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Development of perioperative glycemic control using an artificial endocrine pancreas

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Abstract— **It is well known that tight glycemic control (TGC) in patients with diabetes mellitus is the most important to reduce complications, such as nephropathy, neuropathy, and retinopathy. Also, surgical stress induced hyperglycemia leading to glucose toxicity is the main cause of infectious complications after surgery. Recently perioperative TGC has been proven an effective method to reduce postoperative infectious complications and accelerate enhanced recovery after surgery (ERAS), with the main purpose of short staying hospital. However, conventional TGC with open-loop glycemic control system is likely to induce not only occurrence of hypoglycemia but also unstable glycemic control. To solve these problems, we have involved introduction of novel glycemic control using an artificial pancreas (AP) with closed-loop glycemic control system since 2006. To date, this novel perioperative glycemic control was performed in more than 400 surgical patients. As a result, we established stable and safe TGC using an AP to improve surgical outcomes without hypoglycemia. In this paper, we report current scientific evidence focusing on perioperative glycemic control using an AP.**

I. Introduction

It is well known that tight glycemic control (TGC) in patients with diabetes mellitus is the most important technique to reduce complications, such as nephropathy, neuropathy, and retinopathy (1). Also, surgical stress induced hyperglycemia leading to glucose toxicity is the main cause of infectious complications after surgery (2). Figure 1 shows the vicious cycle of relationship between surgical invasion and surgical stress induced hyperglycemia. Oxidant stress and inflammatory cytokines are produced by surgical invasion during surgery. These productions lead to disturbances of insulin secretion, insulin resistance, and gluconeogenesis. Surgical stress induced hyperglycemia is caused by these abnormalities. Perioperative nutritional support has a tendency to increase the blood glucose levels resulting in more hyperglycemia. Moreover, dysfunctions of neutrophil and mitochondria leading to various infections and organ failures are induced by this hyperglycemia. Finally, this vicious cycle is accelerated more and more resulting in worse surgical outcomes. Namely, surgical stress induced hyperglycemia is glucose toxicity because this hyperglycemia is induced by not only deterioration of insulin secretion but also abnormality of insulin resistance.

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Recent many reports (3-5) suggest that perioperative TGC is the effective method to reduce postoperative infectious complications. However, conventional TGC with open-loop glycemic control system is likely to induce not only occurrence of hypoglycemia but also unstable glycemic control. To solve these problems, we have involved introduction of novel glycemic control using an artificial pancreas (AP) with closed-loop glycemic control system since 2006 (6-10). To date, this novel perioperative glycemic control was performed in more than 400 surgical patients. As a result, we elucidated effective and safe TGC to improve surgical outcomes without hypoglycemia. In this paper, we introduce development of perioperative glycemic control using an AP.

II. Artificial Endocrine Pancreas

We have used bed-side type AP produced by Nikkiso Company (Tokyo in Japan). As described previously (6-10), the Nikkiso Company (Tokyo in Japan) developed a bed-side type AP with closed-loop glycemic control system as STG-22 in a conventional device (9) and STG-55 in current device (10) (Figure 2).

Detailed mechanisms and characteristics of STG-22 and/or STG-55 were reported previously (9, 10). Briefly, peripheral venous blood for glucose monitoring was sampled continuously at less than 2 mL/h. STG-22 (9) and STG-55 (10) (Figure 2) are capable of measuring continuously the blood glucose with its glucose sensor, and automatically infuses insulin and/or glucose to adjust the blood glucose level in accordance with a target blood glucose value, which is the so called closed-loop system (9, 10). The artificial pancreas can perform continuous blood glucose monitoring with a closed-loop system for 2 or 3 days (6-8) and insulin resistance can be accurately estimated using the glucose clamp technique (10). Also this system can provide a personalized reference for patients transferred to an insulin control system.

III. Experimental Studies

The physiology of pancreatogenic diabetes is related pancreatic hormone deficiency and the altered response of the liver and peripheral organs to lower than normal hormone levels (11). Total pancreatectomy (TP) causes 100% of pancreatogenic diabetes (11). In 2005, we reported that perioperative glycemic control using a closed-loop AP for total pancreatectomized dogs could perform stable blood glucose control near the normoglycemia (12). In addition, we found that complement of pancreatic polypeptide (PP) reduced insulin requirements to achieve strict perioperative glycemic control accordance to target blood glucose levels.

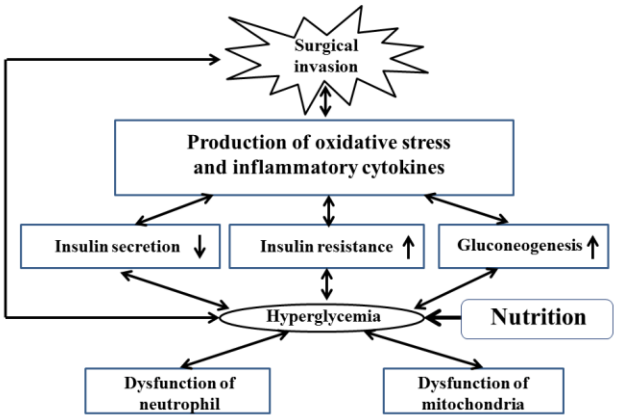

Figure 1. Relationship between surgical invasion and surgical stress induced hyperglycemia.

