Perioperative tight glycemic control using artificial pancreas decreases infectious complications via suppression of inflammatory cytokines in patients who underwent pancreaticoduodenectomy: a prospective, non-randomized clinical trial

Hiroya Akabori, MD, PhD[1], Masaji Tani, MD, PhD[1], Naomi Kitamura, MD, PhD[1], Hiromitsu Maehira, MD[1], Yasuhiko Imashuku, MD, PhD[2], Yasuyuki Tsujita, MD, PhD[3], Tomoharu Shimizu, MD, PhD[1], Hirotoshi Kitagawa, MD, PhD[2], Yutaka Eguchi, MD, PhD[3]

[1]Department of Surgery, [2]Department of Anesthesiology, [3]Department of Critical and Intensive Care Medicine, Shiga University of Medical Science, Shiga, Japan

Reprint requests and address correspondence to:

Hiroya Akabori, Department of Surgery, Shiga University of Medical Science, Seta-Tsukinowa-cho, Otsu, Shiga, Japan, 520-2192

(phone) +81-77-548-2238; (e-mail) hakabori@belle.shiga-med.ac.jp

Introduction

Perioperative hyperglycemia exacerbates the cytokine, inflammatory, and oxidative stress response. It is associated with increased rates of postoperative infectious complications (POICs), such as surgical site infection (SSI), in patients with diabetes after abdominal surgery[1,2], including pancreaticoduodenectomy (PD).[3] In addition, increased perioperative glycemic variability (GV) in combined with hyperglycemia is more detrimental than hyperglycemia alone,[4,5] which may result in a high risk of POICs.

Artificial pancreas (AP) consists of a continuous glucose monitor and an insulin pump[6], designed to automatically adjust blood glucose values in real time, making tight glycemic control (TGC) possible with reduced GV.[7] Therefore, TGC using AP (TGC-AP) can prevent not only perioperative hyperglycemia, but also hypoglycemia, despite a large amount of insulin.[8] Although the anti-inflammatory mechanism has yet to be established, TGC-AP improves the rate of POICs after pancreatic surgery.[9]

Insulin has been considered a key metabolic hormone with effects on glucose and lipid metabolism. In addition, its anti-inflammatory effects in

patients with traumatic hyperglycemia are rapid and activated within 2 hours.[10,11]

Adiponectin, an adipocyte-derived secretory protein that plays a key role in glucose metabolism, exhibits anti-inflammatory properties and inverse associations between adiponectin and interleukin (IL)-6 levels.[12] The relative decrease in preoperative adiponectin levels, as well as in the adiponectin ratio (postoperative adiponectin levels/preoperative adiponectin levels), is an independent risk factor for POICs after gastrointestinal surgery.[13,14] These findings suggest that perioperative adiponectin levels contribute to the development of the inflammatory response following abdominal surgery.

In this study, we report the results of a single-center, prospective, and non-randomized clinical trial of perioperative TGC-AP in patients with impaired glucose tolerance (IGT) following PD. We hypothesized that TGC-AP, using a large amount of insulin, would reduce the rate of POICs, at least in part, by modulating inflammatory mediators, including adiponectin, after surgery.

Materials and methods

The study conformed to the Clinical Research Guidelines of Shiga

University of Medical Science and was approved by the institutional ethics committee (approval number 27-47) followed by pre-registration in the UMIN Clinical Trials Registry (UMIN ID 000023460). The trial was performed in accordance with the principles of the Declaration of Helsinki.

Patients

We recruited patients who underwent PD for a biliary pancreatic tumor at Shiga University of Medical Science Hospital between April 2016 and March 2018. Inclusion criteria included age of 20 years or older and inpatients with diabetes (hemoglobin A1c ≥6.5%, fasting plasma glucose level ≥126 mg/dL, or requiring hypoglycemic agents) or “borderline” diabetes according to a 75-g oral glucose tolerance test (OGTT), defined as a plasma glucose concentration of 140-199 mg/dL 2 h after the oral intake of a 75-g glucose load.[15] Patients with severe respiratory disease or who underwent dialysis were excluded. All patients provided written informed consent prior to enrollment.

