Perioperative intensive insulin therapy using an artificial endocrine pancreas with closed-loop glycemic control system: the effects of no hypoglycemia

Kazuhiro Hanazaki, M.D., Ph.D. a, *, Hiroyuki Kitagawa, M.D., Ph.D. a, Tomoaki Yatabe, M.D., Ph.D. b, Masaya Munekage, M.D., Ph.D. a, Ken Dabanaka, M.D., Ph.D. a, Yuka Takezaki a, Yuuki Tsukamoto, Ph.D. a, c, Takuji Asano, Ph.D. c, Yoshihiko Kinoshita c, Tsutomu Namikawa, M.D., Ph.D. a

aDepartment of Surgery, b Department of Anesthesiology, Kochi Medical School, Kochi University, Kohasu, Okocho, Nankoku-City, Kochi 783-8505, Japan; c Nikkiso Co. Ltd., Tokyo, Japan

KEYWORDS:
Perioperative intensive insulin therapy; Artificial pancreas; Hypoglycemia; Closed-loop glycemic control system; Stable glycemic control

Abstract

BACKGROUND: We examined whether perioperative intensive insulin therapy (IIT) using an artificial pancreas (AP) with a closed-loop glycemic control system can be used to prevent hypoglycemia in surgical patients.

METHODS: Between 2006 and 2012, perioperative glycemic control using an AP was performed in 427 patients undergoing general surgery. A total of 305 patients undergoing IIT using an AP in the target blood glucose range of 80 to 110 mg/dL were enrolled in the study. Data were collected prospectively and were reviewed or analyzed retrospectively.

RESULTS: No patients had hypoglycemia. Perioperative mean blood glucose level and achievement rates in target blood glucose range of 80 to 110 mg/dL were 100.5 ± 11.9 mg/dL and 88.1% ± 16.0%, respectively. For the 3 primary operative methods, including hepatic, pancreatic, and esophageal resections, there were no significant differences in glycemic control stability between the types of surgery.

CONCLUSION: Perioperative IIT using an AP with a closed-loop glycemic control system can be used to prevent hypoglycemia and maintain stable glycemic control with less variability of blood glucose concentration.

Hyperglycemia is a marker of severe, acute illness; it may worsen outcomes by contributing to inflammation, oxidative stress, poor immune function, and endothelial dysfunction. 1-4 Hyperglycemia is common in surgical patients with and without diabetes and is associated with poor surgical outcomes. 5-9 Therefore, appropriate glycemic control against perioperative hyperglycemia improves surgical outcomes and reduces morbidity and mortality.

In 2001, Van den Berghe et al. 10 proposed that intensive insulin therapy (IIT) with a target blood glucose range of...
80 to 110 mg/dL in surgical intensive care unit (ICU) patients contributed to lower morbidity and mortality compared with conventional glycemic control with a target blood glucose range of 180 to 200 mg/dL. After this landmark article regarding tight glycemic control (TGC) for surgical ICU patients was published, various large trials were performed in critically or noncritically ill hospitalized patients. However, these studies did not identify consistent benefits of IIT, and significant hypoglycemia of <40 mg/dL was reported in 5.0% to 18.7% of the patient population. Hypoglycemia was also found to be more common in patients on the surgical floors.

Although IIT appears to reduce mortality and morbidity in surgical ICU patients, the clinical effects of IIT in surgical patients are controversial. Recently, one systemic review identified no effects; another systemic review and meta-analysis identified the potential effects of reducing the infection risk. Conventional IIT with an open-loop system, proposed by Van den Berghe in 2001, inevitably resulted in hypoglycemia, a very serious problem in critically ill patients. In 2008, Van den Berghe proposed the need for accurate, continuous blood glucose monitoring devices in the ICU to avoid hypoglycemia caused by IIT, and suggested the use of closed-loop systems for computer-assisted blood glucose control. Thus, we examined whether perioperative IIT using an artificial pancreas (AP) with a closed-loop glycemic control system can be used to prevent hypoglycemia in surgical patients. Clinically, previous studies suggested that effective glycemic control in type 1 and type 2 diabetic patients was performed by AP. However, these studies were primitive because they were not consisted by large number of patients and also were not referred to practical significance in critically ill patients including surgical patients.

