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ORIGINAL ARTICLE

Artificial Liver, Pancreas

Glucose control using a closed-loop device decreases inflammation after cardiovascular surgery without increasing hypoglycemia risk

Takahiko Tamura[1] · Tomoaki Yatabe[1] · Tsutomu Namikawa[2] · Kazuhiro Hanazaki[2] · Masataka Yokoyama[1]

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Abstract

Although tight glucose control might reduce inflammation after cardiac surgery, it remains unclear whether inflammation can be controlled by maintaining glucose levels within 110–180 mg/dL. We hypothesized that a glucose target range of 110–180 mg/dL decreases inflammation after cardiovascular surgery. This retrospective study included 72 cardiovascular surgery patients divided into two groups according to the glucose control approach. Patients allocated to the closed-loop group received closed-loop glucose control (target glucose levels at 110–180 mg/dL) from admission to the intensive care unit until 9 a.m. on postoperative day (POD) 1. Patients allocated to the conventional group received conventional glucose control using a sliding scale method to maintain blood glucose levels < 200 mg/dL. Primary outcomes were C-reactive protein (CRP) levels on PODs 1, 2, and 7. Data were reported as mean ± standard deviation. Comparisons were performed using the chi-squared test and unpaired *t* test, with $p < 0.05$ indicating statistical significance. The closed-loop group had significantly lower average glucose levels (169 ± 24 vs. 201 ± 36 mg/dL, $p < 0.001$) and standard deviation of glucose levels (22 ± 13 vs. 44 ± 20 mg/dL; $p < 0.001$). The CRP levels on PODs 2 and 7 were significantly lower in the closed-loop group than in the conventional group (10.8 ± 5.6 vs. 14.1 ± 5.7 mg/dL, $p = 0.02$; 4.6 ± 2.5 vs. 7.3 ± 4.0 mg/dL, $p < 0.001$; respectively). Our findings suggest that glucose control using a closed-loop device might decrease inflammation after cardiovascular surgery without increasing hypoglycemia risk.

Keywords Artificial pancreas · Glucose control · Glucose variability · Cardiac surgery · Inflammatory response

Introduction

Because hyperglycemia is an important factor in inflammation, glycemic control is important. Indeed, tight glycemic control was found to reduce the levels of inflammatory cytokines such as nuclear factor kappa B and tumor necrosis factor (TNF)-α after coronary bypass surgery [1]. In cardiac surgery, atrial fibrillation (Af) is a common complication, leading to increased morbidity and prolonged hospitalization [2]. Tight control of serum glucose levels within 125–200 mg/dL was found to reduce the incidence of Af after cardiac surgery [3]. Inflammation is also associated with perioperative Af after cardiovascular surgery [4]. Thus, adequate glycemic control might contribute to improving postoperative outcomes via reduction of inflammation after cardiovascular surgery.

A closed-loop glycemic control device (STG-55; NIKKISO, Tokyo, Japan) has been developed to maintain blood glucose levels within the target range through automatic infusion of insulin and glucose. We previously reported that glycemic control using a closed-loop device could maintain glucose levels close to the target set in our clinical practice, without inducing hypoglycemia in critically ill patients [5]. Although tight glycemic control using this device decreased inflammatory response in cardiac surgery patients [6], tight glycemic control is associated with a higher risk of hypoglycemia [7]. Several guidelines

✉ Takahiko Tamura
tamura_t@kochi-u.ac.jp

✉ Tomoaki Yatabe
yatabe@kochi-u.ac.jp

[1] Department of Anesthesiology and Intensive Care Medicine, Kochi Medical School, Kohasu, Oko-cho, Nankoku, Kochi 783-8505, Japan

[2] Department of Surgery, Kochi Medical School, Nankoku, Kochi, Japan

recommend that the optimal target blood glucose range is below 180 mg/dL [8]. However, it remains unclear whether inflammation can be effectively controlled by maintaining glucose levels within a target range of 110–180 mg/dL. We hypothesized that a glucose target range of 110–180 mg/dL maintained using a closed-loop glycemic control device decreases inflammation and reduces the incidence of complications after cardiovascular surgery without increasing the risk of hypoglycemia. Therefore, we conducted a single-center retrospective study to investigate this hypothesis.

Materials and methods

Ethical approval

All subjects enrolled in this research have given their informed consent to undergo the procedures described below, which has been approved by our hospital's committee on human research, and this protocol has been found acceptable by them. The ethics committee of our hospital approved this retrospective study (approval no. ERB-102588). The requirement for obtaining written informed consent from the patients for participation in the present study was waived due to the retrospective nature of this investigation.