Trial design

This was a prospective, non-randomized, single-center study with a 24-hour intervention and a 30-day follow-up. The enrolled patients were divided into two groups according to the period of time to assess the value of AP for POICs.

In the first-half period, conventional glycemic control was performed (control group). Then, in the last-half period, TGC-AP was performed (AP group) (Figure 1). There were no changes in perioperative management or surgical members throughout this study period.

Trial procedures

Glycemic monitoring was typically performed just after the start of surgery and was continued for 24 h (perioperative period) using AP, followed by sliding-scale insulin administration for the control of elevated glucose for patients in both groups, without the use of strict insulin regimens to prevent hyperglycemia greater than 180 mg/dL. The AP uses a dual lumen catheter blood sampling technique every 2 s and can automatically infuse insulin and /or glucose to adjust blood glucose levels. The perioperative period was divided into two parts: intraoperative (start to the end of surgery) and postoperative (immediately after surgery up to the following 24 hours); blood glucose control was performed in each period.

Tight glycemic control: The AP group continuously maintained their target glucose range of 80 to 110 mg/dL during the perioperative period using AP[7] (STG-55 system; Nikkiso Inc., Tokyo, Japan). The AP system, a closed-loop glycemic

control system[7], is a reliable and accurate device to measure blood glucose levels, compared to the ABL800 FLEX machine (Radiometer Medical ApS, Denmark) recommended by the National Committee for Clinical Laboratory.[16]

Conventional glycemic control: The control group only continuous monitoring of blood glucose by AP and routine checking at 2-h intervals by nursing staff to remain within the target blood glucose range. Insulin infusion was performed when the blood glucose level exceeded 180 mg/dL[17] during the perioperative period.

Primary and secondary outcomes

The primary outcome was the POIC rate during the 30-day postoperative observation period. POICs in this study were defined as the occurrence of 1 or more reports of incisional and organ/space SSI[18] and remote infections within the first 30 days of surgery. All patients were checked daily for signs of infection, and results were interpreted by an investigator blinded to the treatment assignment. Diagnosis of infection was confirmed bacteriologically by a positive culture. According to the Centers for Disease Control and Prevention[19], the criteria for all SSIs were at least one of the following: (i) purulent discharge with or without laboratory confirmation from the superficial incision; (ii) organisms isolated from

an aseptically obtained culture of fluid or tissue from the superficial incision; (iii) at least one of the indicated signs or symptoms of infection (pain or tenderness, localized swelling, redness, or heat from the superficial incision deliberately made by surgeon, unless the incision is culture-negative); and (iv) a diagnosis of superficial SSI by the surgeon or attending physician. Secondary outcomes were perioperative factors (duration of surgery, estimated blood loss, blood transfusion, and length of postoperative hospital stay), and hematological examinations for infection. Insulin secretion was evaluated using the serum level in the C-peptide response, as an indicator of endogenous insulin production, and insulin resistance was evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR), which was calculated using the following formula: fasting plasma glucose (G0) x fasting insulin (I0) / 405. We used glucose data collected throughout the trial period (intraoperative and postoperative period) and analyzed it for GV according to the coefficient of variation (CV; standard deviation (SD) / mean blood glucose). Hypoglycemic events (blood glucose level of < 70 mg/dL), as well as the total amount of insulin required for glycemic control throughout the trial period, were measured and analyzed in each patient group.

