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ORIGINAL ARTICLE

Performance of a 2-step insulin infusion protocol with adjustment of insulin doses for Asians in the medical intensive care unit following cardiothoracic surgery

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Abstract

Background Most previous insulin infusion protocols are titrated for Westerners and are not simple to follow. In this study, we tested the efficacy and safety of our simple insulin infusion protocol utilizing lower insulin doses for Asians.

Methods A total of 152 patients with type 2 diabetes undergoing cardiothoracic surgery were included. After surgery, blood glucose (BG) was initially managed according to our algorithm protocol, and subsequently by the post-algorithm protocol. Insulin infusion rates in the algorithm protocol were titrated in two steps according to (1) current BG levels and (2) the difference between current and previous BG levels. In the post-algorithm protocol, insulin lispro was injected subcutaneously in addition to intravenous insulin infusion according to BG levels. The efficacy was assessed as achievement rates of two target BG ranges (140–199 and 80–199 mg/dL), and safety was assessed as hypoglycemia (< 70 mg/dL) and protocol error rates.

Results With the use of the algorithm protocol, 58.7% of 1749 BG measurements achieved a range of 140–199 mg/dL, and 95.9% achieved levels within the 80–199 mg/dL range. Hypoglycemia and protocol error rates were 0.47 and 0.51%, respectively. With the post-algorithm protocol, 48.7 and 98.3% of 898 BG measurements achieved each target range. Hypoglycemia and protocol error rates were 0.78 and 0.22%, respectively. Severe hypoglycemia (< 40 mg/dL) was not observed.

Conclusions Our insulin infusion protocol seems to be efficacious, safe, and widely feasible for Asian patients because of its simplicity and lower insulin dose.

Keywords Insulin · Insulin infusion protocol · Surgical diabetes · Hypoglycemia · Cardiac surgery · Intensive care unit

Introduction

Postoperative acute hyperglycemia following cardiac surgery is associated with an increased risk of infection and mortality [1–5]. In 2001, the Leuven I Study first revealed that intensive insulin therapy to maintain blood glucose (BG) levels between 80 and 110 mg/dL in surgically ill patients reduced mortality rates [6], suggesting that tight glycemic control to near normoglycemia during surgical stress was effective in reduction of postoperative mortality. However, the NICE-SUGAR Study in 2009 reported that tight glycemic control to a BG range of 81–108 mg/dL in critically ill patients apparently increased mortality compared to more conservative control to levels below 180 mg/dL [7]. Although the reason for this is still unknown, severe hypoglycemia (< 40 mg/dL) was more often observed in the tight glycemic control group, suggesting that severe hypoglycemia adversely affects prognosis in ill patients. In that study, to tightly control BG, a manual 3-step protocol for insulin titration was applied. However, the frequency of severe hypoglycemia was still high, occurring in 6.8% of the patients (206/3016), and average BG levels were 118 ± 25 mg/dL, which was higher than the target range (81–108 mg/dL). This result reveals that it is very difficult to achieve tight glycemic control without hypoglycemia with the use of a manual insulin infusion protocol. Based on this point, some

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societies recommend moderate glycemic control following surgery to avoid harmful hyperglycemia and hypoglycemia. The 2018 American Diabetes Association (ADA) guideline has recommended a perioperative target BG range of 80–180 mg/dL [8]. Although this target is clinically acceptable, it lacks a robust evidence base for the setting of this target BG range [8].

However, even moderate glycemic control carries the potential risk of inducing hypoglycemia, because high insulin doses are often needed in surgical patients to achieve target BG levels. On the other hand, the use of lower insulin doses to avoid hypoglycemia induces harmful hyperglycemia. To resolve this paradox, computerized insulin infusion protocols or artificial endocrine pancreas have been shown to be more effective tools for safely achieving the target BG levels [9], although the utilization of these systems is restricted to a few well-equipped facilities. Therefore, the manual insulin infusion protocol, which is feasible for use in any facility, needs to be made easier and safer. Although many insulin infusion protocols, including the Yale insulin infusion protocol (Yale protocol) [10], which is thought to be one of the most known and most widely used protocols, have been reported so far, there is no standardized manual insulin infusion protocol because most protocols have some disadvantages, such as complicated procedures or inappropriate insulin doses for patients. In particular, most previously reported insulin infusion protocols have been established for Westerners whose body mass index (BMI) and insulin resistance tend to be higher than that of Asians [11]. Hence, when these protocols are utilized for Asians, they need to be modified by decreasing the insulin dose to avoid hypoglycemia, because Western insulin doses are thought to be excessive for Asians, considering the difference in insulin sensitivity.

We developed a new insulin infusion protocol that is simple to use, effective, and safe, and which can be applied to Asians. Our protocol consists of two parts: one is a 2-step algorithm protocol for the acute postoperative phase and the other is a post-algorithm protocol for the subsequent phase. We, herein, describe the performance of our insulin infusion protocol for Japanese patients with type 2 diabetes mellitus undergoing cardiothoracic surgery at our institute.

Methods

Patients

This was a retrospective observational study. Patients with type 2 diabetes undergoing cardiothoracic surgery at Kagoshima Medical Center who were treated with the current insulin infusion protocol in the intensive care unit (ICU) between January 2013 and December 2016 were included in this study. Here, type 2 diabetes was defined as HbA1c $\geq$ 6.5% or oral antidiabetic drug therapy before hospitalization even if HbA1c was < 6.5%. The observation period extended from initiation of application of the insulin infusion protocol in the ICU until initiation of oral feeding. The exclusion criteria in this study were patients: (1) with an established diagnosis of type 1 diabetes and (2) without a diagnosis of type 2 diabetes. This study was approved by the Ethics Committee of National Hospital Organization Kagoshima Medical Center (date of approval, 6 February 2017; approval no. 28-71), and it received ethical approval for the use of an opt-out methodology based on the low risk to the patient and the potential benefit for the patient in terms of receiving adequate management. Participants had the opportunity to opt out to this study by visiting the website of Kagoshima Medical Center (http://kagomc.jp/medical/section/rinsyokenkyu/rinri/).

