Postoperative Closed-loop Glycemic Control Using an Artificial Pancreas in Patients After Esophagectomy

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Abstract. *Aim: This study investigated the efficacy of an artificial pancreas in managing postoperative glycemic levels for patients after esophagectomy. Patients and Methods: We reviewed 107 patients with esophageal cancer who underwent esophagectomy, and had postoperative glucose management using the artificial pancreas. The target blood glucose level (TBGL) range was 90-140 mg/dl. Achievement rate of TBGL, total insulin use, number of severe hypoglycemic (<40 mg/dl) events, surgical complications and length of hospitalization (LOH) were evaluated. Results: Mean achievement rate of TBGL was 78.2%. Mean total insulin use was 47.9 units. Mean blood glucose level was 136.3 mg/dl (mean SD=20.7). The incidences of pneumonia, anastomotic leak, and surgical site infection were 11.2%, 12.1%, 23.4%, respectively. The mean LOH was 29.6 days. No patient developed severe hypoglycemia. Conclusion: Artificial pancreatic systems could minimize blood glucose variability and prevent severe hypoglycemic events for patients after esophagectomy.*

Esophagectomy for esophageal cancer is a technically challenging and invasive procedure (1). In Japan, postoperative complications after esophagectomy have been reported in more than 40% of cases (2). One important factor that may reduce the risk of poor surgical outcomes in post-esophagectomy patients is perioperative nutritional support. Recent studies have shown that adopting an early postoperative nutrition strategy may reduce infectious complications such as pneumonia and surgical site infection (SSI) (3). However, more aggressive early nutrition strategies may be more likely to result in hyperglycemia, that can independently increase the risk of postoperative infection.

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Large randomized control trials comparing tight glycemic control (80-110 mg/dl) using intensive insulin therapy (IIT) with standard glycemic control (<200 mg/dl) methods in patients in the Surgical Intensive Care Unit (SICU) have demonstrated that IIT reduces mortality and other surgical morbidities (4-6). Problematically, however, several recent studies have demonstrated that tight glycemic control after surgery may put patients at-risk for hypoglycemia (7, 8). Hypoglycemia has been associated with poor post-surgical outcomes and may offset any benefits achieved by using IIT. Previously, however, no reliable techniques were available to prevent hypoglycemic events from occurring during IIT. In recent years, the development of accurate continuous blood glucose-monitoring devices and closed-loop systems, which provide computer-assisted blood glucose control in the ICU, have shown promise in reducing hypoglycemic events for patients managed with IIT (9).

In 2006, we first piloted the technique of using tight glycemic control during IIT for patients undergoing major gastrointestinal surgery using a closed-loop glycemic control system (10, 11). This method has helped prevent severe hypoglycemic events during IIT and has allowed us to safely and predictably achieve normoglycemia in postoperative patients (12, 13).

Although the importance of perioperative glycemic control of perioperative glycemic control has been recently demonstrated in patients undergoing cardiac surgery (14), accurate data regarding the benefits of IIT following esophagectomy are not yet available. The aim of this study was to evaluate the outcomes in patients who received glycemic control using an artificial pancreas closed-loop glycemic control system after the esophagectomy.

Patients and Methods

Patients. We retrospectively reviewed data from 107 patients who underwent esophagectomy by thoraco-abdominal approach for esophageal cancer between June 2006 and September 2015 at the Kochi Medical School, Japan. Demographic and patient data were obtained from the medical records. All patients underwent a complete physical examination and clinical history prior to surgery. Specific

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variables such as preoperative body mass index (BMI) and diagnosis of type 2 diabetes mellitus (DM) were assessed for each patient included in the study. Postoperatively, all patients were admitted to the SICU and received postoperative nutrition (420 kcal/h for first 12 h) by total parenteral nutrition (TPN) according to resting energy expenditure as measured with indirect calorimeter (15).

Blood glucose levels (BGL) were controlled by using the artificial pancreas (AP) system (Nikkiso, Tokyo, Japan). Patients received programmed infusions of insulin that were determined by an algorithm of the closed-loop system, with a target blood glucose level (TBGL) set between 90-140 mg/dl. We recorded the incidence of severe hypoglycemia (<40 mg/dl), postoperative complications including pneumonia and SSI, and the length of hospitalization after surgery (LOH). SSI also included infections that occurred after anastomotic leak. We obtained written informed consent for all patients included in this study.