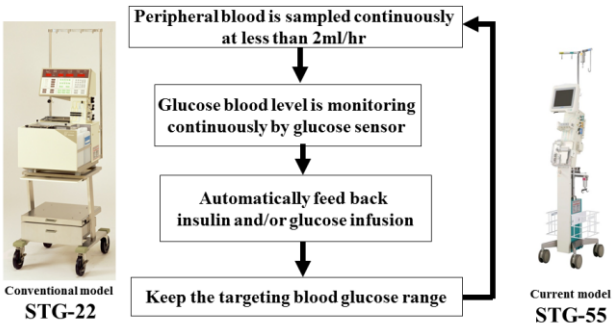

Figure 2. A bedside-type artificial endocrine pancreas with closed-loop system, conventional type (STG-22) and current type (STG-55).

The total insulin requirement of the group with PP was significantly lower than that of the group without PP. PP administration might alleviate the difficulties associated with controlling glucose levels. PP administration reportedly upregulates hepatic sensitivity to insulin and therefore might improve the clinical outcome of glycemic control (12). PP replacement may have potential as new approach to treating patients with pancreatogenic diabetes after TP. Based on these basic findings, in the near future, it may be noteworthy to examine the effects of PP administration in patients undergoing TP. In addition to endocrine insufficiency after pancreatic resection, other factors such as surgical stress, inflammatory proteins, sympathomimetic drug therapy, and aggressive nutritional support can also make glycemic control difficult (11).

Intraoperative continuous glucose monitoring revealed that liver ischemia/reperfusion causes a rapid and profound transition in glucose concentration. We hypothesized that the washout of the glucose stored in the liver leads to a rapid transition in blood glucose concentration (13). Six beagles were studied. A portosystemic shunt was established, and the glucose levels in the jugular, hepatic, and portal veins were continuously monitored. As a result, we found that glucose release from the hepatic vein and sinusoid leads to a rapid elevation in systemic blood glucose levels after liver ischemia/reperfusion. This finding might help in the development of new strategies for blood glucose management during hepataectomy.

IV. Clinical Studies

Based on previous experimental study in 2005 (12), since 2006, we have introduced clinically perioperative glycemic control using an AP (6-10).

Hyperglycemia induced by surgical stress often results in dysregulation of liver metabolism and immune function, which can impair postoperative recovery. TGC in surgical intensive care unit (ICU) patients improves morbidity and mortality by maintaining normal blood glucose levels of 80 – 110 mg/dL (3). While measures such as intensive insulin therapy (IIT) in the target blood glucose range of 80–110 mg/dL are being adopted worldwide, it results in a higher prevalence of hypoglycemia in comparison to standard blood glucose control. To address the issue of hypoglycemia in IIT, we used an artificial endocrine pancreas and employed IIT without inducing hypoglycemia (6-10).

Between 2006 and 2012, perioperative glycemic control using an AP was performed in 427 patients undergoing general surgery undergoing hepatic resection, pancreatic resection, esophageal resection, and so on. Of note, IIT using an AP had no hypoglycemia and high achievement rate of approximately 90% (data not shown) targeting blood glucose range of 80-110 mg/dL. Consequently, strict perioperative glycemic control using a closed-loop artificial endocrine pancreas system is recommended for safe and effective performance of IIT.

Our previous prospective randomized studies (6, 7) reported that IIT using an AP was significantly reduced the incidence of surgical site infection (SSI) compared to conventional glycemic control (sliding-scale method) in hepatectomized (7) and pancreatectomized (6) patients. Moreover, in hepatectomized patients (7), this novel glycemic control could contribute to enhanced recovery after surgery (ERAS) because postoperative short staying hospital and cost benefit in hospital stay in IIT using an AP group was significantly superior to those in sliding-scale group.

Blood glucose management is one of the most important therapies in the ICU. However, blood glucose management using the sliding-scale method increases the workload of ICU nurses. Our previous study (14) suggested that glycemic control using an AP in the ICU reduced the workload of ICU nurses compared to using the sliding-scale method. It also contributed to the reduction of the ICU nurses' anxiety related to the management of blood glucose.

V. Discussion

We found that perioperative TGC using an AP with closed-loop system could perform safer and more stable glycemic control compared with conventional TGC with open-loop system. Of note, IIT using an AP had no hypoglycemia even in dogs (12) and patients (6, 15) undergoing TP associated with inevitable brittle diabetes. Also this novel glycemic control reduced not only labor burden but also number of incident reports in the ICU staff.