Insulin infusion protocol

The flow of our protocol is shown in Fig. 1. Our insulin infusion protocol consisted of two parts. The algorithm protocol was applied in the acute postoperative phase, and subsequently, once the criteria mentioned below were met, the insulin infusion was switched to the post-algorithm protocol. The post-algorithm protocol was continued until initiation of oral feeding in accordance with the cardiovascular surgeon's decision. The insulin used for continuous intravenous infusion consisted of 50 units of regular insulin (Humulin R®, Eli Lilly Inc., Indianapolis, USA) in 50 mL saline. Regular insulin was also mixed to intravenous drips including glucose at a proportion of 1 unit insulin to 10 g glucose. Blood samples for BG measurements were obtained using finger pricks and BG was measured using Medisafe FIT® (Terumo Inc., Tokyo, Japan). Blood potassium levels were also monitored every one to four hours as a part of arterial blood gas analysis using a blood gas analyzer (Stat Profile pHOx Ultra, Nova Biochemical Inc., Waltham, MA, USA) and were maintained between 3.5 and 4.5 mEq/L by administering potassium chloride (KCL injection 10 mEq Kit, Terumo Inc., Tokyo, Japan) continuously if potassium levels were less than 3.5 mEq/L.

Algorithm protocol

The algorithm protocol for insulin infusion is shown in Fig. 2. The target range of BG levels was 140–199 mg/dL. We determined the initial rate of insulin infusion according to BG levels first measured within 30 min when the patients were transferred to the ICU after cardiothoracic surgery. Insulin infusion rates were titrated by a one-step or two-step procedure according to the magnitude and direction of the change in BG levels from previous BG levels. If BG levels increased, the insulin infusion rate was increased as a

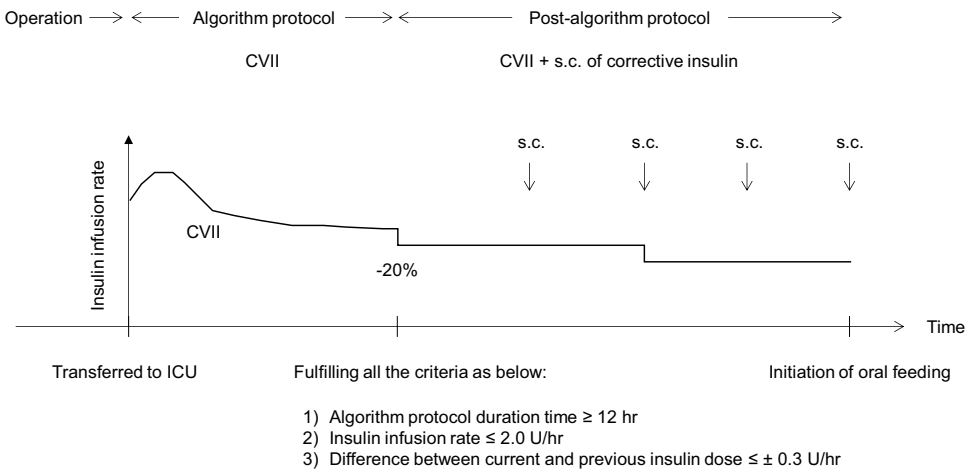

Fig. 1 Schema of our insulin infusion protocol flow. After patients were transferred to the ICU, the algorithm protocol was applied and maintained until they fulfilled the three criteria shown in the figure. Once the criteria were fulfilled, the post-algorithm protocol was applied instead of the algorithm protocol and was maintained until initiation of oral intake. In the algorithm protocol, insulin administration consisted only of an intravenous infusion of regular insulin, while under the post-algorithm protocol, subcutaneous injection of a rapid-acting insulin analog was given as required, in addition to the intravenous insulin infusion. The graph shows an example course of insulin doses. When we switched to the post-algorithm protocol from the algorithm protocol, the insulin infusion rate was reduced by 20% and a rapid-acting insulin analog was subcutaneously given along with the intravenous insulin infusion as "corrective insulin". *CVII* continuous intravenous insulin infusion, *s.c.* subcutaneous injection, *ICU* intensive care unit

1-step procedure according to current BG levels. In case of a decrease in BG levels, a 2-step procedure was utilized for titrating the insulin infusion rate by checking: (1) current BG levels and (2) the decrement in BG levels from previous BG levels. We determined that the maximum allowable insulin infusion rate to prevent hypoglycemia was 4.0 U/h based on the results of our preliminary study (data not shown). BG levels were checked hourly until insulin infusion rates were stable. If the infusion rate was unchanged after three consecutive measurements, the frequency of BG measurements was reduced to every 2 h and then to every 4 h if it remained unchanged for two measurements. If the insulin infusion rate needed to be changed when checking BG every 4 h, the measurement interval was reduced back to every 2 h. If the insulin infusion was continued at the maximum allowed rate (4.0 U/h), BG levels were checked hourly. In case of hypoglycemia (< 70 mg/dL), the infusion was discontinued and 20 g of glucose (40 mL of 50% glucose) was administered intravenously. BG levels were rechecked after 20 min, and if the levels recovered to 80 mg/dL or more, the insulin infusion was restarted and its rate was decreased by 0.5 U/h from the previous insulin infusion rate. Once all the following criteria were fulfilled, the algorithm protocol was switched to the post-algorithm protocol: (1) algorithm protocol was applied for more than 12 h; (2) insulin infusion rate was 2.0 U/h or less; and (3) the difference between current and previous insulin infusion rates was within plus or minus 0.3 U/h. If any one of these criteria was unsatisfied, the algorithm protocol was continued until all criteria were fulfilled.

Post-algorithm protocol

The post-algorithm protocol is shown in Fig. 2. The insulin infusion rate was changed from the algorithm protocol when the protocol switching criteria mentioned above were fulfilled. According to this protocol, insulin was administered as a combination of intravenous infusion of regular insulin and subcutaneous injection of the rapid-acting insulin analog lispro (Humalog®, Eli Lilly Inc., Indianapolis, IN, USA). In the post-algorithm protocol, the insulin infusion rate was reduced by 20% of the final algorithm protocol rate. BG levels were checked every 4 h and insulin lispro was injected subcutaneously according to BG levels as "corrective insulin". The hourly dose of insulin lispro was described by dividing the number of units injected by 4 (h) on the assumption that lispro remains active for 4 h. If BG levels were less than 100 mg/dL, the insulin infusion rate was decreased by 0.2 U/h. If BG levels were less than 70 mg/dL, insulin infusion was discontinued and 20 g of glucose (40 mL of 50% glucose) was administered intravenously. BG levels were rechecked after 20 min, and if BG levels recovered to 100 mg/dL or more, the insulin infusion was restarted and its rate was decreased by 0.3 U/h from the previous insulin infusion rate. The post-algorithm protocol was continued until initiation of oral feeding. After initiation of oral feeding, intravenous insulin infusion was switched to subcutaneous injection of the long-acting insulin analog glargine (Glargine®, Eli Lilly Inc., Indianapolis, IN, USA) at an equivalent dose of total daily intravenous insulin, and the

Standard insulin drip: 50 U of regular insulin in 50 mL saline

Mixture of insulin: Regular insulin is added to intravenous drips including glucose at a proportion of 1 U insulin to 10 g glucose.