Closed-loop glycemic control by using artificial pancreas systems. We used the STG-22 and STG-55 closed-loop glycemic control systems (Nikkiso, Tokyo, Japan) in this study (Figure 1). The STG-22 and STG-55 systems comprise of a glucose sensor, which monitors glucose concentrations, and a pump that infuses appropriate amounts of insulin or glucose. The system pumps are computer regulated based on a predefined TBG value. Peripheral blood is sampled continuously at 2 ml/h to monitor glucose levels. The STG-55 system is a new type of AP that is compact in size and has a liquid crystal display (Figure 2) (16).

Statistical analysis. We used descriptive statistics, reporting the mean (±standard deviation) for continuous variables. All analyses were performed using JMP® 6 (SAS Institute Inc., Cary, NC, USA).

Results

Patient baseline characteristics and postoperative findings are shown in Table I. There were 87 (81.3%) male and 20 (18.7%) female patients. The mean age was 65.3±8.0 years. Common preoperative comorbidities included DM (n=18), cardiovascular disease (n=45), hypertension (n=61), and liver disease (n=30). The mean BMI was 21.4±3.3 kg/m^2.

The majority of patients had advanced-stage cancer (TNM seventh edition) (17). More than half of the participants received neoadjuvant chemotherapy prior to surgery. In 2009, we introduced thoracoscopic esophagectomy. The majority of patients (74.8%) underwent esophagectomy *via* thoracoscopic approach. The mean operative time and intra-operative blood loss were 604±80 min and 299±260 ml, respectively.

Table II shows postoperative outcomes. Figure 3 shows the change in mean BGL over time. The mean BGL and standard deviation were 136.3±13.2 mg/dl and 20.7±6.3 mg/dl, respectively. The mean total insulin use per patient during the 12-h postoperative period was 47.9±26.4 units. The mean achievement rate of TBGL was 78.2±20.2%. The incidences of postoperative pneumonia, anastomotic leak, and SSI were 11.2%, 12.1%, and 23.4%, respectively. The mean LOH was 29.6±26.9 days. No severe hypoglycemic events (<40 mg/dl) occurred during the postoperative period.

Table I. *Demographic characteristics and operative findings of patients undergoing esophagectomy.*

Characteristic	(N=107)
Gender (male/female), n	87/20
Age, mean±SD (years)	65.3±8.0
Diabetes mellitus, n (%)	18 (16.8)
Cardiovascular disease, n (%)	45 (42.1)
Hypertension, n (%)	61 (57.0)
Liver disease, n (%)	30 (28.0)
BMI, mean±SD (kg/m^2)	21.4±3.3
Stage, n (%)	
IA	24 (22.4)
IB	12 (11.2)
IIA	7 (6.5)
IIB	13 (12.1)
IIIA	26 (24.3)
IIIB	7 (6.5)
IIIC	8 (7.5)
IV	61 (57.0)
Neoadjuvant chemotherapy, n (%)	
Salvage surgery, n (%)	3 (2.8)
Surgical approach, n (%)	
Thoracotomy/laparotomy	2 (1.9)
Thoracotomy/laparoscopy	25 (23.4)
Thoracoscopy/laparotomy	10 (9.3)
Thoracoscopy/laparoscopy	70 (65.4)
Operative time, mean±SD (min)	604±80
Blood loss, mean±SD (ml)	299±260

BMI: Body mass index.

Table II. *Postoperative outcomes of patients undergoing esophagectomy.*

	(N=107)
Mean BGL using AP (mg/dl)	136.3±13.2
Standard deviation of the BGL, mean±SD (mg/dl)	20.7±6.3
Total insulin use, mean±SD (units)	47.9±26.4
TBGLA, mean±SD (%)	78.2±20.2
Postoperative complications, n (%)	
Pneumonia	12 (11.2)
Anastomotic leak	13 (12.1)
Surgical site infection	25 (23.4)
LOH, mean±SD (days)	29.6±26.9

BGL, Blood glucose level; AP, artificial pancreas; TBGLA, target blood glucose level achievement rate; LOH, length of hospitalization.

