Professor Special Lecture: 152nd Regular Meeting of the Medical Society of Toho University

Review Article

Efficacy and Future Prospects for Intraoperative Glycemic Management Using a New Artificial Pancreas with a Closed-Loop Blood Glucose Monitoring System

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ABSTRACT: Glucose metabolism is modified throughout the perioperative period, resulting in hyperglycemia. Many factors affect glucose metabolism in patients undergoing surgery, and the underlying mechanisms are complicated. Due to the lack of complete elucidation of mechanisms underlying perioperative changes in glucose metabolism, the guidelines for perioperative glycemic management have not been established. Nevertheless, adequate glycemic management is absolutely required, because perioperative hyperglycemia is considered an independent risk factor of mortality and morbidity associated with surgery. In critically ill patients, hypoglycemia as well as hyperglycemia are considered risk factors for death. It was also reported that variability of blood glucose levels is an independent predictor of mortality in critically ill patients. Today, a new artificial pancreas with a closed-loop blood glucose monitoring system is available in clinical settings. Recent clinical studies suggested that safe and stable glycemic management for patients undergoing major surgery can be achieved with perioperative application of the artificial pancreas. We assume that future clinical investigations using the artificial pancreas will contribute to further elucidation of perioperative glucose metabolism and the establishment of guidelines for perioperative glycemic management. This article reviews recent studies focusing on perioperative management of glucose metabolism and discusses the efficacy and future prospects of intraoperative glycemic control using the artificial pancreas.

Toho J Med 4 (4): 107–115, 2018

KEYWORDS: artificial pancreas, glucose metabolism, insulin, stress-induced hyperglycemia, surgical prognosis

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DOI: 10.14994/tohojmed.2018-020

Received Aug. 30, 2018
Toho Journal of Medicine 4 (4), Dec. 1, 2018
ISSN 2189–1990, CODEN: TJMOA2

Table 1 The effects of anesthetic management on blood glucose levels during surgery

Subjects	Surgery	Anesthetic management	Effects on blood glucose levels during surgery	Reference
Human	Abdominal hysterectomy	A) Halothane anesthesia B) Epidural anesthesia	Intraoperative blood glucose levels under halothane anesthesia were significantly higher than those under epidural anesthesia.	4)
Human	Lower abdominal gynecological surgery	A) Halothane anesthesia B) Epidural anesthesia combined with halothane anesthesia	Intraoperative blood glucose levels under halothane anesthesia were significantly higher than those under epidural anesthesia combined with halothane anesthesia.	5)

Features of Intraoperative Glucose Metabolism

Perioperatively, glucose metabolism is modified by many factors with complicated mechanisms.[1,2] The predominant factor altering glucose metabolism is surgical stress. Due to the endocrine/metabolic responses to surgical stress, plasma levels of catabolic hormones are elevated. Glycolysis, proteolysis and lipolysis are accelerated, and glucose production is enhanced.[1–3] Simultaneously, insulin secretion is attenuated, and insulin resistance is induced; therefore, glucose use is impaired.[1–3] Both enhanced glucose production and impaired glucose use contribute to surgical diabetes.

Anesthesia is another factor modifying glucose metabolism. Effects of anesthetic management on intraoperative blood glucose levels are summarized in Table 1. Rem and colleagues reported that intraoperative blood glucose levels increased under general anesthesia, while such increases were not observed under epidural anesthesia.[4] Buckley and colleagues reported that intraoperative blood glucose levels under general anesthesia were significantly higher than those under epidural anesthesia combined with general anesthesia.[5] These results suggest that hyperglycemic responses to surgical stress can be suppressed by epidural anesthesia, but not by general anesthesia.