**Patients and Methods**

**Study population**

Between August 2006 and July 2012, perioperative glycemic control using an AP (STG-22, STG-55, Nikkiso Co., Ltd, Tokyo, Japan) was performed in 427 patients undergoing general surgery, such as hepatic, pancreatic, or esophageal resection. Among these patients, 36 were excluded because of insufficient data resulting from blood sampling defects and 86 cases were excluded because of other glycemic control different from IIT targeting a blood glucose range of 80 to 110 mg/dL. The remaining 305 cases undergoing perioperative IIT were reviewed and analyzed.

**Study design**

Perioperative glycemic control using an AP is typically performed 1 to 2 days before starting general anesthesia and continued until the end of administration in the ICU after surgery. The detailed mechanisms and characteristics of the AP have been reported previously.

Briefly, the AP is a device which is composed of the measurement unit, the control unit, and the infusion unit. These components are connected in such a way as to form a closed-loop system for the target blood glucose levels. Venous blood is sampled to the measurement unit for computer-assisted blood glucose control. Thus, we examined whether perioperative IIT using an artificial pancreas (AP) with a closed-loop glycemic control system can be used to prevent hypoglycemia in surgical patients. Clinically, previous studies suggested that effective glycemic control in type 1 and type 2 diabetic patients was performed by AP. However, these studies were primitive because they were not consisted by large number of patients and also were not referred to practical significance in critically ill patients including surgical patients.
reliability of a continuous blood glucose monitoring during use of an AP have been established by our previous studies, both intraoperatively and postoperatively.

In perioperative nutritional support care, calorie intake in all patients was calculated using the Harris–Benedict formula; unified standard calorie intake and standard care in our hospital were provided to all patients. On their operation days, patients were fed continuously with intravenous total parental nutrition. Combined intravenous total parental nutrition and enteral feeding were provided on the next day. After staying in the ICU for 1 to 2 days, patients were moved to the hospital ward, and total enteral feeding was attempted as early as possible.

Data collection

Patients were informed of the purpose and details of the study, and written informed consent was obtained from them before enrolment. The study was approved by the local ethics committee at the Kochi Medical School and carried out in accordance with the Helsinki Declaration. All patients of this study were enrolled prospectively at the Kochi Medical School between August 2006 and July 2012.

Data were collected prospectively. Collective data were reviewed and/or analyzed retrospectively. The primary end point was hypoglycemia <40 mg/dL. Secondary end points included achieving target blood glucose of 80 to 110 mg/dL and stabilizing glycemic control with low variability in the blood glucose concentration.

Statistical analysis

Blood glucose data and infusion rates of insulin/glucose used in this study were stored electronically. Rate of achieving the target blood glucose range of IIT was calculated using the following formula: (total time of glycemic control) − (time out of range of 80–110 mg/dL)/(total time of glycemic control) × 100 (%).

Data are presented as the mean ± standard deviation. Statistical analyses were performed using a statistical software package (JMP 8; SAS Institute Japan, Tokyo, Japan). Changes in the glucose level at all time points were analyzed using repeated measures analysis of variance (ANOVA) with post hoc testing. Furthermore, serum insulin values were subjected to analysis of variance with post hoc testing. P values of <.05 were considered statistically significant.

Results

Study population

Table 1 shows the characteristics of the 305 patients undergoing surgery. Of the 305 patients, 155 patients (51%) had liver diseases and underwent hepatic resection, 67 (22%) had pancreas disease and underwent pancreatic resection, and 26 (9%) had esophagus disease and underwent esophageal resection. Nearly all patients had malignant neoplasms, except those who underwent emergency operations because of peritonitis.

