was 0% in both groups, and all patients were discharged. Follow-up was completed to February 2008; there was no difference in the all-cause mortality between the SS and AP patients. Patient follow-up as of April 2007 ranged from 7.3 to 24.0 months (median, 12.3 months; mean, 14.4 months).

POSTOPERATIVE BLOOD GLUCOSE LEVELS

Postoperative blood glucose levels in the SS and the AP groups during the first 18 hours following surgery are

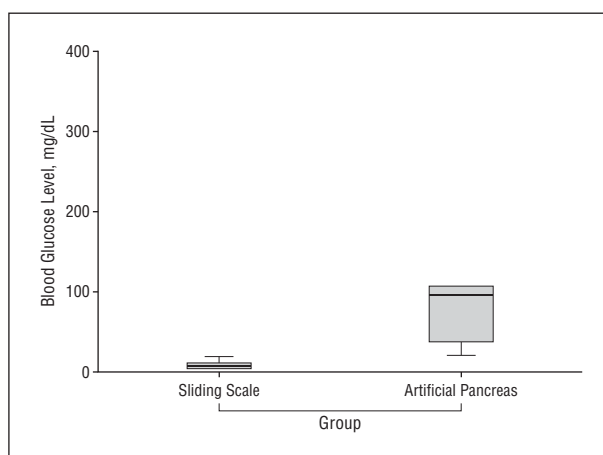


Figure 3. Total insulin requirement of the sliding scale (n=13) and artificial pancreas (n=17) groups after pancreatic surgery. $P < .01$.

shown in **Figure 2**. In the SS group, blood glucose levels gradually increased for the first 6 hours after pancreatectomy, reaching a plateau of approximately 200 mg/dL between 4 and 7 hours. Thereafter, the concentrations gradually decreased toward 150 mg/dL by 18 hours after surgery. In contrast, the average blood glucose level in patients from the AP group gradually decreased to the target zone (80-110 mg/dL). Blood glucose trends were therefore significantly different between the patient groups from 2 to 18 hours after pancreatectomy ($P < .05$). No patient in either group became hypoglycemic during their stay in the surgical intensive care unit.

TOTAL INSULIN USE AFTER PANCREATIC RESECTION

Figure 3 shows the total insulin use in this study. Patients in the SS group required 8(6) IU of insulin per patient, according to the routine sliding scale (range, 0-20 IU; n=13). In contrast, AP group patients needed 107(109) IU of insulin (range, 21-390 IU; n=17) per patient for intensive glycemic control by the STG-22 during the first 18 hours after pancreatic resection. The

difference in total insulin use between the 2 groups was significant ($P < .001$).

COMMENT

Insulin therapy is frequently problematic in patients with pancreatogenic diabetes following pancreatic resection. Insufficient insulin replacement leaves patients hyperglycemic, while amounts that are barely excessive lead to hypoglycemia.¹² This clinical study revealed for the first time that perioperative use of an artificial endocrine pancreas for pancreatogenic diabetes after pancreatic resection enables strict glycemic control of euglycemia without severe hypoglycemia. Our results additionally showed that hyperglycemia induced by surgical stress could not be controlled with the conventional sliding scale method.^{14,15}

In our previous study of patients who had liver resection for hepatic disease, postoperative blood glucose levels rose initially and reached a plateau of approximately 250 mg/dL between 4 and 7 hours after hepatectomy before returning to normal levels by 16 hours.¹⁸ However, levels in the current SS group reached a lower plateau of approximately 200 mg/dL between 4 and 6 hours after pancreatectomy and then remained high during the 18 hours of postoperative intensive care. These results suggested the occurrence of hyperglycemia associated with pancreatogenic diabetes following metabolic disturbance from surgery.

The postoperative incidence of diabetes is directly related to the extent of pancreatic resection.¹² A preoperative clinical assessment must consider the possibility of significant impairment of the entire pancreatic parenchyma prior to surgery or a high risk of endocrine cell mass reduction. It is also problematic that patients who have major pancreatic resection are highly sensitive to insulin and may have episodic iatrogenic hypoglycemia. Tight glycemic control with intensive insulin therapy, therefore, reduces postoperative morbidity and mortality, thereby improving patient outcome.^{7,8,20} However, effective procedures for preventing hypoglycemia under these conditions remain to be established.

This is the first prospective randomized evaluation of a closed-loop glucose-sensing and insulin-delivery system such as the STG-22 for the postoperative treatment of pancreatectomized patients in a surgical intensive care unit. Our results indicated that the continuous monitoring of blood glucose and programmed infusion of insulin according to the STG-22 control algorithm is an ideal way to control postoperative hyperglycemia. Blood glucose levels are gradually controlled using this artificial pancreas, avoiding unnecessary metabolic disturbances and hypoglycemia postoperatively. We achieved strict control of blood glucose levels, even in patients with diabetes mellitus. Some surgeons advocate total pancreatectomy in favor of proximal partial pancreatectomy, claiming that diabetes developing after total pancreatectomy is easier to stabilize.²¹ However, the AP group in the present study contained 2 patients who had total pancreatectomy, and postoperative blood glucose levels were successfully controlled in both. Total insulin requirements

were significantly higher in the AP group than in the SS group, and such a high amount of insulin could not be injected using the manual method of blood glucose control without inducing hypoglycemia. Therefore, manual insulin injections using the sliding scale are of limited use for the control of postoperative hyperglycemia in patients having pancreatic resection. In the AP group, no superficial surgical site infection was observed. Our results supported the idea that postoperative infectious morbidities were reduced by tight glycemic control.^{6,7}

In conclusion, we showed that the STG-22 closed-loop system is of great clinical value in patients who have pancreatic resection. It is an easy and effective way to control postoperative hyperglycemia induced by pancreatogenic diabetes and surgical stress. Perioperative use of the STG-22 enabled strict but gradual control of blood glucose to near-normal levels without severe hypoglycemia, even in patients who had total pancreatectomy. The artificial pancreas promises to revolutionize insulin treatment for patients with pancreatogenic diabetes following pancreatic resection.