General anesthetics are divided into two major categories: volatile anesthetics (e.g. isoflurane, sevoflurane, and desflurane) and intravenous anesthetics (e.g. opioids, midazolam, propofol, thiopental, and ketamine). Results of studies investigating the effects of anesthetics on glucose metabolism are summarized in Table 2. Schricker and colleagues reported that intraoperative blood glucose levels under general anesthesia using enflurane, a volatile anesthetic, were significantly higher than those under propofol/sufentanil anesthesia.[6] Kitamura and colleagues reported that intraoperative blood glucose levels under sevoflurane/fentanyl anesthesia were significantly higher than those under propofol/fentanyl anesthesia.[7] Tanaka and colleagues reported that sevoflurane anesthesia as well as isoflurane anesthesia impaired insulin secretion and glucose use in a dose-independent manner in surgical patients.[8] Kitamura and colleagues reported that intraoperative blood glucose levels under sevoflurane anesthesia were significantly higher than those under propofol anesthesia in rats; furthermore, glucose use was impaired by sevoflurane, but not by propofol.[9] These results suggest marked differences in the effects of volatile anesthetics and propofol on blood glucose levels. Impaired glucose use by volatile anesthetics contributes, at least in part, to intraoperative hyperglycemia. Glucose use is defined by insulin secretion and insulin sensitivity. Adenosine triphosphate-sensitive potassium channels (K_{ATP} channels) in β-islet cells regulate insulin secretion; insulin secretion is enhanced by inhibiting the channels and is attenuated by activating the channels.[10] The structure of K_{ATP} channels is cell-specific and consists of a pore-forming subunit (Kir) and a regulatory subunit (sulfonylurea receptor: SUR). The pore-forming subunit and the regulatory subunit of K_{ATP} channels in β-islet cells are Kir6.2 and SUR1, respectively.[11–13] Zuurbier and colleagues reported that isoflurane anesthesia, sevoflurane anesthesia and ketamine/medetomidine anesthesia induced hyperglycemia in rats, while pentobarbital anesthesia and propofol/opioids anesthesia produced no significant effects on blood glucose levels; furthermore, isoflurane impaired glucose-induced insulin secretion by activating K_{ATP} channels in β-islet cells.[14] Sato and colleagues reported that sevoflurane anesthesia impaired glucose-induced insulin secretion by activating K_{ATP} channels in β-islet cells via SUR1 in rats, while propofol anesthesia induced hyperinsulinemia.[15]

Table 2 The effects of general anesthetics on glucose metabolism

Subjects	Surgery	General anesthetics	Effects on glucose metabolism	Reference
Human	Abdominal hysterectomy	A) Enflurane B) Propofol with sufentanil	Intraoperative blood glucose levels under enflurane anesthesia were significantly higher than those under propofol/sufentanil anesthesia.	6)
Human	Head and neck surgery	A) Sevoflurane with fentanyl B) Propofol with fentanyl	Intraoperative blood glucose levels under sevoflurane/fentanyl anesthesia were significantly higher than those under propofol/fentanyl anesthesia.	7)
Human	Minor surgery	A) Sevoflurane B) Isoflurane	Both sevoflurane anesthesia and isoflurane anesthesia induced glucose intolerance.	8)
Rats	Sigmoid colostomy	A) Sevoflurane B) Propofol	Intraoperative blood glucose levels under sevoflurane anesthesia were significantly higher than those under propofol anesthesia.	9)
Rats	Without surgical stress	A) Without anesthesia B) Sevoflurane C) Propofol	Sevoflurane impaired glucose use. Propofol produced no significant effects on glucose use.	9)
Rats	Without surgical stress	A) Isoflurane B) Sevoflurane C) Ketamine with medetomidine D) Pentobarbital E) Propofol and opioids	Hyperglycemia was induced by isoflurane, sevoflurane and ketamine/medetomidine anesthesia. Pentobarbital and propofol/opioids anesthesia produced no significant effects on blood glucose levels. Isoflurane anesthesia impaired glucose-induced insulin secretion by activating K_{ATP} channels in β-islet cells.	14)
Rats	Without surgical stress	A) Sevoflurane B) Propofol	Sevoflurane anesthesia impaired glucose-induced insulin secretion by opening K_{ATP} channels in β-islet cells via SUR 1. Propofol anesthesia induced hyperinsulinemia and insulin resistance.	15)

K_{ATP} channels: adenosine triphosphate-sensitive potassium channels. SUR: sulfonylurea receptor.