Blood glucose control

Primary outcome. Of the 305 patients, 242 (79%) were administered conventional AP (STG-22), and the remaining 63 (21%) were administered novel AP (STG-55) (Table 1). All patients underwent continuous blood glucose monitoring without difficulty. No patient experienced hypoglycemia of <40 mg/dL, as well as 70 mg/dL, as defined by the American Diabetes Association.

Secondary outcome. Fig. 2 shows the perioperative (intraoperative + postoperative) continuous blood glucose levels in all patients. Stable glycemic control was carried out during IIT within the target blood glucose range of 80 to 110 mg/dL. Intraoperative, postoperative, and perioperative mean blood glucose levels in all patients were 98.2 ± 12.7 mg/dL, 102.2 ± 16.2 mg/dL, and 100.5 ± 11.9 mg/dL, respectively. Intraoperative, postoperative, and perioperative achievement rates of the target blood glucose range of 80 to 110 mg/dL in all patients were 91.6% ± 11.6%, 86.3% ± 18.9%, and 88.1% ± 16.0%, respectively. Intraoperative and postoperative requirements of mean insulin dosage to maintain the target blood glucose range of IIT were 12.1 ± 11.9 U and 63.4 ± 65.6 U, respectively.

Perioperative blood glucose levels were measured in the 155 patients undergoing hepatic resection, 67 patients undergoing pancreatic resection, and 26 patients undergoing esophageal resection. For the 3 primary operative methods of hepatic, pancreatic, and esophageal resections, perioperative glycemic control was safe and stable, with low variability in blood glucose concentration. Additionally, no significant differences in the stability of glycemic control using the various surgical methods were observed. In the 155 patients undergoing hepatic resection, intraoperative, postoperative, and perioperative mean blood glucose levels were 100.3 ± 13.0, 103.4 ± 12.8, and
102.5 ± 11.6 mg/dL, respectively. Intraoperative, postoperative, and perioperative rates of achieving the target blood glucose range of 80 to 110 mg/dL in these patients were 90.3% ± 11.6%, 85.8% ± 20.0%, and 86.8% ± 17.2%, respectively. In the 67 patients undergoing pancreatic resection, intraoperative, postoperative, and perioperative mean blood glucose levels were 93.0 ± 8.5, 101.2 ± 24.7, and 97.4 ± 9.6 mg/dL, respectively. Intraoperative, postoperative, and perioperative rates of achieving the target blood glucose range of 80 to 110 mg/dL in these patients were 94.1% ± 10.9%, 88.0% ± 14.8%, and 90.8% ± 11.8%, respectively. In the 26 patients undergoing esophageal resection, intraoperative, postoperative, and perioperative mean blood glucose levels were 105.0 ± 9.2, 108.9 ± 11.7, and 107.4 ± 9.9 mg/dL, respectively.

No patients experienced hypoglycemia, and all showed stable glycemic control compatible with high achievement rates of IIT near normoglycemia and no relationship with operative methods.

**Comments**

Although postoperative hyperglycemia is associated with complications after various types of surgery, the optimal perioperative blood glucose levels for improving outcomes in surgical patients is unknown. However, it is known that hypoglycemia is an undesirable complication of IIT and should be avoided. In this study, which included major surgeries such as hepatic (51%), pancreatic (22%), and esophageal (9%) resections, we found that perioperative IIT using an AP with closed-loop system could be used to prevent hypoglycemia of <40 mg/dL, which is an inevitable complication in the conventional IIT procedure proposed by Van den Berghe in 2001. Additionally, no patients had hypoglycemia of <70 mg/dL, the value specified by the American Diabetes Association for hypoglycemia.