Laboratory procedures

Blood samples were used to measure plasma IL-6 and IL-10 levels using a commercial enzyme-linked immunosorbent assay (R&D Systems Inc., Minneapolis, MN, USA), and adiponectin levels were measured using a latex particle-enhanced turbidimetric assay (Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan), as described previously[20] before surgery and on the first postoperative day (POD). In addition, the adiponectin ratio was calculated as the adiponectin value on POD1 divided by the preoperative adiponectin value.[13]

Statistical analysis

Sample size calculation was based on the effectiveness of TGC-AP in patients for whom PD was indicated. Anticipating anti-inflammatory effectiveness in TGC-AP (30-day POIC rate 50% vs. 10%) based on previous studies[21,22], approximately 16 patients per group would be needed in order to detect any significant effects of TGC-AP, with a one-sided alpha level of less than 0.05 and a beta level of 0.2. Continuous variables were presented as SD without skewed distribution and as medians (interquartile ranges) with skewed distribution. Dichotomous variables were presented as number and percentage. Differences among the study groups were determined using the chi-square test (two-tailed) or Fisher's exact test (two-tailed) for comparison of proportions, by the Wilcoxon

rank sum test for non-normally distributed numerical data and by Student's t-test for normally distributed numerical data. A two-sided P-value of less than 0.05 was considered statistically significant. Calculations were performed with the statistical program R (http://cran.r-project.org).

Results

Patient characteristics

Of the 52 consecutive patients who underwent PD were assessed for eligibility by glucose tolerance before surgery, 32 patients were divided into two groups: TGC (AP group; n=16) or conventional glycemic control (control group; n=16) (Figure 1). We withdrew one patient in each group after allocation because the procedure was changed from PD to total pancreatectomy. Another patient in the AP group was excluded due to problems with the use of AP, resulting in inadequate TGC. Therefore, the final 29 patients eligible for this study were subjected to the intervention. The baseline and operative characteristics of the patients were similar, and there was no significant difference between the two groups (Table 1).

Alteration of perioperative blood glucose level

The mean blood glucose levels were maintained close to the target range in each group during the perioperative period without hypoglycemia (<70mg/dL) (Figure 2), but the mean GV was significantly different between the control and AP groups during the postoperative period (19.7±2.4% *vs.* 15.0±3.6%; *P*=0.004) and perioperative period (16.4±5.9% *vs.* 13.5±3.5%; *P*=0.038) (Table 2).

Postoperative clinical outcomes

There was a significant difference in the POIC rate between the control and AP groups (73.3% *vs.* 28.6%; *P*=0.027), but the length of postoperative stay was not markedly different (32 *vs.* 17 days; *P*=0.065) (Table 3). A total of forty-two microorganisms were isolated, the most common being Enterococcus species, Staphylococcus species, and Enterobacter species (Table 4). Total insulin requirements during the first 24 hours from the start of the surgery were significantly different in the two groups (control 10.2±16.2 *vs* AP 27.0±13.4 U; *P*=0.002).

Postoperative systemic inflammatory changes

The preoperative values of the white blood cell count and C-reactive protein, IL-6, IL-10, and adiponectin levels were not significantly different between the control and AP groups. Only the IL-6 level on POD1 (98.3±89.1 *vs.* 26.3±33.8

pg/mL; *P*=0.036) and the adiponectin ratio (0.6±0.3 *vs*. 0.8±0.2; *P*=0.021) were significantly different in the two groups (Table 5).

Discussion

In this trial involving patients with IGT, those who received TGC with a fully automated, closed-loop system had significantly better infection control than those who received conventional glycemic control. The GV, serum IL-6 level on POD1, and perioperative adiponectin ratio were significantly different in the two groups after PD. TGC-AP may exert an anti-inflammatory effect on patients by improving the GV as well as the systemic inflammatory response that originates from adipose tissue inflammation after surgery.

The incidence of POICs was relatively higher (73%) than that in previous reports, although recent studies reported a POIC rate of approximately 70% in some cases.[23,24] The important point is that approximately 30% of the patients enrolled in this study were preoperatively diagnosed with borderline diabetes using the OGTT test. In general, patients with borderline diabetes are not included in the “diabetes” group, because it is difficult to detect without a glucose tolerance test. Patients with borderline diabetes have higher perioperative

morbidity rate than those without diabetes and those with known diabetes.[25,26] Consequently, patients with IGT, including those with borderline diabetes, were at risk of POICs, as reported previously.[1,2] These findings suggest that borderline diabetes may contribute to a further increase in the POIC rate and may also be an explanation for the different results on the POIC rate.