<Algorithm protocol>

Target blood glucose (BG) levels: 140 -199 mg/dL

1. Initiating insulin infusion

Determine the initial insulin infusion rate according to glucose levels as below

BG (mg/dL)	Insulin infusion rate (U/hr)
150 - 199	0.5
200 - 249	2.0
250 - 299	2.5
300 - 349	3.0
350 - 399	3.5
400 -	4.0

2. Titrating insulin infusion rate

1) Check the current BG

Check BG levels hourly and adjust the infusion rate as described below. If insulin infusion rate is unchanged with three consecutive BG measurements, measurement frequency is reduced to every 2 hours and then to every 4 hours if the infusion rate remains unchanged twice. If the insulin infusion rate is changed when monitoring BG every 4 hours, the interval is changed back to every 2 hours.

2) Calculate the difference between current and previous BG levels

A. If current BG levels are unchanged or increase from previous BG levels, the insulin infusion rate is titrated as below.

	Current BG (mg/dL)						
	70 – 99	100 – 139	140 – 199	200 – 249	250 – 299	300 – 349	350 -
	-0.3 U/hr	-0.1 U/hr	Unchanged	+0.3 U/hr	+0.6 U/hr	+0.9 U/hr	+1.2 U/hr

Maximum allowable insulin infusion rate is 4.0 U/hr. Do not increase the rate further. If the insulin infusion rate needs to be increased above 4.0 U/hr, maintain it at 4.0 U/hr and check BG levels hourly.

B. If current BG levels decrease from previous BG levels, the insulin infusion rate is titrated as below.

	Current BG (mg/dL)						
△BG	70 – 99	100 – 139	140 – 199	200 – 249	250 – 299	300 – 349	350 -
< 20	-0.3 U/hr	-0.1 U/hr	Unchanged	+0.3 U/hr	+0.6 U/hr	+0.9 U/hr	+1.2 U/hr
20 - 39	-0.6 U/hr	-0.3 U/hr	Unchanged	Unchanged	+0.3 U/hr	+0.6 U/hr	+0.9 U/hr
40 - 59	-0.9 U/hr	-0.6 U/hr	-0.3 U/hr	Unchanged	Unchanged	+0.3 U/hr	+0.6 U/hr
≥ 60	-1.2 U/hr	-0.9 U/hr	-0.6 U/hr	-0.3 U/hr	Unchanged	Unchanged	+0.3 U/hr

△BG (mg/dL): difference between current and previous BG levels.

3. Hypoglycemia

If BG is < 70 mg/dL: disconnect insulin infusion. Give 20 g glucose intravenously (40 mL of 50% glucose); recheck BG after 20 minutes. When BG is ≥ 80 mg/dL, restart infusion at -0.5 U/hr less than the most recent rate; otherwise, repeat the administration of glucose.

Fig. 2 Insulin infusion protocol

4. Protocol switching criteria

When all the following criteria are fulfilled, switch to the post-algorithm protocol.

1) Algorithm protocol is applied for more than 12 hours.

2) Insulin infusion rate is 2.0 U/hr or less.

3) The difference between current and previous insulin infusion rates is within plus or minus 0.3 U/hr.

<Post-algorithm protocol>

1. Titrating the insulin infusion rate

The insulin infusion rate is reduced by 20% of the final rate according to the algorithm protocol and is maintained at this rate.

Check BG levels every 4 hours.

If BG is < 100 mg/dL: decrease insulin infusion by 0.2 U/hr.

If BG is < 70 mg/dL: disconnect insulin infusion. Give 20 g glucose intravenously (40 mL of 50% glucose); recheck BG after 20 minutes. When BG is ≥ 80 mg/dL, restart the infusion at -0.3 U/hr less than the most recent rate; otherwise, repeat the administration of glucose.

2. Administration of corrective insulin

Check BG levels every 4 hours and inject a rapid-acting insulin analog subcutaneously according to BG as below.

BG (mg/dL)	Rapid-acting insulin dose (U)
150 - 199	2
200 - 249	4
250 - 299	6
300 - 350	8
350 - 399	11
400 -	14

Fig. 2 (continued)

insulin lispro was injected subcutaneously after each meal according to food intake.

Data collection

Data on patient profiles and clinical parameters, such as age, gender, duration of diabetes, BMI, hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR), C-peptide index (CPI), diabetic treatment, type of surgery, BG levels, insulin infusion rate, and insulin dose, were collected retrospectively from the patients' clinical records and charts. The clinical endpoints assessed were the time to achieve the target BG levels, subsequent achievement rate of target BG levels, mean BG levels, standard deviation (SD) of BG levels as an indicator of variation, BG measurement interval, hypoglycemia rate, severe hypoglycemic rate, and protocol error rate during application of the algorithm protocol. The target BG levels assessed were: (1) 140–199 mg/dL for the algorithm protocol and (2) 80–199 mg/dL as clinically acceptable levels. Hypoglycemia and severe hypoglycemia were BG levels less than 70 and 40 mg/dL, respectively. Hypoglycemia rate and severe hypoglycemia rate was the number of times hypoglycemia and severe hypoglycemia occurred relative to the total number of BG measurements. Protocol error was defined as a failure of insulin titration because of miscalculation of BG levels or misreading the reference table, and an inappropriate interval of BG level measurements. The protocol error rate was the incidence of protocol error occurrence relative to the total number of BG measurements.

During application of the post-algorithm protocol, the achievement rate of target BG levels, mean BG levels, SD of BG levels as an indicator of variation, hypoglycemia rate, severe hypoglycemia rate, and protocol error rate were also evaluated.

When hourly BG levels and insulin infusion rates from the algorithm protocol period through the post-algorithm protocol period in each patient were tabulated, missing BG values and insulin infusion rates because of skipping BG measurements according to each protocol were calculated from the hours before and after the missing BG values and insulin infusion rates. During application of the post-algorithm protocol, the calculated hourly doses of insulin lispro, as above, were added to the insulin infusion rates.

Statistical analysis

All clinical data are expressed as mean ± SD.