Both glibenclamide, a K_{ATP} channel inhibitor, and diazoxide, a K_{ATP} channel opener, have high affinity for SUR1.[16, 17] In rats, glibenclamide significantly enhanced insulin secretion under propofol anesthesia, while diazoxide produced no significant effects.[15] Kawano and colleagues reported that the inhibitory effect of propofol on a K_{ATP} channel, consisting of Kir6.2 and SUR1, was mediated by Kir6.2.[18] Taken together, volatile anesthetics attenuate insulin secretion by activating K_{ATP} channels in β-islet cells via SUR1, and propofol enhances insulin secretion by inhibiting the channels via Kir6.2. Generally, a lipid-based formulation of propofol is administered; thus, propofol anesthesia is accompanied by acute lipid load. Acute lipid load impairs insulin sensitivity.[19–22] Sato and colleagues reported that propofol anesthesia induced insulin resistance in rats.[15] Li and colleagues reported that the main cause of insulin resistance under propofol anesthesia was acute lipid load in rats.[23] Further investigations are required for the complete elucidation of the effects of anesthetics on glucose metabolism.

Energy Demand/Supply Balance in Patients Undergoing Surgery

Perioperatively, energy demand/supply balance should be assured; however, several factors induce energy demand/supply imbalance. As substrates for energy supply, carbohydrates, protein, and fat are utilized.[24] Insufficient energy supply via glycolysis accelerates proteolysis and lipolysis.[24, 25] Thus, adequate management of glucose metabolism is important.

Most patients are made to fast prior to surgery. Energy demand/supply imbalance related to preoperative fasting induces metabolic changes.[3] The enhanced recovery after surgery protocol recommends intake of a carbohydrate-rich drink during the preoperative fasting period, because it reduces thirst and hunger, prevents loss of nitrogen and protein, maintains lean body mass and muscle strength and ameliorates insulin resistance.[3, 26–36]

Endocrine/metabolic responses to surgical stress induce glucose intolerance and accelerate catabolism. Therefore, intraoperative glucose administration has been controversial. Mikura and colleagues reported that

intraoperative glucose administration suppressed surgery-induced muscle protein breakdown in fasted rats.[37] Mori and colleagues reported that preoperative and/or intraoperative glucose administration suppressed lipolysis without affecting insulin secretion as well as insulin sensitivity in fasted rats.[38] Yamasaki and colleagues reported that intraoperative glucose administration suppressed proteolysis and lipolysis in surgical patients.[39] These results suggest advantageous effects of intraoperative glucose administration.

Although postoperative nutritional management has not been established, it is generally accepted that enteral nutrition should be given priority over parenteral nutrition, and that enteral nutrition should be initiated as soon as possible after surgery.[40] The enhanced recovery after surgery protocol recommends early enteral or oral feeding in the postoperative period, because the risk of infection and the length of stay in hospital can be reduced.[26] Casaer and colleagues reported that late initiation of supplemental parenteral nutrition contributed to better prognosis in critically ill patients who were managed with a protocol for early initiation of enteral nutrition.[41]

Significances of Perioperative Management of Glucose Metabolism

Hyperglycemia boosts inflammation and increases the risk of infection. Thus, hyperglycemia should be prevented in surgical patients.

Gandhi and colleagues reported that intraoperative hyperglycemia is an independent risk factor for mortality and morbidity after cardiac surgery; increases in the mean glucose level of 20 mg/dL were associated with 30% or more increases in the incidence of postoperative adverse events.[42] Ammori and colleagues reported that intraoperative hyperglycemia during liver transplantation was associated with a significantly higher incidence of infection within 30 days after surgery and a significantly higher mortality rate at 1 year as well as 2 years after surgery.[43] Malmstedt and colleagues reported that poor perioperative glycemic control in diabetic patients undergoing infrainguinal bypass surgery was associated with wound complications within 30 days after surgery as well as death, major amputation, and graft occlusion within 90 days after surgery.[44] McGirt and colleagues reported that perioperative hyperglycemia in patients undergoing carotid endarterectomy was associated with an increased postoperative risk of mortality as well as morbidity.[45] These results strongly suggest that adequate glycemic control improves prognosis of patients undergoing major surgery.