Patients and study design

This was a before–after study of patients who underwent cardiovascular surgery in our hospital between October 2012 and March 2015. Patients aged < 18 years, patients with chronic Af or a history of emergency surgery, and patients receiving hemodialysis were excluded. Patients were divided into two groups depending on the approach employed for blood glucose control, namely closed-loop control (closed-loop group) and conventional control (conventional group).

Closed-loop group

In our hospital, the closed-loop device for glycemic control after cardiovascular surgery was introduced in clinical practice in September 2013. Thus, the closed-loop group included patients managed between September 2013 and March 2015. In this group, blood glucose level was controlled within 110–180 mg/dL from admission to the intensive care unit (ICU) until 9 a.m. on postoperative day (POD) 1. After this period, glucose levels were maintained at < 200 mg/dL using a sliding scale method until ICU discharge.

Conventional group

The conventional group included patients who underwent cardiovascular surgery between October 2012 and August 2013. Using a sliding scale method, glucose levels were maintained at < 200 mg/dL from admission to the ICU until ICU discharge. The ICU nurses measured arterial glucose levels every 4 h and adjusted the continuous insulin injection according a sliding scale.

Standard ICU management

The patients received ventilation under sedation with dexmedetomidine and propofol. During mechanical ventilation, the patients received infusion with 10% glucose solution at a rate corresponding to a nutritional intake of 192 kcal/day. Oral intake was started at 6–12 h after extubation. Swan-Ganz™ thermodilution catheters (Edwards Lifesciences, Irvine, California, USA) for continuous measurement of end-diastolic volume and cardiac output were installed in the pulmonary artery via the right internal jugular vein. The cardiac index and mixed venous oxygen saturation were continuously monitored using a Vigilance monitor (Edwards Lifesciences).

Data collection

Average glucose levels and standard deviation (SD) of glucose levels were collected from the STG-55 records for patients in the closed-loop group, and from the electronic medical records for patients in the conventional group. Additionally, the following data were collected from the electronic medical records: age, height, weight, Acute Physiology And Chronic Health Evaluation (APACHE) II score at ICU admission; type of operation, intra operative data; C-reactive protein (CRP) levels and white blood cell (WBC) counts on PODs 1, 2, and 7; incidence of Af within 1 week after surgery; average lactate levels, cardiac index, catecholamine index, and minimum potassium levels from ICU admission until 9 a.m. on POD 1; incidence of hypoglycemia and dose of insulin from ICU admission until 9 a.m. on POD 1; hospital mortality and length of hospital stay. The catecholamine index was calculated as the levels of dopamine + dobutamine + (epinephrine + norepinephrine) × 100 (in μg/kg/min).

Outcome measures

Primary outcomes were CRP levels on PODs 1, 2, and 7. Secondary outcomes were: average glucose levels, SD of glucose levels; incidence of Af within 1 week after surgery;

WBC counts on PODs 1, 2, and 7; average lactate levels; average cardiac index; catecholamine index; insulin use; minimum potassium levels; and incidence of hypoglycemia. We defined hypoglycemia as blood glucose levels below 40 mg/dL.

Statistical analysis

Statistical analysis was performed using JMP version 9.0 (SAS Institute Japan, Tokyo, Japan) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Data were reported as mean ± standard deviation or as frequency. The Fisher's exact test and unpaired *t* test were used for comparisons, and $p < 0.05$ was considered to indicate statistical significance. Between-group comparisons of CRP levels and WBC counts were conducted using one-way repeated ANOVA. If a significant difference was detected, a post hoc Bonferroni test was used to determine where the difference was significant. We calculated the sample size based on a previous study [3]. Considering a power of 0.8 and error of 0.05, a minimum sample size of 27 patients was required for each group.

Results

Patient characteristics

Of the 72 patients enrolled in this study, 33 were female and 39 were male. There was no significant difference between the closed-loop and conventional groups regarding patient characteristics (Table 1).

Outcomes

The average glucose levels and SD of glucose levels were significantly lower in the closed-loop group than that in the conventional group (169 ± 24 vs. 201 ± 36 mg/dL, $p < 0.001$; 22 ± 13 vs. 44 ± 20 mg/dL, $p < 0.001$; respectively). Hypoglycemia was not noted in either group.

The CRP levels on PODs 2 and 7 were significantly lower in the closed-loop group than in the conventional group (10.8 ± 5.6 vs. 14.1 ± 5.7 mg/dL, $p = 0.02$; 4.6 ± 2.5 vs. 7.3 ± 4.0 mg/dL, $p < 0.001$; respectively) (Fig. 1; Table 2). The CRP levels on POD 1 and the WBC counts on PODs 1, 2, and 7 were similar between the groups.