Results

Patient characteristics

The patients' baseline characteristics are shown in Table 1. Of the 161 patients undergoing cardiothoracic surgery, nine were excluded, six because they did not fulfill our criteria of type 2 diabetes as above, and three of whom were diagnosed as type 1 diabetes. Of the 152 patients with type 2 diabetes, 111 patients (73.0%) received antidiabetic treatment and 41 patients (27.0%) were not treated for diabetes before surgery. Mean patient age was 67.5 ± 8.9 years, BMI was 24.0 ± 3.4 kg/m^2, duration of diabetes was 7.2 ± 2.1 years, and HbA1c was 7.4 ± 2.2%. In all, 77 of 152 patients (50.7%) underwent coronary artery bypass grafting (CABG), 51 patients (33.6%) underwent valve surgery, and 24 patients (15.8%) underwent thoracic artery surgery.

Table 1 Characteristics of patients with type 2 diabetes undergoing cardiothoracic surgery

Number of patients	152
Age (years)	67.5 ± 8.9
Gender (male/female)	115/37
Duration of diabetes (years)	7.2 ± 2.1
BMI (kg/m^2)	24.0 ± 3.4
HbA1c (%)	7.4 ± 2.2
eGFR (ml/min/1.73 m^2)	57.6 ± 16.2
CPI	1.4 ± 0.8
Diabetes treatment	
Oral antidiabetic drugs, *n* (%)	66 (43.4)
Insulin, *n* (%)	45 (29.6)
None, *n* (%)	41 (27.0)
Cardiothoracic surgery	
CABG, *n* (%)	77 (50.7)
Valve, *n* (%)	51 (33.6)
Thoracic artery, *n* (%)	24 (15.8)

Protocol performance

Algorithm protocol

Serial mean BG levels during application of the algorithm protocol are shown in Fig. 3, and the data are summarized in Table 2. The duration of the algorithm protocol was 18.2 ± 5.0 h, initial BG levels were 245.6 ± 51.5 mg/dL, and the initial rate of insulin infusion was 1.9 ± 0.9 U/h. Insulin infusion rates increased and achieved peak rates (2.3 ± 1.3 U/h) at 4 h, subsequently decreasing according to the decrement in BG levels. The time required to achieve target BG levels (140–199 mg/dL) was 4.0 ± 2.6 h. Thereafter, BG levels decreased to a minimum value of 137.9 ± 36.4 mg/dL despite a reduction in insulin rates, and increased gradually again to around 150 mg/dL. The mean BG level after achievement of the target was 156.7 ± 38.8 mg/dL, and the SD of BG levels was 26.2 mg/dL. Once BG levels decreased below 200 mg/dL, 58.7% (1026 of 1749 BG measurements) achieved the target range of 140–199 mg/dL, and 95.9% (1678 of 1749 BG measurements) were within the range of

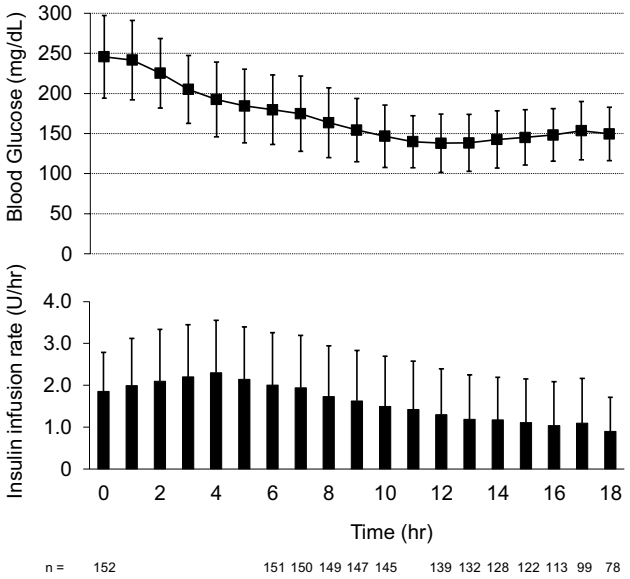

Fig. 3 Performance of the algorithm protocol. The upper graph represents BG levels and the lower graph insulin infusion rates for the first 18 h. Data are shown as mean ± SD. The numbers below the graph represent the number of patients applying the algorithm protocol at each time point. Time zero represents the start of applying algorithm protocol. The algorithm protocol was continued until switching to the post-algorithm protocol on condition of fulfilling the protocol switching criteria

Table 2 Results of application of our insulin infusion protocol in patients with type 2 diabetes undergoing cardiothoracic surgery

	Algorithm protocol	Post-algorithm protocol	Total protocol period (each patient)[c]
Duration (h)	18.2 ± 5.0	24.6 ± 5.5	42.8 ± 10.4
BG measurement interval (h)	1.2 ± 0.4	4.1 ± 0.2	2.0 ± 0.3
Time to target BG (h)	4.0 ± 2.6	–	–
BG (mg/dL)	156.7 ± 38.8[a]	136.7 ± 30.9	143.2 ± 33.8
SD of BG (mg/dL)	26.2 ± 11.9[a]	19.5 ± 7.4	22.8 ± 9.6
Achievement rate of target BG (%)			
Within 140–199 mg/dL	58.7	48.7	–
Within 80–199 mg/dL	95.9	98.3	–
Insulin infusion rate (U/h)	1.6 ± 1.1	0.7 ± 0.6	1.2 ± 0.9
Corrective insulin dose (U/h)	–	0.2 ± 0.1[b]	–
Hypoglycemia rate, *n* (%)	11/2339 (0.47)	7/898 (0.78)	18/3227 (0.56)
Severe hypoglycemia rate, *n* (%)	0/2339 (0)	0/898 (0)	0/3227 (0)
Protocol error, *n* (%)	12/2339 (0.51)	2/898 (0.22)	14/3227 (0.43)

80–199 mg/dL. The mean rate of insulin infusions according to the algorithm protocol was 1.6 ± 1.1 U/h. Mean BG measurement intervals were 1.2 ± 0.4 h.

Among 2339 total BG measurements, 11 hypoglycemic episodes (0.47%) with BG levels below 70 mg/dL were observed in 8 patients. The minimum BG level was 54 mg/dL, and severe hypoglycemia below 40 mg/dL was not observed in this study.

Throughout application of the algorithm protocol, 12 protocol errors (0.51%) that were assessed using the patients' medical records and charts were recognized in 12 patients. Eight protocol errors were due to incorrect BG measurement intervals and four were due to errors in calculations. These protocol errors did not, however, cause severe adverse effects, such as hypoglycemia.

