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.

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of surgery, the early resolution of pancreaticogenic 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.

### 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 automatic infusion of regular human insulin, according to the commonly used sliding scale (SS group, n=15), and another that received programmed infusions of insulin determined by the control algorithm of the artificial pancreas (AP group, n=17).

#### 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. 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 chi-squared test (2-tailed) or Fisher exact test (2-tailed). All analyses were performed using SPSS (SPSS Inc, Chicago, Illinois).

#### RESULTS

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 pancreatectoduodenectomy; 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).

### 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), and another that received programmed infusions of insulin determined by the control algorithm of the artificial pancreas (AP group, n=17).

#### INSULIN THERAPY BY ARTIFICIAL PANCREAS

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. This closed-loop glycemic control system maintains stable blood glucose concentrations by the automatic infusion of regular insulin or glucose into the circulation. 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. However, hyperglycemia 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. 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. In this study, we used the artificial pancreas machinery.
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 in the SS and the AP groups during the first 18 hours following surgery are 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 PANCREATECTOMY

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
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. 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. 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 disturbances from surgery.

Tight glycemic control with intensive insulin therapy, therefore, reduces postoperative morbidity and mortality, thereby improving patient outcome.17,18 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 a 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.22 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.
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(5):911-915.