The current guidelines for patients undergoing surgery recommend perioperative TGC[27], even though its application demonstrates contradicting results. Unlike our study, some previous studies showed no benefit of TGC in critically ill patients who had undergone cardiac surgery.[28,29] More specifically, TGC was controlled only after surgery and not during the perioperative period, as was done in this study, which may be one of the reasons for its contradicting results. Several results, similar to those of this study, have been reported in a study of performing TGC during the perioperative period of cardiac surgery.[30,31]

Although there is no consensus target range currently, the Society of Thoracic Surgeons Practice Guidelines suggest that a glucose level >180 mg/dL after surgery should be treated with intravenous insulin and maintained at <180 mg/dl.[17] The control group in this study conformed to the target range with reference to this guideline and blood glucose was controlled via blood sampling

every 2 hours.

Cytokines such as IL-6 and IL-10 are thought to play a pivotal role in the pathogenesis of surgical trauma, and macrophages are likely the source of most of cytokine production in several tissues, including adipose tissue.[32] Adipose tissue inflammation, which is known to play an important role in the pathology of chronic inflammation, is also involved in acute inflammation during the perioperative period.[33,34] Considering the fact that intraperitoneal adipose tissue is directly traumatized in most surgical procedures during abdominal surgery, it is likely that macrophages recruited in adipose tissue contribute to acute inflammatory reactions after PD.

The ability of insulin to attenuate the systemic inflammatory response by decreasing the pro-inflammatory cascade while increasing the anti-inflammatory cascade has been well established.[35,36] In addition, insulin has been reported to decrease pro-inflammatory proteins, including IL-6, within macrophages.[37] The present results, which demonstrated that the total insulin requirements were significantly higher in the AP group than in the control group, indicating its anti-inflammatory effect, occurred, at least in part, due to exogenous insulin itself. Considering the fact that adipose tissue is one of the target organs of insulin, their

interrelationship may be important in the perioperative period.

Adiponectin, one of the adipocytokines secreted primarily from adipose tissue, has been identified as having anti-inflammatory properties that inhibit macrophage function.[38] Recently, we reported that the adiponectin ratio is the earliest postoperative measure available that reflects the perioperative inflammatory factor.[19] In this study, the adiponectin ratio was markedly lower in the control group than in the AP group (*P*=0.021), reflecting the compensatory nature of adiponectin to the inflammatory response seen with surgery during the perioperative period and further supporting the association of perioperative adiponectin levels with anti-inflammatory action after PD.

There is a possibility that the GV, rather than the absolute value of blood glucose levels, is responsible for the observed beneficial effect after PD. In this study, postoperative GV in the control group was significantly higher because the mean glucose level increased gradually after surgery. Therefore, our findings suggest that high postoperative GV is associated with the development of an inflammatory response to surgery.

This study must be interpreted in the context of its limitations and additional research is needed in order to provide more definitive answers on the

potential benefit of TGC during surgery. Future research should (1) address the differences between diabetic and non-diabetic patients with respect to TGC and outcomes; (2) evaluate the proper blood glucose range to confer the optimal benefit during the perioperative period; (3) include larger, randomized, multicentered collaborative studies; and (4) examine the trends of inflammatory mediators after surgery in more detail and for a longer period.

Conclusions

We found that TGC-AP by intravenous insulin treatment had beneficial effects on POICs in patients with IGT who underwent PD. Adiponectin may be involved in an anti-inflammatory response to abdominal surgery and in conjunction with exogenous insulin using AP, thereby preventing postoperative infectious complications.