Post-algorithm protocol

Serial mean BG levels during application of the post-algorithm protocol following the algorithm protocol are shown in Fig. 4, and the data are summarized in Table 2. The mean duration of application of the post-algorithm protocol was 24.6 ± 5.5 h. The mean initial BG levels were 145.7 ± 33.8 mg/dL, the initial rate of insulin infusion was 0.8 ± 0.7 U/h, and initial dose of insulin lispro was 0.2 ± 0.3 U/h. Subsequently, the post-algorithm protocol resulted in stable maintenance of BG levels. The mean BG levels were 136.7 ± 30.9 mg/dL, and SD was 19.5 mg/dL. Although target BG levels were not set in this protocol, we evaluated the achievement rate of the same target BG levels as in the algorithm protocol. As a result, 48.7% (437 of 898 BG measurements) achieved the range of 140–199 mg/dL and 98.3% (883 of 898 BG measurements) were within the range of 80–199 mg/dL. The mean insulin infusion rate during

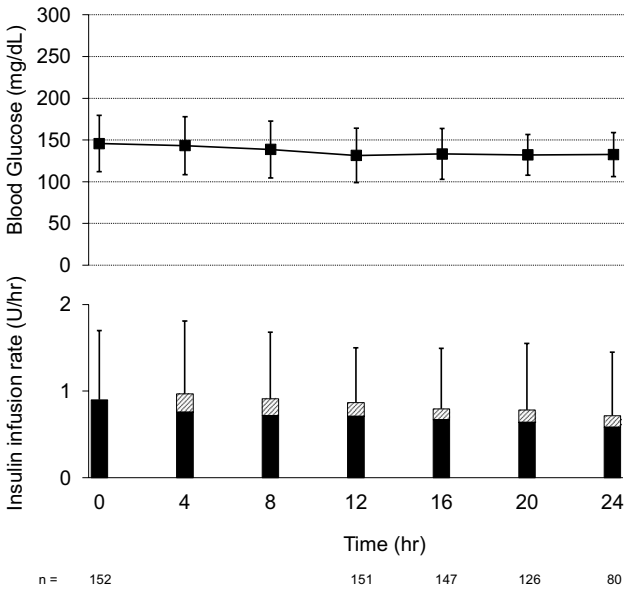

Fig. 4 Performance of the post-algorithm protocol. BG was measured and insulin infusion rates were titrated every 4 h. The upper graph represents BG levels and the lower graph represents total insulin infusion rates after switching from the algorithm to the post-algorithm protocol. In the lower graph, the black column represents intravenous insulin infusion rates and the oblique line column represents subcutaneous insulin infusion rates, which were calculated by dividing the number of units of the rapid-acting insulin analog lispro injected by 4. Data are shown as mean ± SD. The numbers below the graph represent the number of patients applying the post-algorithm protocol at each time point. Time zero represents the start of applying post-algorithm protocol. The post-algorithm protocol was continued until initiation of oral feeding in accordance with the cardiovascular surgeon's decision

this period was 0.7 ± 0.6 U/h, and the mean dose of insulin lispro was 0.2 ± 0.1 U/h. Mean BG measurement intervals were 4.1 ± 0.2 h.

Among the 898 BG measurements, 7 hypoglycemic episodes (0.78%) with BG levels below 70 mg/dL were observed in 4 patients. The minimum BG level was 54 mg/dL and severe hypoglycemia below 40 mg/dL was not observed.

During application of the post-algorithm protocol, two protocol errors (0.22%) were recognized in two patients. Both of these were due to failure of reduction in the insulin infusion rate despite BG levels decreasing below 100 mg/dL. These protocol errors did not, however, cause severe adverse effects such as hypoglycemia.

Total insulin infusion protocol performance

Hourly BG levels and insulin infusion rates from application of the algorithm protocol through the post-algorithm protocol period in each patient are shown in Fig. 5, and the data are summarized in Table 2. The total duration of application of our insulin infusion protocol was 42.8 ± 10.4 h, mean BG levels were 143.2 ± 33.8 mg/dL, and SD was 22.8 mg/dL. Mean BG measurement intervals were 2.0 ± 0.3 h. Among the total of 3237 BG measurements, 18 hypoglycemic episodes (0.56%) with BG levels below 70 mg/dL were observed in 10 patients. Two patients experienced hypoglycemia during application of both the algorithm protocol and the post-algorithm protocol. The minimum glucose level was 54 mg/dL and severe hypoglycemia of below 40 mg/dL was not observed. In total, protocol errors occurred 14 times (0.43%) in 14 patients.

Discussion

In this study, we developed an original manual insulin infusion protocol for Asians. Our algorithm protocol, which is characterized by a simple 2-step procedure and adjustment of insulin doses for Asians, demonstrated suitable efficacy and safety following cardiothoracic surgery. The subsequent post-algorithm protocol also demonstrated maintenance of the efficacy and safety of the algorithm protocol without the need for frequent BG measurements.

Many insulin infusion protocols, including computerized protocols, have so far been reported for the perioperative control of BG levels. In the case of cardiothoracic surgery, seven protocols have been reported including Yale protocol, which is thought to be one of the most popular protocols for use in critically ill patients (Table 3) [12–18]. Despite the diversities of the protocols, all of them achieved target BG levels better than did conventional protocols. However, these