The risk of increased glucose variability has been associated with an increased risk of poor outcomes. Achieving stable glycemic control with low variability in blood glucose concentration is very important in critically ill patients. As described above, goals of glycemic control include reducing both hypoglycemia and hyperglycemia. In this study, perioperative mean blood glucose level was 100.5 ± 11.9 mg/dL, which is near normoglycemia. We also found that perioperative IIT using an AP could maintain stable glycemic control, with a high achievement rate of 88.1% in targeting blood glucose levels of 80 to 110 mg/dL. Particularly, the intraoperative achievement rate of IIT was 91.6%. Fig. 3 shows a comparison of achievement rates in target blood glucose range using IIT described in previous reports and in this study. Our study showed that a high achievement rate of IIT was higher than or comparable to that of previous large studies.

Moreover, stability of IIT compatible with a target blood glucose range of 80 to 110 mg/dL was not dependent on operation type; there were no significant differences among the results for patients undergoing hepatic, pancreatic, and esophageal resections. Perioperative mean blood glucose levels in hepatic, pancreatic, and esophageal resections were 102.0 ± 11.6, 97.4 ± 9.6, and 107.4 ± 9.9 mg/dL, respectively. Additionally, a similar high achievement rate in the target range of IIT between 80 and 110 mg/dL was obtained in all operations; perioperative achievement rates.
in hepatic, pancreatic, and esophageal resections were 86.8% ± 17.2%, 90.8% ± 11.8%, and 86.3% ± 14.5%, respectively. As reported previously, pancreatogenic diabetes after pancreatic resection results in an unstable glycemic status, referred to as "brittle diabetes."33,34 When pancreatogenic diabetes occurs once, conventional glycemic control appears to be insufficient for entirely avoiding hypoglycemia and hyperglycemia because of variations in blood glucose concentration exhibited by patients suffering from brittle diabetes.33,34 Indeed, our previous study showed that the stability of conventional glycemic control using a sliding-scale method against pancreatogenic diabetes after pancreatic resection was useless compared with TGC using an AP.34,35 This study showed a high perioperative achievement rate of 90% in pancreatectomized patients. We also showed that standard glycemic care in patients undergoing hepatic and/or esophageal resections with unstable glycemic control differed significantly from IIT using an AP.25,36 In hepatetomized patients, achieving these rates may be difficult in patients with hepatogenous diabetes associated with injured and cirrhotic liver.36 Thus, since this novel perioperative glycemic control using an AP is less affected by operation type and is associated with a high perioperative achievement rate of >86%, this method may also be effective for other invasive and/or emergent operations, such as liver and pancreas transplantation or cardiac and vascular surgery, to obtain stable glycemic control with low variability in blood glucose concentration.

Although nutritional support for surgical patients is crucial for improving postoperative morbidity and mortality,37,38 it tends to further increase hyperglycemia. In contrast, it appears to be difficult to use TGC such as IIT for maintaining target blood glucose levels under surgical diabetes and/or sufficient nutritional support. Hence, it is difficult to simultaneously achieve accurate TGC and sufficient nutrition. Indeed, nearly all previous studies10,11,14,31,32 using conventional IIT and performing nutritional support showed insufficient calorie intake because of the instability of these techniques, and patients became hyperglycemic. In contrast to these previous studies,10,11,14,31,32 in this study, calorie intake in all patients was calculated using the Harris–Benedict formula26. Therefore, our method of IIT using an AP can balance the needs for achieving TGC and adequate nutritional support.

Hyperglycemia associated with insulin resistance is common in critically ill patients, even in those who have not previously had diabetes.10 Blood glucose management is important in surgical or medical ICU patients.10,11 However, conventional glycemic control methods such as IIT with an open-loop system and the sliding-scale method increase the workload of ICU nurses.21,22 Regarding this problem, our previous study39 suggested that using AP for glucose management in ICU patients increased the degree of attention given by nurses to glucose management and contributed to improved security, resulting in a reduced overall workload of ICU nurses compared to the sliding-scale method. This study showed that IIT using an AP could continuously and automatically monitor blood glucose levels without the fear of hypoglycemia. This novel TGC will be helpful for many ICU nurses to reduce workload regarding glucose management.