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Table 1

Baseline and operative characteristics of 29 patients who underwent pancreatoduodenectomy

Baseline characteristic	Control	Artificial pancreas	*P*-value
Age (years)	69 (66-76)	72 (58-76)	0.930
Sex: male/female	10/5	11/3	0.681
Diagnosis: Pancreatic cancer/others	8/7	7/7	0.710
Body mass index	21.3 (19.9-23.7)	23.0 (21.3-24.0)	0.198
Glucose tolerance: borderline/diabetes	4/11	4/10	0.763
C-peptide response (ng/mL)	1.27 (0.91)	1.28 (0.64)	0.980
HOMA-IR	1.25 (0.48-1.78)	1.09 (0.98-1.34)	0.898
Blood chemistry			
Hemoglobin (g/dl)	12.2 (1.4)	12.9 (1.8)	0.287
Total protein (g/dl)	6.3 (0.6)	6.7 (0.7)	0.171
Albumin (g/dl)	3.5 (0.4)	3.8 (0.5)	0.138
Amylase (units/L)	97 (80)	89 (62)	0.763
Cholesterol (mg/dL)	184 (34)	189 (49)	0.814
Triglycerides (mg/dL)	108 (43)	95 (33)	0.447
Fasting blood glucose (mg/dL)	110 (21)	102 (16)	0.375
Hemoglobin A1C (%)	6.7 (0.7)	6.9 (1.0)	0.690
Operative characteristic			

Duration of surgery (minutes)	481 (104)	478 (125)	0.570
Estimated blood loss (g)	752 (566-1,088)	739 (602-1,108)	0.880
Blood transfusion: +/-	4/11	2/12	0.651
Pancreatic texture hard/soft	7/8	8/6	0.715
MPD (mm)	2.5 (2.0-3.8)	3.8 (2.3-5.0)	0.230

HOMA-IR, homeostasis model of assessment of insulin resistance; MPD, main pancreatic duct; SD, standard deviation.

Data are presented as mean (SD) for continuous variables without skewed distribution and median (interquartile range) for continuous variables with skewed distribution.

Table 2

Perioperative glucose values of 29 patients who underwent pancreatoduodenectomy

	Control	Artificial pancreas	*P*-value
Intraoperative period			
Mean blood glucose (mg/dL)	113 (105-116)	99 (97-100)	0.001
GV: SD/mean blood glucose (%)	13.9 (7.0)	11.1 (1.7)	0.429
Postoperative period			
Mean blood glucose (mg/dL)	136 (127-149)	112 (108-114)	<0.001
GV: SD/mean blood glucose (%)	19.7 (2.4)	15.0 (3.6)	0.004
Perioperative period			
Mean blood glucose (mg/dL)	126 (114-145)	108 (99-113)	< 0.001
GV: SD/mean blood glucose (%)	16.4 (5.9)	13.5 (3.5)	0.038

GV, glycemic variability; SD, standard deviation.

Data are presented as mean (SD) for continuous variables without skewed distribution and median (interquartile range) for continuous variables with skewed distribution.

Table 3

Postoperative outcomes

Outcome	Control	Artificial pancreas	*P*-value
Infectious complications Total, n (%)	11 (73.3)	4 (28.6)	0.027
Surgical site infections (n)	10	4	0.066
Superficial/deep incisional	1	1	
Organ/space	9	3	
Postoperative pancreatic fistula (n)	6	3	0.497
Grade B	6	3	
Grade C	0	0	
Remote infection (n)	9	3	0.060
Bacteremia	3	2	
Pneumonia	3	1	
Cholangitis	1	0	
Enteritis	2	0	
Urinary tract infection	0	0	
Total insulin requirement (U)	0 (0-12.6)	25.7 (15.6-34.9)	0.002
mean (standard deviation)	10.2 (16.2)	27.0 (13.4)	
Postoperative stay (days)	32 (28-45)	17 (13-33)	0.065

Data are presented as mean (standard deviation) for continuous variables without skewed distribution and median (interquartile range) for continuous

variables with skewed distribution.