Discussion

Few studies in the literature describe post-surgical glycemic control in patients undergoing esophagectomy (18). To our knowledge, this is the first study reporting use of a closed-loop glycemic control through use of an AP system after esophagectomy. Our data demonstrate that the AP can achieve glycemic control within TBLG, even while administrating

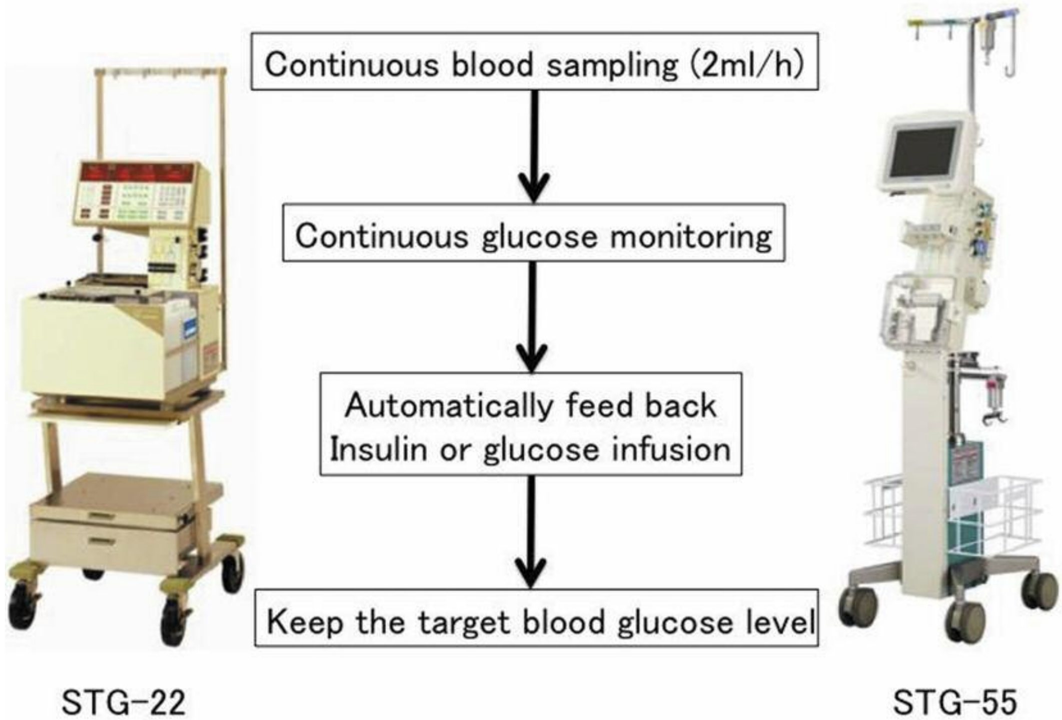

Figure 1. *Concept of closed-loop glycemic control using the artificial pancreas.*

calories after esophagectomy. In addition, our data revealed no occurrence of postoperative hypoglycemic events.

The concept of enhanced recovery after surgery or 'fast-track' surgery has been noted in the literature on perioperative management (19). It has been reported that the use of total enteral nutrition (TEN) and TPN can reduce postsurgical stress and preclude postoperative insulin resistance, an outcome that has been associated with reductions in adverse outcomes (20). The European Society for Parenteral and Enteral Nutrition guidelines recommend introducing enteral nutrition early in the postoperative period for patients undergoing gastric surgery (21). We adhere to these guidelines at our Institution; and for patients undergoing esophagectomy, start TPN or TEN using jejunostomy tube at a rate of 420 kcal/h during the first 12 h after surgery. However, we have found that the BGL tends to rise early in the postoperative period. The main cause of this is thought to be insulin resistance, induced by postoperative stress hormone release (22).

Van den Berghe *et al*. reported that the maintenance of strict normoglycemia by using IIT reduces morbidity and mortality in critically-ill patients (4-6). However, some researchers have highlighted the consequences of hypoglycemia, that can be a common side-effect of IIT (23). A recent study, NICE-SUGAR, reported the significant increased risk of hypoglycemia due to IIT, that presented no

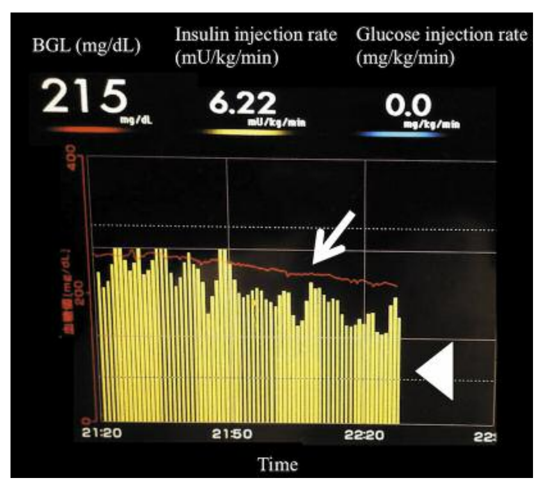

Figure 2. *The STG-55 display. The red line shows the blood glucose level (BGL) (arrow), and yellow bars shows the insulin injection rate (mU/kg/min) (arrowhead).*

mortality benefit in patients who needed to be treated in the ICU (24). However, IIT may still be useful in controlling blood glucose levels of patients admitted to the SICU (25).