Unfortunately, the optimal target range of blood glucose levels in the perioperative period remains unclear. Van den Berghe and colleagues reported that intensive insulin therapy reduced mortality and morbidity of patients admitted to the surgical intensive care unit.[46] In that study, glucose levels were maintained at 80-110 mg/dL and 180-200 mg/dL by intensive insulin therapy and conventional treatment, respectively. However, The NICE-SUGAR Study investigators reported that intensive glucose control increased mortality rate and incidence of hypoglycemia in critically ill patients admitted to the intensive care unit.[47] In that study, glucose levels were maintained at 81-108 mg/dL by intensive glucose control and at 180 mg/dL or less by conventional glucose control. The NICE-SUGAR Study investigators also reported that hypoglycemia caused by intensive glucose control increased the risk of mortality in critically ill patients.[48] Gandhi and colleagues reported that intensive insulin therapy during cardiac surgery did not decrease the risk of mortality and morbidity.[49] Based on a meta-analysis of 5 randomized control trials, Hua and colleagues reported that intensive insulin therapy during cardiac surgery did not decrease the risk of mortality, although it decreased the incidence of infection.[50] Rujirojindakul and colleagues reported that intensive insulin therapy during cardiac surgery increased the incidence of hypoglycemia without producing beneficial effects on surgical prognosis.[51]

Egi and colleagues reported that standard deviation and coefficient of variation of blood glucose levels were independent predictors of mortality in critically ill patients, suggesting that variability of blood glucose levels should be reduced.[52]

Due to the lack of the complete elucidation of perioperative glucose metabolism, a guideline for perioperative glycemic management has not been established; nevertheless, there appear to be four important elements: Energy demand/supply balance should be maintained, hyperglycemia should be avoided, hypoglycemia should be avoided and variability of blood glucose levels should be reduced.

A New Artificial Pancreas with a Closed-Loop Blood Glucose Monitoring System

Along with the evolution of technology, the artificial

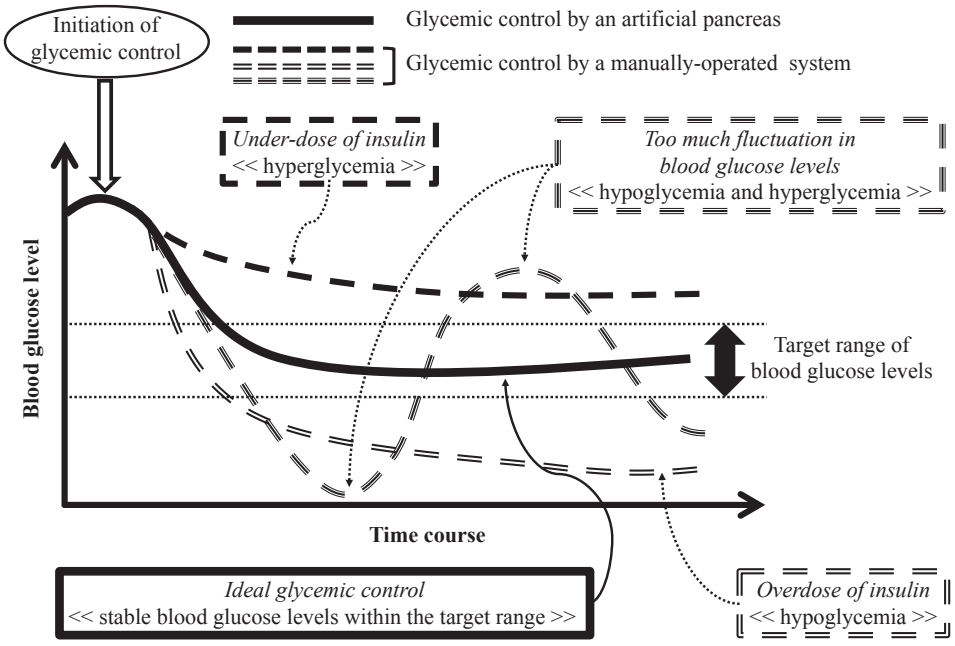

Fig. 1 A typical pattern of time-course changes in blood glucose levels after the initiation of glycemic control using an artificial pancreas with a closed-loop blood glucose monitoring system. A manually-operated glycemic control may induce hyperglycemia by insufficient insulin administration as well as hypoglycemia by overdose of insulin; however, an artificial pancreas with a closed-loop blood glucose monitoring system assures stable blood glucose levels within the target range without inducing hyperglycemia or hypoglycemia.

pancreas has been improved. Today, STG-55 (Nikkiso, Tokyo, Japan), a new artificial pancreas with a closed-loop blood glucose monitoring system, is available in clinical settings. STG-55 has several advantageous features.[53] The new glucose sensor for STG-55 does not require long periods of warm-up before use. The tubing set for blood glucose monitoring is very simple to assemble. Furthermore, STG-55 is compact and slim in size.