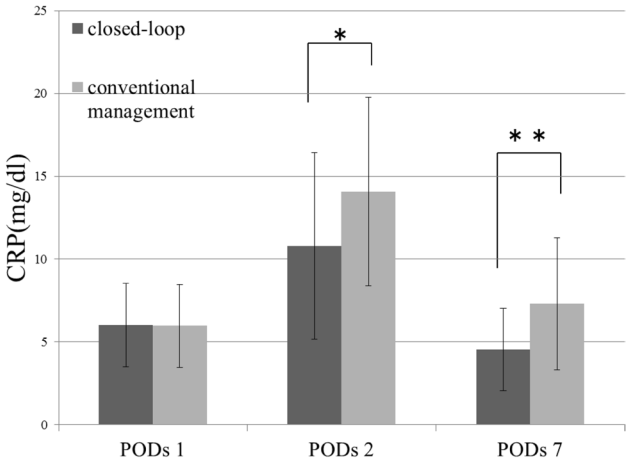

Fig. 1 C-reactive protein (CRP) levels on postoperative days (PODs) 1, 2, and 7. We enrolled 72 patients divided into two groups according to glucose control approach (closed-loop device, 36 patients; conventional management, 36 patients). Significant between-group differences are labeled as *$p < 0.05$ and **$p < 0.001$

Table 1 Patient characteristics

Characteristics	Closed-loop group ($n = 36$)	Conventional group ($n = 36$)	*p* value
Age, years	71 ± 11	74 ± 13	0.53
Weight, kg	55 ± 10	56 ± 12	0.77
Female sex, *n* (%)	17 (47)	16 (44)	1.0
Diabetes, *n* (%)	12 (33)	11 (31)	1.0
Duration of anesthesia, min	536 ± 173	556 ± 130	0.63
On-pump surgery, *n* (%)	24 (67)	31 (86)	0.09
Perioperative β-blocker usage, *n* (%)	10 (28)	5 (14)	0.55
Urine during anesthesia, mL	1222 ± 776	1101 ± 810	0.53
Bleeding during anesthesia, mL	2885 ± 3547	2851 ± 1463	0.95
APACHE II score	18 ± 5	19 ± 7	0.33
Glucose level at ICU administration, mg/dL	206 ± 56	204 ± 47	0.88

Patients were stratified according to the approach for glucose control (closed-loop device vs. conventional control). Continuous data are shown as mean ± standard deviation

APACHE acute physiology and chronic health evaluation, *ICU* intensive care unit, *n* number

Table 2 Postoperative data and outcomes

Outcomes	Closed-loop group ($n=36$)	Conventional group ($n=36$)	p value
Average blood glucose, mg/dL	169 ± 24	201 ± 36	< 0.001*
SD of blood glucose levels, mg/dL	22 ± 13	44 ± 20	< 0.001*
Hypoglycemia, *n* (%)	0 (0)	0 (0)	1.00
Insulin, IU	22 ± 24	17 ± 16	0.28
Minimum potassium, mEq/L	3.7 ± 0.4	3.7 ± 0.4	0.50
CRP on day 1, mg/dL	6.0 ± 2.5	6.0 ± 2.5	0.95
CRP on day 2, mg/dL	10.8 ± 5.6	14.1 ± 5.7	0.02*
CRP on day 7, mg/dL	4.6 ± 2.5	7.3 ± 4.0	< 0.001*
WBC on day 1, $\times 10^3$ cells/μL	10.4 ± 3.0	10.8 ± 3.6	0.62
WBC on day 2, $\times 10^3$ cells/μL	13.3 ± 4.0	14.3 ± 4.7	0.34
WBC on day 7, $\times 10^3$ cells/μL	8.8 ± 3.1	9.2 ± 4.4	0.67
Lactate, mmol/L	3.42 ± 2.0	3.88 ± 2.1	0.35
Cardiac index, L/min/m^2	2.4 ± 0.5	2.5 ± 0.5	0.65
Catecholamine Index	4.4 ± 4.0	6.7 ± 5.3	0.04*
Incidence of Af, *n* (%)	10 (28)	16 (44)	0.22
Hospital mortality, *n* (%)	0 (0)	1 (3)	> 0.99

Patients were stratified according to the approach for glucose control (closed-loop device vs. conventional control). Continuous data are shown as mean ± standard deviation

Af atrial fibrillation, *CRP* C-reactive protein, *WBC* white blood cell

*$p < 0.05$

There was no significant difference in the incidence of Af within 1 week postoperatively (28 vs. 44%, $p=0.22$), average lactate levels (3.4 ± 2.0 vs. 4.1 ± 2.0 mmol/L, $p=0.14$), and average cardiac index (2.4 ± 0.5 vs. 2.5 ± 0.5 L/min/m^2, $p=0.65$). The catecholamine index in the closed-loop group was significantly lower than that in the conventional group (4.4 ± 4.0 vs. 6.7 ± 5.3, $p=0.04$). There was no significant difference between the groups regarding insulin use, minimum K levels, length of hospital stay, and hospital mortality (Table 2).