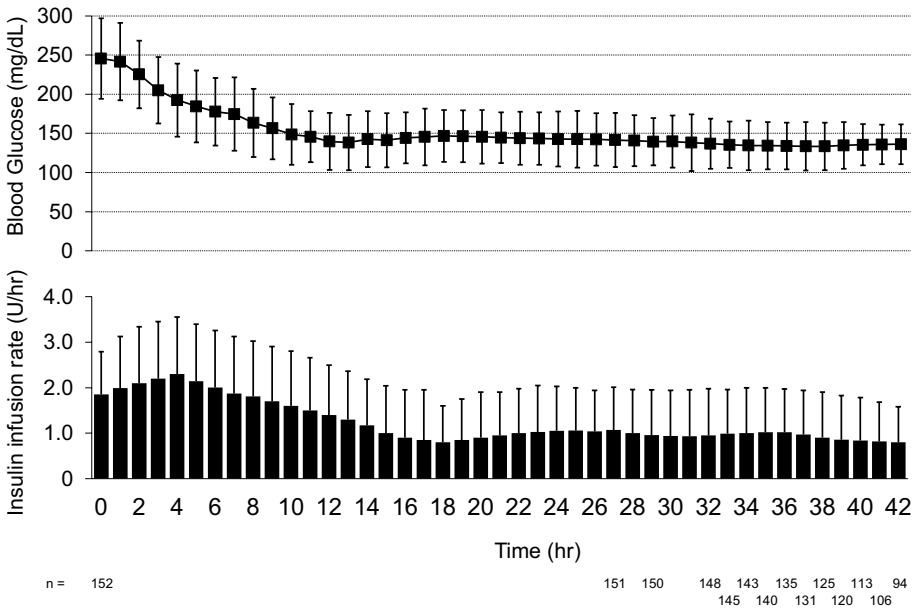

Fig. 5 Performance of the insulin infusion protocol in each patient. The upper graph represents hourly BG levels and the lower graph hourly insulin infusion rates over the algorithm and post-algorithm protocol period in each patient. Missing BG values and insulin infusion rates were calculated from the hours before and after the missing BG values and insulin infusion rates. During the post-algorithm protocol, the calculated doses of subcutaneous insulin lispro were added to the intravenous insulin infusion rates. Data are shown as mean ± SD. The numbers below the graph represent the number of patients applying total insulin infusion protocol including both of the algorithm and post-algorithm protocol continuously. Time zero represents the start of applying algorithm protocol and insulin infusion protocol was continued until initiation of oral feeding

Table 3 Comparison of the current and previous insulin infusion protocols in cardiothoracic surgery patients

	No. of steps	Cal.	BG measurement interval (h)	Target (mg/dL)	Time to target (h)	Percentage of patients who achieved the target (%)	Hypoglycemia rate (%)	Protocol error rate (%)	SD of BG (mg/dL)	BMI (kg/m^2)	IIR (U/h)
Our protocol											
Algorithm	2	Yes	1–4	140–199 80–199	4.0 ± 2.6	58.7 95.9	0.47 (< 70 mg/dL) 0 (< 40 mg/dL)	0.51	26.2	24.0 ± 3.4	1.6 ± 1.1
Post-algorithm	1	No	4	(140–199) (80–199)	–	48.7 98.3	0.78 (< 70 mg/dL) 0 (< 40 mg/dL)	0.22	19.5	–	0.9 ± 0.6
Goldberg [12] (Yale P)	3	Yes	1–4	100–139 80–139 80–199	(5.0, m)	58 73 94	0.2 (< 60 mg/dL)	–	–	29.2 ± 7.0	–
Studer [13] (Yale P)	3	Yes	1–4	100–139	–	57.3	0 (< 50 mg/dL)	–	–	28.9 ± 4.1	–
Tamaki [14] (m-Yale P)	3	Yes	1–4	80–140 80–110	3.1 ± 2.1	78 ± 15.2 39 ± 15.5	0.05 ± 0.59 (< 60 mg/dL)	–	–	23.9 ± 3.7	–
Leibowitz [15]	2	No	2–4	110–150	–	53.2	0.2 (< 70 mg/dL)	–	–	27.8 ± 5.5	–
Zimmerman [16]	2	No	1–4	80–150	(2.1, m)	61	16.7 (< 65 mg/dL) 7.1 (< 40 mg/dL)	–	–	–	–
Lecomte [17]	2	No	1–2	80–110	–	59.5	0.22 (< 60 mg/dL)	0.7	–	27.2 ± 5.1	4.1 ± 1.6
Magaji [18]	3	Yes	1–2	110–140	5.0	43.3	0.84 (< 69 mg/dL) 0 (< 40 mg/dL)	–	27.9	30.4 ± 6.4	3.0

Cal. calculation required, *BG* blood glucose, *SD* standard deviation, *BMI* body mass index, *IIR* insulin infusion rate, *Yale P* Yale protocol, *m-Yale P* modified Yale protocol, *m* median values

protocols had two problems: (1) each protocol needed multi-step calculations and continuous hourly measurements of BG levels, which is not simple; and (2) insulin infusion rates tended to be high because they are based on the insulin doses for Westerners'. In particular, if these protocols are directly applied for Asians, they often result in hypoglycemia due to excessive insulin doses. To solve these problems, we focused on fewer insulin doses and simplicity of procedures.

First, to avoid excessive insulin doses, we characterized our algorithm protocol as the following two features for insulin titration: (1) the magnitude of BG changes were not reflected in case of an increasing BG trend and (2) maximum insulin dose was set. The reflection of magnitude of BG changes for insulin titration could cause a large change in insulin infusion rates, especially if BG levels largely changed. In Yale protocol, insulin doses are likely to be high when BG levels largely elevate, because the magnitude of BG changes is reflected even in case of an increasing BG trend. Although this is effective for decreasing BG levels in Westerners who are more insulin resistant than Asians, it has the potential risk of occurring hypoglycemia for Asians because of high insulin doses. On the other hand, if BG levels show a downward trend, the reflection of magnitude of BG change is very important because insulin doses should be rapidly reduced to prevent hypoglycemia. That is why we adopted the different way of the insulin titration depending on BG trend in our algorithm protocol. Moreover, in our preliminary study, insulin rates of more than 4.0 U/mL sometimes induced hypoglycemia, because the reduction of insulin doses did not catch up with decreasing BG levels (data not shown). Therefore, we limited the maximum insulin infusion rate to 4.0 U/mL for the prevention of excessive insulin doses in our algorithm protocol. As a result of considering those two points as above, insulin infusion rates in our cohort were obviously lower than in the participants in previous report (mean insulin infusion rate; 1.6 vs. 3.0–4.1 U/h [17, 18]), and our algorithm protocol resulted in low hypoglycemia rates of 0.47% and severe hypoglycemia rates of 0%, which was comparable to the results in other reports [12–18] (Table 3). Even though insulin doses were fewer in our algorithm protocol, its efficacy was not impaired such as the time to achievement of target BG levels and the achievement rate of target BG levels, which were also comparable to the results in other reports [12–18] (Table 3). Possible reason for this was that Asians were higher insulin sensitivity due to low BMI than Westerners'. Actually, BMI in our cohort were obviously lower than in the participants in these protocols (mean BMI; 23.9 vs. 27.2–30.4 kg/m^2 [12, 13, 15–18]) except for that in Tamaki's [14] study, in which modified Yale protocols were applied for Japanese (Table 3).