It is thought that postoperative hyperglycemia may repress the immune system and result in postoperative infections

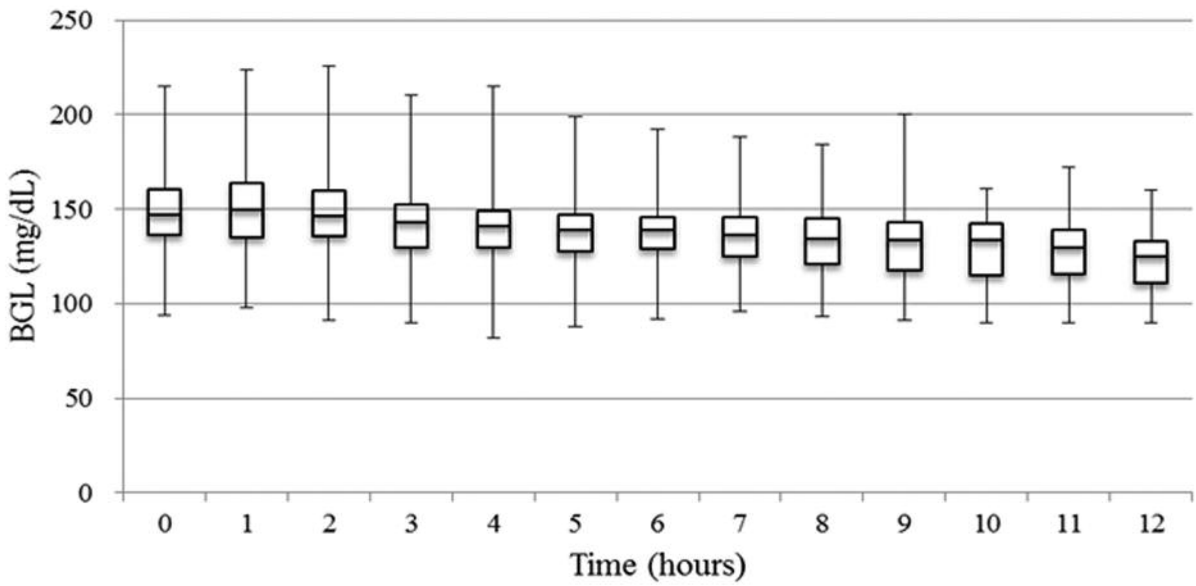

Figure 3. *Time change of the blood glucose level of 107 patients as controlled by artificial pancreas after esophagectomy. The box represents the lower to upper quartile, the horizontal bar represent the median.*

(26, 27). Research by Egi *et al*. has shown that change in blood glucose concentration is a significant independent predictor of hospital mortality. They noted that the mean standard deviation for glucose concentration in survivors was 1.7 mmol/l (30.6 mg/dl) *versus* 2.3 mmol/l (41.4 mg/dl) in non-survivors (28). Taken together, this shows we should monitor the BGL over short intervals of time and keep blood glucose levels below 140 mg/dl, and minimize the blood glucose variability to reduce mortality after surgery. The data from this study demonstrates that the AP meets these standards, offering high-quality glycemic control with minimal blood glucose variability and low risk of hypoglycemia. We found that a large amount of insulin (47.9 units) was needed to control the patients' BGL within the TBGL in the initial 12-h postoperative period given postoperative nutrition. However, no patients experienced a hypoglycemic event. In addition, the AP served dual purposes, both frequently sampling blood glucose levels and administering insulin injections. Due to this functionality, the AP may help not only to ameliorate the workload of ICU staff, but also minimize human clinical error (29).

Our study had several limitations, including a relatively small sample size, use of retrospective data, and lack of an available control group for postoperative blood glucose comparison. Additionally, we were unable to compare efficacy of the AP *versus* traditional manual sliding-scale insulin method in management of postoperative blood glucose levels.

The AP system can achieve stable target blood glucose levels and prevent the hypoglycemic events for patients undergoing esophagectomy. We believe the AP is a promising modality to ensure safe blood glucose levels during esophagectomy, and should be considered as a therapeutic option for reducing the risk of SSI. However, prospective studies with adequate sample size evaluating the efficacy of the AP in controlling postoperative blood glucose levels are required.

Funding

None.

Conflicts of Interest

None.

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