Discussion

We conducted the present retrospective study to evaluate the influence of glucose control using a closed-loop device on postoperative inflammation. Our findings indicated that glucose control using a closed-loop device is associated with decreased inflammation after cardiovascular surgery without increasing hypoglycemia risk. In addition, the incidence of postoperative Af in the closed-loop group tended to be lower than that in the conventional group.

The present study found that glucose management using a closed-loop device was associated with decreased CRP levels on PODs 2 and 7. Surgical stress evokes systemic inflammatory response and stress-induced hyperglycemia [9]. Hyperglycemia itself is associated with accentuated inflammation and oxidative stress. Previous studies reported that tight glucose control reduced inflammatory response and oxidative stress after cardiac surgery [6, 10]. Hasegawa et al. conducted a randomized controlled trial (RCT) to evaluate the influence of perioperative intensive insulin therapy (maintained at 100 mg/dL) on the inflammatory response in cardiac surgery with cardiopulmonary bypass [6]. This RCT revealed that serum levels of TNF-α, interleukin (IL)-6 and high-mobility group box 1 were lower in the intensive insulin therapy group than in the conventional group (glucose levels maintained at < 200 mg/dL) [6]. Vlasselaers et al. conducted another RCT to evaluate the influence of tight glucose control (levels maintained at 50–80 mg/dL) on the inflammatory response after neonatal cardiac surgery [9]. In this RCT, tight glucose control (maintenance at 180–215 mg/dL) was associated with lower levels of inflammation (IL-6 and IL-8, as well as CRP) than those noted in the control group [9]. Another prospective study revealed that IL-6 plasma concentration is elevated in the period between ICU admission and the morning after cardiac surgery, exhibiting a peak at ICU arrival [11]. Tight blood glucose control immediately after cardiac surgery might reduce peak cytokine levels and thus have a profound impact on inflammation levels later on, as reflected in our findings regarding the reduced CRP levels on PODs 2 and in patients who received closed-loop control of blood glucose immediately after surgery.

However, recent guidelines recommend that the target glucose levels should be maintained at 144–180 mg/dL, and not merely above 110 mg/dL [8]. Our present results

indicated that maintaining blood glucose levels within the target range of 110–180 mg/dL was indeed effective in reducing CRP levels after cardiac surgery. On the other hand, another RCT reported that the levels of CRP, IL-6, and oxidative stress markers were similar between the group with tight glycemic control (maintenance at 100–140 mg/dL) and the group with conventional control (maintenance at 141–180 mg/dL) [12]. Therefore, to reduce inflammatory response, it might be important to maintain glucose levels below 180 mg/dL.

A recent observational study reported that high glucose variability was associated with a higher incidence of surgical site infection and postoperative Af in cardiac surgery patients [13]. Another retrospective study revealed that increased perioperative glucose variability and not hyperglycemia was associated with increased risk of postoperative acute kidney injury in liver transplantation patients [14]. We found that the SD of glucose levels was lower in the closed-loop group than in the conventional group (21.8 vs. 36.6 mg/dL) and the incidence of postoperative Af in the closed-loop group tended to be lower than that in the conventional group (28% vs. 44%). A previous animal study reported that atrial inflammation was associated with Af duration [4]. These data suggested that glucose variability might affect inflammatory response. Our present findings taken together with those of a previous study suggest that the closed-loop device ensures small glucose variability [5]. Further RCTs are warranted to determine the effect of minimal glucose variability on inflammatory response and to analyze clinical outcomes such as the incidence of Af after cardiac surgery.

In this study, the average blood glucose levels and SD of blood glucose levels were lower in the closed-loop group than in the conventional group despite the fact that there was no significant difference between the groups regarding the amount of administered insulin. The closed-loop device evaluates blood glucose levels and recalculates the optimal infusion rate of glucose or insulin at 1-min intervals [5]. This fine adjustment might have allowed for better utilization of insulin within the body, thus contributing to improved glucose control without requiring a higher amount of infused insulin.

Our study had several limitations. First, this was a single-center retrospective study with a limited number of patients. Thus, multicenter studies are needed to confirm our results. Although we checked the medical records carefully, the incidence of Af might have been underestimated because of the retrospective design of the study. Second, cytokine levels were not measured in this study. Thus, we could not clarify the mechanism by which glycemic control using a closed-loop device decreases postoperative CRP levels. Finally, we only analyzed blood glucose levels during a very short period after cardiovascular surgery (namely from ICU admission until 9 a.m. on POD 1) which might limit the extrapolation of our conclusions regarding the superiority of closed-loop blood glucose control after POD 1.

Conclusion

Our results suggest that glucose control using a closed-loop device might decrease inflammation after cardiovascular surgery without increasing hypoglycemia risk.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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