Secondary, we reduced the number of steps required for our algorithm protocol as possible to simplify its procedure. As described above, insulin doses were titrated by 1-step (confirming current BG levels) in case of an increase in BG levels, and by 2-step (confirming current BG levels and the difference between current and previous BG levels) in case of a decrease in BG levels. In the Yale protocol, insulin doses are titrated by 3-step because current insulin infusion rate is also a factor considered in the insulin dose titration, in addition to current BG levels and the magnitude of BG changes. This protocol is very effective in the large reduction of insulin doses when BG levels decrease on condition that high insulin doses were administrated. However, in our algorithm protocol, insulin doses were titrated safely without considering the factor of current insulin infusion rate even in case of decreasing BG levels because of setting the limitation of max insulin doses as above. As a consequence of reducing the number of steps, our algorithm protocol had a low protocol error rate (0.51%) compared with previous reports (Lecomte et al., 0.7% [17], Watts et al., 4% [19]), suggesting that it is easy to operate due to its simplicity.

Our algorithm protocol, characterized by low insulin doses and its simplicity of procedures, also led to a good result in glucose variability in addition to the achievement rate, the hypoglycemia rate, and the protocol error rate. Perioperative glucose variability, including both acute hyperglycemia and severe hypoglycemia, reportedly increases postoperative complications, such as infections [20, 21]. Egi et al. reported that the SD of BG levels is significantly different between survivors and non-survivors among critically ill patients (30.6 ± 23.4 and 41.4 ± 28.8 mg/dL, respectively) [22]. In our algorithm, the SD of BG levels after achieving target BG levels was 26.2 ± 11.9 mg/dL, which is thought to be clinically acceptable compared to other protocols; Magii et al. reported SDs of BG levels of 27.9 mg/dL [18], Chant et al., 32 mg/dL [23], Furnary et al., 30 mg/dL [24], Kanji et al., 75.6 mg/dL [25], and Krinsley et al., 55.1 mg/dL [26].

Although our algorithm protocol is simplified as possible, the ICU nurses would be bothered because BG levels often needed measuring hourly. Therefore, we did not continue the algorithm protocol and instead, switched to the post-algorithm protocol in which the BG measurement interval was extended to every 4 h. As a result, despite less frequent BG measurements, achievement rates of BG levels between 140–199 and 80–199 mg/dL were 48.7 and 98.3% in our post-algorithm protocol, respectively. The SD of BG levels was 19.5 mg/dL, hypoglycemia rate was 0.78%, and severe hypoglycemia rate was 0%. These results were comparable to other protocols [12–18] (Table 3) and implied that even our simple conventional protocol enabled stable maintenance of BG levels once the acute phase of surgical hyperglycemia had passed with application of the algorithm protocol. In addition, during the entire algorithm protocol and post-algorithm protocol application period in each patient, BG measurement intervals were particularly wider than the intervals in Tamaki's report (2.0 ± 0.3 vs. 1.6 ± 0.4 h [14]),

suggesting that post-algorithm protocol was useful in reducing the nurses' work load.

The present study includes several limitations. First, our target BG levels might have been slightly higher than those of the other reported protocols. Although the target BG range in the perioperative period is still controversial, several societies have recommended the range of 80–180 mg/dL [8, 27, 28]. Only the Centers for Disease Control and Prevention recommended a target BG range of < 200 mg/dL for prevention of surgical site infections [29]. Considering these background, we set the target BG range from 140 to 199 mg/dL so that the subsequent titration would begin with BG levels of 200 mg/dL, since it is visually and instinctively easier to identify which BG range the hyperglycemia falls into if ranges are in multiples of 50, thus decreasing protocol errors. Second, the present study was designed to be a retrospective uncontrolled study. A prospective comparative study is needed to strongly demonstrate the superiority of our algorithm protocol relative to conventional protocols from the point of view of efficacy and safety; furthermore, the primary endpoint should not be protocol performance, but clinical endpoints such as survival rate, duration of hospitalization, and postoperative complication rate. Third, the performance of our algorithm protocol in subjects with type 1 diabetes is unknown, because we limited the subjects to those with type 2 diabetes. Further studies are needed to evaluate the efficacy and safety of our protocol in patients with type 1 diabetes. Fourth, we did not take insulin resistance into consideration in our insulin infusion protocol, because the insulin-resistance-guided infusion protocol needed complicated procedure [30]. Although it is thought to be not necessary for Asians with the lower insulin resistance, if some Asian patients might exhibit marked insulin resistance in the perioperative period, there is a possibility that insulin doses might be not enough to decrease BG levels in our algorithm protocol. In this case, additional insulin infusions may be temporally considered as the deviation of our algorithm protocol. Fifth, we analyzed our insulin infusion protocols only for Japanese patients with type 2 diabetes. To evaluate our insulin protocols for Asians, further studies are needed in other Asian country. Recently, ethnic differences in the relationship between insulin sensitivity and insulin response were reported, and East Asians (including Japan, China and Korean) tended to be higher insulin sensitivity and lower insulin response compared to other ethnic such as Africans and Caucasians [31]. This result implied our insulin infusion protocols are expected to be good performance for at least East Asians because of their similar characteristics of insulin sensitivity. Finally, we started applying our algorithm protocol when patients were transferred to the ICU because we could not apply it intraoperatively due to an understaffing situation at our institute. If possible, the algorithm protocol should be applied intraoperatively.

In conclusion, the present study found that our 2-step algorithm protocol involving adjustment of insulin doses for Asians showed comparable efficacy and safety as other protocols, including the 3-step Yale protocol, in Japanese patients with type 2 diabetes undergoing cardiothoracic surgery. Both the algorithm and post-algorithm insulin infusion protocols evaluated in this study do not need dedicated software or clinical instruments, such as artificial endocrine pancreas, and seem to be widely feasible for Asian patients with type 2 diabetes.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

Disclosures Yoshihiko Nishio has received honoraria for scientific lectures from Eli Lilly. Kazuma Ogiso, Nobuyuki Koriyama, Takahiko Obo, Akinori Tokito, and Takayuki Ueno have nothing to disclose.

Human rights statement All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (National Hospital Organization Kagoshima Medical Center, Ethics Committee, date of approval: 6 February 2017, approval no. 28-71) and with the Helsinki Declaration of 1964 and later versions.