Table 4

Details of positive cultures

Parameter	Control	Artificial Pancreas
Positive cultures	18	4
Monomicrobial	3	1
Polymicrobial	8	3
Isolated microorganisms		
Enterococcus species	5	0
Staphylococcus species	4	1
Enterobacter species	4	1
Streptococcus species	3	1
Candida species	3	1
Neisseria species	3	0
Pseudomonas species	0	2
Klebsiella species	1	1
Corynebacterium species	2	0
Aeromonas species	2	0
Morganella species	2	0
Propionibacterium species	1	0
Citrobacter species	0	1
Serratia species	1	0
Stomatococcus species	1	0
Stenotrophomonas species	1	0
Clostridium species	1	0
Total	34	8

Table 5

Perioperative changes in WBC count and CRP, IL-6, IL-10, and adiponectin levels

Parameter		Control	Artificial pancreas	*P*-value
WBC				
	Pre	5,460 (1,544)	5,700 (1,268)	0.640
	POD1	9,100 (3,025)	9,679 (3,181)	0.390
CRP, mg/mL				
	Pre	1.0 (1.9)	0.6 (1.2)	0.504
	POD1	9.2 (2.9)	8.9 (2.9)	0.832
IL-6, pg/mL				
	Pre	B.D.V.	B.D.V.	
	POD1	98.3 (89.1)	26.3 (33.8)	0.036
IL-10, pg/mL				
	Pre	2.6 (5.2)	5.7 (10.7)	0.477
	POD1	4.3 (3.9)	8.8 (11.5)	0.296
Adiponectin, mg/dL				
	Pre	7.7 (3.7)	4.0 (2.1)	0.050
	POD1	3.8 (2.1)	2.9 (1.1)	0.341
	Ratio	0.6 (0.3)	0.8 (0.2)	0.021

WBC, white blood cell; B.D.V., below detection value. CRP, C-reactive protein; IL, interleukin; POD, postoperative day; B.D.V., below detection value.

Data are presented as mean (standard deviation) for continuous variables without skewed distribution.

Figure legends

Figure 1. Study flow chart

Figure 2. Intraoperative and postoperative mean blood glucose levels in the control and artificial pancreas groups during the first 24 hours following PD