Fig. 1 shows the typical pattern of glycemic control using the artificial pancreas. Insulin administration of a manually-operated glycemic control system depends on intermittent measurement of blood glucose levels; therefore, hyperglycemia is induced by insufficient insulin administration and hypoglycemia is induced by overdose of insulin administration. The artificial pancreas eliminates these disadvantages. Hyperglycemia as well as hypoglycemia can be avoided and stable blood glucose levels within the target range are assured.

It is necessary to input four kinds of coefficients to operate STG-55: IA, IB, ID and GD. ID is the target glucose level for insulin administration and GD is the target level of glucose administration. Glucose levels are controlled between ID and GD. IA is the coefficient of the difference between the blood glucose level at each time-point (BG (t)) and ID. IB is the coefficient of the changing rate of the blood glucose level at each time-point (ΔBG (t)). The insulin infusion rate at each time-point (IIR (t)) is calculated by the following equation (IC is a constant):

$$IIR(t) = IA \cdot (BG(t) - ID) \cdot 10^{-2} + IB \cdot \Delta BG(t) \cdot 10^{-2} + IC$$

Efficacy and Future Prospects of the Artificial Pancreas

A manually-operated glycemic control system may induce hypoglycemia. Considering the adverse outcomes related to hypoglycemia, prompt detection of hypoglycemia as well as adequate treatment for hypoglycemia is required; nevertheless, it is difficult to detect hypoglycemia during surgery under general anesthesia. Recent clinical studies suggest the efficacy of the artificial pancreas with a closed-loop blood glucose monitoring system for perioperative glycemic control. Hanazaki and colleagues reported that application of perioperative intensive insulin therapy using the artificial pancreas for patients undergoing general surgery provided stable blood glucose levels without inducing hypoglycemia.[54] Hayashi and colleagues applied the artificial pancreas for

perioperative glycemic control in liver transplantation recipients and reported no incidence of hypoglycemia.[55] These results suggest that strict glycemic control that does not induce hypoglycemia throughout the perioperative period of major surgery can be achieved by the application of the artificial pancreas.

Mechanisms underlying perioperative modifications of glucose metabolism can be elucidated by analyzing data obtained from perioperative glycemic control using the artificial pancreas. The analyses of time-course changes in blood glucose levels contribute to exploration of the perioperative factors altering blood glucose levels. Kawahito and colleagues continuously monitored intraoperative blood glucose levels using the artificial pancreas in patients undergoing aortic surgery with hypothermic circulatory arrest. No significant increases in blood glucose levels were observed during the period from the start of cardiopulmonary bypass to lower body ischemia, while steep increases in blood glucose levels were observed just after reperfusion and hyperglycemia continued until the end of cardiopulmonary bypass.[56] The amount of insulin required to maintain blood glucose levels within a target range reflects insulin sensitivity. It is thus possible to explore the perioperative factors modifying insulin sensitivity by analyzing time-course changes in the insulin infusion ratio. Furthermore, clinical investigations using the artificial pancreas may contribute to determine the optimal range of perioperative blood glucose levels, leading to the establishment of guidelines for perioperative glycemic management.

Conclusion

Surgical prognosis can be improved by adequate glycemic management. Both hyperglycemia and hypoglycemia should be avoided; however, it is difficult to detect hypoglycemia in surgical patients under general anesthesia. A manually-operated glycemic control system may induce hypoglycemia by administration of too much insulin, whereas an artificial pancreas with a closed-loop blood glucose monitoring system enables strict glycemic control without the risk of hypoglycemia. Furthermore, the complicated mechanisms underlying the modifications of glucose metabolism in surgical patients can be elucidated by analyzing data obtained from glycemic management using the artificial pancreas.

Conflicts of interest: None declared.

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