References

1. Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A. Glucose control lowers the risk of wound infection in diabetics after open heart operations. Ann Thorac Surg. 1997;63:356–61.
2. Kotagal M, Symons RG, Hirsch IB, Umpierrez GE, Dellinger EP, Farrokhi ET, Flum DR. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. Ann Surg. 2015;261:97–103.
3. Ascione R, Rogers CA, Rajakaruna C, Angelini GD. Inadequate blood glucose control is associated with in-hospital mortality and morbidity in diabetic and nondiabetic patients undergoing cardiac surgery. Circulation. 2008;118:113–23.
4. Doenst T, Wijeysundera D, Karkouti K, Zechner C, Maganti M, Rao V, Borger MA. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg. 2005;130:1144.
5. Jones KW, Cain AS, Mitchell JH, Millar RC, Rimmasch HL, French TK, Abbate SL, Roberts CA, Stevenson SR, Marshall D, Lappé DL. Hyperglycemia predicts mortality after CABG: postoperative hyperglycemia predicts dramatic increases in mortality after coronary artery bypass graft surgery. J Diabetes Complicat. 2008;22:365–70.
6. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359–67.
7. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ, NICE-SUGAR

Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
8. American Diabetes Association 14. Diabetes care in the hospital: standards of medical care in diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S144–51.
9. Marvin MR, Inzucchi SE, Besterman BJ. Minimization of hypoglycemia as an adverse event during insulin infusion: further refinement of the Yale protocol. Diabetes Technol Ther. 2016;18:480–6.
10. Goldberg PA, Siegel MD, Sherwin RS, Halickman JI, Lee M, Bailey VA, Lee SL, Dziura JD, Inzucchi SE. Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit. Diabetes Care. 2004;27:461–7.
11. Torréns JI, Skurnick J, Davidow AL, Korenman SG, Santoro N, Soto-Greene M, Lasser N, Weiss G. Study of Women's Health Across the Nation (SWAN). Ethnic differences in insulin sensitivity and beta-cell function in premenopausal or early perimenopausal women without diabetes: the Study of Women's Health Across the Nation (SWAN). Diabetes Care. 2004;27:354–61.
12. Goldberg PA, Sakharova OV, Barrett PW, Falko LN, Roussel MG, Bak L, Blake-Holmes D, Marieb NJ, Inzucchi SE. Improving glycemic control in the cardiothoracic intensive care unit: clinical experience in two hospital settings. J Cardiothorac Vasc Anesth. 2004;18:690–7.
13. Studer C, Sankou W, Penfornis A, Pili-Floury S, Puyraveau M, Cordier A, Etievent JP, Samain E. Efficacy and safety of an insulin infusion protocol during and after cardiac surgery. Diabetes Metab. 2010;36:71–8.
14. Tamaki M, Shimizu T, Kanazawa A, Tamura Y, Hanzawa A, Ebato C, Itou C, Yasunari E, Sanke H, Abe H, Kawai J, Okayama K, Matsumoto K, Komiya K, Kawaguchi M, Inagaki N, Watanabe T, Kanazawa Y, Hirose T, Kawamori R, Watada H. Efficacy and safety of modified Yale insulin infusion protocol in Japanese diabetic patients after open-heart surgery. Diabetes Res Clin Pract. 2008;81:296–302.
15. Leibowitz G, Raizman E, Brezis M, Glaser B, Raz I, Shapira O. Effects of moderate intensity glycemic control after cardiac surgery. Ann Thorac Surg. 2010;90:1825–32.
16. Zimmerman CR, Mlynarek ME, Jordan JA, Rajda CA, Horst HM. An insulin infusion protocol in critically ill cardiothoracic surgery patients. Ann Pharmacother. 2004;38:1123–9.
17. Lecomte P, Foubert L, Nobels F, Coddens J, Nollet G, Casselman F, Crombrugge PV, Vandenbroucke G, Cammu G. Dynamic tight glycemic control during and after cardiac surgery is effective, feasible, and safe. Anesth Analg. 2008;107:51–8.
18. Magaji V, Nayak S, Donihi AC, Willard L, Jampana S, Nivedita P, Eder R, Johnston J, Korytkowski MT. Comparison of insulin infusion protocols targeting 110–140 mg/dL in patients after cardiac surgery. Diabetes Technol Ther. 2012;14:1013–7.
19. Watts NB, Gebhart SS, Clark RV, Phillips LS. Postoperative management of diabetes mellitus: steady-state glucose control with bedside algorithm for insulin adjustment. Diabetes Care. 1987;10:722–8.
20. Jeon CY, Furuya EY, Berman MF, Larson EL. The role of preoperative and post-operative glucose control in surgical-site infections and mortality. PLoS One. 2012;7:e45616.
21. Sato H, Hosojima M, Ishikawa T, Aoki K, Okamoto T, Saito A, Tsuchida M. Glucose variability based on continuous glucose monitoring assessment is associated with postoperative complications after cardiovascular surgery. Ann Thorac Cardiovasc Surg. 2017;23:239–47.
22. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology. 2006;105:244–52.
23. Chant C, Wilson G, Friedrich JO. Validation of an insulin infusion nomogram for intensive glucose control in critically ill patients. Pharmacotherapy. 2005;25:352–9.
24. Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. Endocr Pract. 2004;10:21–33.
25. Kanji S, Singh A, Tierney M, Meggison H, McIntyre L, Hebert PC. Standardization of intravenous insulin therapy improves the efficiency and safety of blood glucose control in critically ill adults. Intensive Care Med. 2004;30:804–10.
26. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc. 2004;79:992–1000.
27. Lazar HL, McDonnell M, Chipkin SR, Furnary AP, Engelman RM, Sadhu AR, Bridges CR, Haan CK, Svedjeholm R, Taegtmeyer H. Shemin RJ; Society of Thoracic Surgeons Blood Glucose Guideline Task Force. The Society of Thoracic Surgeons practice guideline series: blood glucose management during adult cardiac surgery. Ann Thorac Surg. 2009;87:663–9.
28. Ban KA, Minei JP, Laronga C, Harbrecht BG, Jensen EH, Fry DE, Itani KM, Dellinger EP, Ko CY, Duane TM. American College of Surgeons and Surgical Infection Society: surgical Site Infection Guidelines, 2016 update. J Am Coll Surg. 2017;224:59–74.
29. Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, Reinke CE, Morgan S, Solomkin JS, Mazuski JE, Dellinger EP, Itani KMF, Berbari EF, Segreti J, Parvizi J, Blanchard J, Allen G, Kluytmans JAJW, Donlan R, Schecter WP; Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017;152:784–91.
30. Caddell KA, Komanapalli CB, Slater MS, Hagg D, Tibayan FA, Smith S, Ahmann A, Guyton SW, Song HK. Patient-specific insulin-resistance-guided infusion improves glycemic control in cardiac surgery. Ann Thorac Surg. 2010;90:1818–23.
31. Kodama K, Tojjar D, Yamada S, Toda K, Patel CJ, Butte AJ. Ethnic differences in the relationship between insulin sensitivity and insulin response: a systematic review and meta-analysis. Diabetes Care. 2013;36:1789–96.