The benefits and disadvantages of IIT titrated to strict glycemic targets in hospitalized patients remain uncertain.16 In a meta-analysis of 21 trials in the ICU, perioperative care, myocardial infarction, and stroke or brain injury settings, IIT did not affect mortality and was associated with an increased risk of severe hypoglycemia. In contrast, limited to surgical settings, TGC such as IIT may reduce the risk of infection,
improving perioperative hyperglycemia. Since it is well-known that perioperative hyperglycemia is the primary risk factor for developing postoperative infection (POI), tight glycemic control (TGC) against hyperglycemia leads to fewer POIs in critically ill surgical patients. Indeed, our previous studies reported that the incidence of surgical site infection (SSI) in intensive insulin therapy (IIT) using an AP in pancreatectomized or hepatectomized patients was significantly decreased compared with conventional glycemic control using a sliding-scale method. Not surprisingly, we also found in this study that perioperative (intraoperative and postoperative) requirements of mean insulin dosage were more than 70 U, similar to our previous studies.

Our results also suggest that IIT using an AP will enable us to prevent the hypoglycemia and stress-induced hyperglycemia associated with surgery. IIT using an AP is a potentially effective glycemic control not only for reducing POI resulting in fast track surgery but also for achieving safe and stable glycemic control without hypoglycemia and hyperglycemia. The true benefits and disadvantages of IIT in various medical or surgical settings should be evaluated under conditions of no risk of hypoglycemia. Further examinations using an AP will be helpful for resolving this issue.

Higher postoperative glucose levels have been shown to be associated with complications after various types of cardiac, general, vascular, and orthopedic surgeries. High glucose variability may enhance this risk. In this study, AP enabled prevention of hyperglycemia and complete stable glycemic control with lower variability in blood glucose levels. Perioperative hyperglycemia increases the risk of POI. Therefore, perioperative glycemic control in surgical patients is beneficial for reducing POI. The closed-loop AP system could be used to perform IIT without increasing the risk of hypoglycemia in this study; thus, this system may be a safe and useful blood glucose control system for critically ill surgical patients. However, optimal blood glucose levels for various types of operations for improving surgical outcomes remain unknown.

The next step is to determine an optimal perioperative glucose range to improve surgical outcomes after surgery. We propose that glycemic control using an AP will play a significant role in detecting an optimal blood glucose range because it simultaneously prevents hypoglycemia and provides appropriate nutritional support associated with stable glycemic control. Regarding the occurrence of SSI, a blood glucose level of >110 mg/dL and/or 140 mg/dL may be a risk factor for increasing the incidence of POI, including SSI. Ideal blood glucose levels for surgical patients remain controversial with respect to the targets of IIT, moderate IIT, or conventional insulin therapy.

Our aim is to determine an optimal blood glucose range for improving morbidity and mortality in various surgical settings for patients with or without diabetes mellitus. This is particularly important for critically ill surgical patients. Although current AP (STG-55) is a smaller apparatus compared with conventional AP (STG-22), it remains to be large size, so-called bed-side type. In the near future, we have to overcome this barrier. Thus, our next step will be exploration of more sophisticated and miniaturized AP with closed-loop system to use more easily and extensively in clinical settings.

The use of AP with a closed-loop system is a safe and useful method for investigating ideal blood glucose levels in various surgical conditions. Ideally, the true significance of IIT initiated by Van den Berghe should be examined without measuring hypoglycemia and with stable glycemic control such as in this study.

In conclusion, perioperative IIT using an AP with closed-loop glycemic control system enabled us to prevent hypoglycemia and maintain stable glycemic control with lower variability of blood glucose concentration and lower susceptibility to operative procedures.

Acknowledgments

We are indebted to Masaki Kobayashi, Motoaki Murakami, Masatoshi Tarumi, and Suguru Mishina for technical assistance regarding AP and support in data collection and analysis from Nikkiso Co., Ltd.

References


18. 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;51:911–5.