# $p<0.01$, * $p<0.05$ compared with Artificial Pancreas

Figure 1

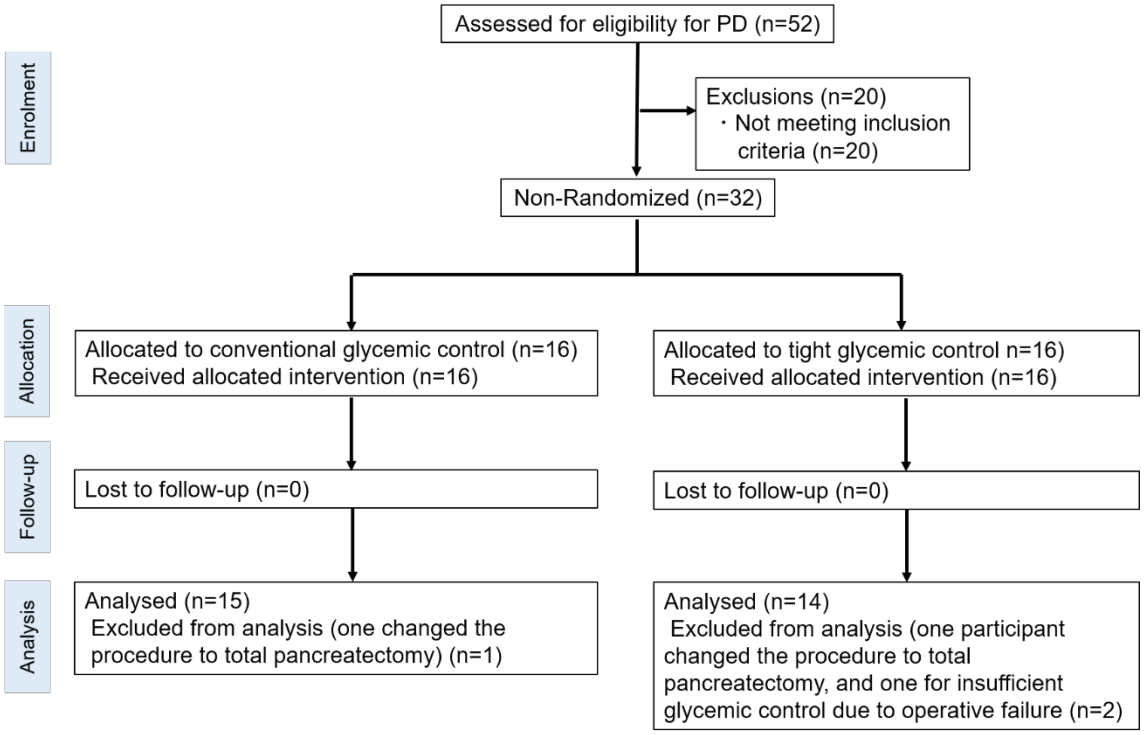
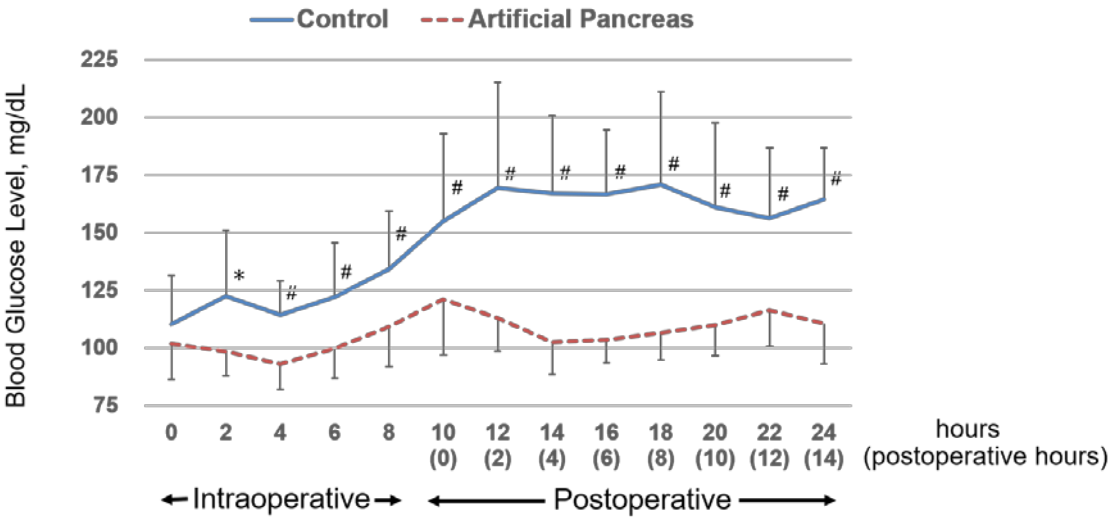

Assessed for eligibility for PD (n=52)
Enrolment
Exclusions (n=20)
・Not meeting inclusion criteria (n=20)
Non-Randomized (n=32)
Allocation
Allocated to conventional glycemic control (n=16)
Received allocated intervention (n=16)
Allocated to tight glycemic control n=16)
Received allocated intervention (n=16)
Follow-up
Lost to follow-up (n=0)
Lost to follow-up (n=0)
Analysis
Analysed (n=15)
Excluded from analysis (one changed the procedure to total pancreatectomy) (n=1)
Analysed (n=14)
Excluded from analysis (one participant changed the procedure to total pancreatectomy, and one for insufficient glycemic control due to operative failure (n=2)

Figure 2



Control													
Mean	110	123	114	122	134	155	169	167	167	171	161	156	165
SD	21	28	15	24	25	38	46	34	28	41	36	31	22
Artificial Pancreas													
Mean	102	98	93	100	109	121	113	103	103	107	110	116	111
SD	16	10	11	13	17	24	15	14	10	12	13	16	17