Accepted for Publication: August 8, 2008.

Correspondence: Takehiro Okabayashi, MD, Department of Surgery, Kochi Medical School, Kohasu-Okochi, Nankoku-City, Kochi 783-8505, Japan (tokabaya@kochi-u.ac.jp).

Author Contributions: *Study concept and design:* Okabayashi, Nishimori, Sugimoto, and Hanazaki. *Acquisition of data:* Okabayashi, Yamashita, Maeda, Yatabe, and Kobayashi. *Analysis and interpretation of data:* Okabayashi and Kohsaki. *Drafting of the manuscript:* Okabayashi, Yamashita, Maeda, Yatabe, and Kohsaki. *Critical revision of the manuscript for important intellectual content:* Okabayashi, Nishimori, Sugimoto, Kobayashi, and Hanazaki. *Statistical analysis:* Okabayashi. *Obtained funding:* Okabayashi. *Administrative, technical, and material support:* Okabayashi, Yamashita, Maeda, Yatabe, and Kohsaki. *Study supervision:* Nishimori, Sugimoto, Kobayashi, and Hanazaki.

Financial Disclosure: None reported.

Funding/Support: This study was supported by the Pancreas Research Foundation of Japan; the Ministry of Education, Culture, Sports, Science, and Technology; and The Kochi University President's Discretionary Grant.

REFERENCES

1. Cely CM, Arora P, Quartin AA, Kett DH, Schein RM. Relationship of baseline glucose homeostasis to hyperglycemia during medical critical illness. *Chest*. 2004; 126(3):879-887.
2. McCowen KC, Malhotra A, Bistran BR. Stress-induced hyperglycemia. *Crit Care Clin*. 2001;17(1):107-124.
3. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;355(9206):773-778.
4. Huo TI, Lui WY, Huang YH, et al. Diabetes mellitus is a risk factor for hepatic decompensation in patients with hepatocellular carcinoma undergoing resection: a longitudinal study. *Am J Gastroenterol*. 2003;98(10):2293-2298.
5. Little SA, Jarnagin WR, DeMatteo RP, Blumgart LH, Fong Y. Diabetes is associated with increased perioperative mortality but equivalent long-term outcome after hepatic resection for colorectal cancer. *J Gastrointest Surg*. 2002;6(1): 88-94.

6. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med*. 2003;31(2):359-366.
7. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345(19):1359-1367.
8. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354(5):449-461.
9. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA*. 2003;290(15):2041-2047.
10. Toft P, Jorgensen HS, Toennesen E, Christiansen C. Intensive insulin therapy to non-cardiac ICU patients: a prospective study. *Eur J Anaesthesiol*. 2006;23(8):705-709.
11. Dronge AS, Perkal MF, Kancir S, Concato J, Aslm M, Rosenthal RA. Long-term glycemic control and postoperative infectious complications. *Arch Surg*. 2006;141(4):375-380.
12. Brunicaudi FC, Andersen DK, Billiar TR, Dunn DL. Part II: pancreas. In: Hunter JG, Pollock RE, eds. *Schwartz's Principles of Surgery*. 8th ed. New York, NY: McGraw-Hill Co Inc; 2004:1221-1296.
13. Kono T, Hanazaki K, Yazawa K, et al. Pancreatic polypeptide administration reduces insulin requirements of artificial pancreas in pancreatectomized dogs. *Artif Organs*. 2005;29(1):83-87.
14. Alfonso A, Koops MK, Mong DP, Vigersky RA. Glycemic control with regular versus lispro insulin sliding scales in hospitalized type 2 diabetics. *J Diabetes Complications*. 2006;20(3):153-157.
15. Dickerson LM, Ye X, Sack JL, Hueston WJ. Glycemic control in medical inpatients with type 2 diabetes mellitus receiving sliding scale insulin regimens versus routine diabetes medications: a multicenter randomized control trial. *Ann Fam Med*. 2003;1(1):29-35.
16. Yamashita K, Okabayashi T, Yokoyama T, et al. The accuracy of a continuous blood glucose monitor during surgery. *Anesth Analg*. 2008;106(1):160-163.
17. Hanazaki K, Nose Y, Brunicaudi FC. Artificial endocrine pancreas. *J Am Coll Surg*. 2001;193(3):310-322.
18. Okabayashi T, Hnazaki K, Nishimori I, et al. Continuous post-operative blood glucose monitoring and control using a closed-loop system in patients undergoing hepatic resection. *Dig Dis Sci*. 2008;53(5):1405-1410.
19. Van den Berghe G. 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*. 2008;51(6):911-915.
20. Brunkhorst FM, Engel C, Bloos F, et al; German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358(2):125-139.
21. Jethwa P, Sodergren M, Lala A, et al. Diabetic control after total pancreatectomy. *Dig Liver Dis*. 2006;38(6):415-419.

Call for Papers

Maintenance of Certification

During 2009, we are soliciting manuscripts on maintenance of certification. The editorial board has selected this topic as our year-long theme. Accepted manuscripts will be given priority publication. Please indicate in your cover letter that your manuscript is to be considered for this theme.