Glucose toxicity is caused by surgical stress induced hyperglycemia such as more than 200 mg/dL. Glucose toxicity leads to the leukocyte deficiencies, granulocyte adherence, impaired phagocytosis, delayed chemotaxis, and depressed bactericidal capacity. These abnormalities are the principal causes of postoperative infection (POI) and they can be improved by appropriate glycemic control (2). However, optimal blood glucose range to prevent postoperative infectious complications remains unclear in various surgical settings (9, 10). The ideal blood glucose levels for surgical patients remain controversial with respect to the targets of IIT, moderate IIT, or conventional insulin therapy (2, 9, 10, 15). Our aim is to find the optimal blood glucose range to improve morbidity and mortality in various surgical settings for patients with or without diabetes mellitus. The acquisition of relevant data, including in recent reports (3-8), is required to determine the ideal blood glucose levels to improve surgical outcomes. This is especially important in critically ill surgical patients. We propose that the use of the artificial endocrine pancreas with a closed-loop system is a safe and useful device to investigate ideal blood glucose levels in various surgical conditions.

A. Indication of Perioperative Glycemic Control Using an Artificial Pancreas

In general, all operations are not warranted to perform perioperative glycemic control using an AP because stable glycemic control is able to do without this device, especially in non-diabetic patients undergoing minimum invasive surgery. Judging from our previous reports (6-15), we suggest that the indication of perioperative glycemic control using an artificial pancreas is shown in Table 1. Total pancreatectomy and insulinoma are best indication of this method because conventional method is impossible to perform stable glycemic control near the normoglycemia. Next indication is hepatectomy and proximal or distal pancreatectomy because it was not able to obtain TGC by conventional method at least within 16 hours immediately after surgery (6, 7, 9). As other indications, we suggest liver and pancreas transplantation, cardiac surgery and esophageal resection. Furthermore, it is indispensable that type II diabetic patients, elder patients with glucose intolerance, and/or severe infection such as pan-peritonitis undergoing surgery are good indication.

TABLE I. Indication of Perioperative Glycemic Control Using an Artificial Pancreas

1	Liver surgery: hepatectomy・transplantation
2	Pancreas surgery: pancreatectomy・transplantation・insulinoma
3	Esophageal resection
4	Cardiac surgery
5	Surgery in type II diabetic patients
6	Surgery in elder patients with glucose intolerance
7	Surgery with severe infection such as panperitonitis

B. Characteristics of Glycemic Control Using an Artificial Pancreas

Table 2 showed characteristics of glycemic control using an artificial pancreas. The most important characteristics are to be able to do real time continuous blood glucose monitoring. In our previous studies (6-15), it can also achieve the stable glycemic control without hypoglycemia according to targeting blood glucose range. Moreover, this method is able to avoid not only hypoglycemia but also hyperglycemia leading to morbidity and mortality (2, 6, 7). Of note, it can reduce workload, anxiety, and occurrence of incidence with frequent blood glucose measurement by medical staff, especially in ICU nurse (14).

C. Future Directions

Reducing the SSI rate can lead to short length of hospitalization and cost benefits resulting in ERAS (10). Therefore, it may be one of the most important programs for ERAS to reduce SSI. Undoubtedly, in various surgical settings, detection of the optimal blood glucose range in surgical patients is important to reduce SSI. This is especially true for diabetic patients, because perioperative hyperglycemia increases the risk of SSI (9, 10). In addition, diabetic patients after surgery have more morbidity and mortality compared with non-diabetic patients. However, to improve surgical outcome, optimal perioperative blood glucose range in diabetic patients undergoing surgery remains unclear and the ultimate perioperative glycemic control for diabetic patients has not been established. Therefore, it is essential to find the optimal glycemic control for surgical patients with diabetes.

TABLE II. Characteristics of Glycemic Control Using an Artificial Pancreas

1	Real time continuous blood glucose monitoring
2	No hypoglycemia
3	High stability of glycemic control
4	Avoidance of glucose toxicity
5	Reduction of workload with frequent blood glucose measurement by medical staff
6	Reduction of incidence associated with frequent blood glucose measurement

We would like to expand use of glycemic control using an AP in the near future. Unfortunately, however, this glycemic control has not yet been acquisition of health insurance for treatment fees in Japan. We are undergoing to make an effort to get health insurance for treatment fees paid to medical institutions under the medical insurance system as soon as possible.

VI. Conclusion

This is now the era of novel perioperative blood glucose control to reduce postoperative infection leading to ERAS. Between 2000 and 2012, we studied perioperative glycemic control using an AP as translational researches. As a result, we established the TGC using an AP not only without hypoglycemia but also with stable glycemic control. In addition, this novel glycemic control contributed to good surgical outcomes including reduction of SSI or promotion of ERAS.

We propose that the TGC using an artificial endocrine pancreas with a closed-loop system may play an important role in the effective infection control after surgery. This novel perioperative glycemic control will enable us to improve surgical outcome by reduction of postoperative infectious complications due to surgical stress induced hyperglycemia.

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