Safety of intranasal insulin administration in patients undergoing cardiovascular surgery: An open-label, nonrandomized, dose-escalation study

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ABSTRACT

Objective: This study aimed to determine the maximum safe dose of intranasal insulin administration during cardiac surgery.

Methods: This open-label, Phase 1, single-center, dose-escalation clinical trial recruited patients scheduled to undergo elective cardiac surgery or major vascular surgery requiring cardiopulmonary bypass between February and September 2021. They were grouped into 5 dose-escalation cohorts and administered 0, 40, 80, 160, and 240 IU insulin (n = 6 in each group) via a metered nasal dispenser after the induction of general anesthesia. Blood samples were collected at 10-minute intervals for the first 60 minutes and at 30-minute intervals thereafter. Hypoglycemia was defined as a blood glucose level <70 mg/dL. Patient recruitment was terminated after hypoglycemia was observed in 2 patients in any of the groups.

Results: In total, 27 of 29 enrolled patients were administered intranasal insulin or saline. Hypoglycemia was not observed after the administration of intranasal insulin in the 0, 40, 80, or 160 IU groups; however, it was observed in 2 of 3 patients in the 240 IU group. The serum insulin concentration was elevated in the 160-IU group, but the C-peptide concentration was not elevated in any of the groups.

Conclusions: The administration of up to 160 IU intranasal insulin did not induce clinically significant hypoglycemia. However, 160 IU intranasal insulin should be administered cautiously because insulin can enter the systemic circulation in a dose-dependent manner. (JTCVS Open 2024;17:172-82)
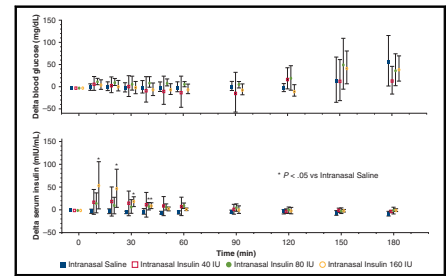
Blood glucose and serum insulin levels after intranasal insulin administration in cardiac surgery.

CENTRAL MESSAGE

Intranasal insulin administration delivers it primarily into the brain. The maximum safe dose during surgery is 160 IU. Higher doses can cause hypoglycemia due to absorption of insulin into the blood.

PERSPECTIVE

Intranasal insulin administration delivers insulin primarily into the central nervous system. Intranasal insulin is a promising new treatment for perioperative neurocognitive disorders, but its safety during surgery has not been well studied. This study provides important data on the maximum safe dose of intranasal insulin, which could help prevent hypoglycemia in patients undergoing cardiac surgery.

Abbreviations and Acronyms
BBB = blood–brain barrier
CPB = cardiopulmonary bypass
IL   = interleukin
CSF = cerebrospinal fluid
INI = intranasal insulin
PND = perioperative neurocognitive disorder
POD = postoperative delirium
TNF = tumor necrosis factor

📎 Supplemental material is available online.

Despite an increase in the perioperative risk profile in patients undergoing cardiac surgery, there has been a reduction in in-hospital mortality owing to the improvements made in the surgical technique, anesthetic monitoring, and therapeutic agents.[1] However, the incidence of perioperative neurocognitive disorders (PND),[2] including postoperative delirium (POD), delayed neurocognitive recovery, and postoperative neurocognitive disorders, remains a growing concern as more older adults are undergoing major surgical procedures.[3] Specifically, the incidence rate of PND after cardiac surgery is approximately 50%,[4] which is considerably higher than that after noncardiac surgeries.[3] POD leads to higher in-hospital morbidity and mortality rates, prolonged hospitalization, long-term cognitive deficits, and poor long-term outcomes.[3] The effectiveness of treating PND with pharmacologic agents remains inconclusive.[5]

Cerebral inflammation has been reported to be a possible pathogenic mechanism in the development of PND.[6] Anesthetic and surgical stress activate the immune system, leading to the release of proinflammatory mediators, such as chemokines and cytokines, and the activation of systemic immune cells. The blood–brain barrier (BBB) becomes permeable, which leads to endothelial dysfunction and infiltration of the peripheral cells into the brain tissue. The astrocytes and microglia within the central nervous system become activated and contribute to overall neural dysfunction, which affects cognitive and memory function.[7] Indeed, in neurodegenerative conditions, such as Alzheimer disease, the disruption of the immune system in the brain are also detected.[6]

Insulin receptors are expressed in the central nervous system, including the hippocampus. When insulin binds to its receptor, it regulates neuroplasticity through the phosphoinositide 3-kinase/protein kinase B signaling cascade. Indeed, increasing hippocampal insulin level has cognitive-enhancing effect.[8] In contrast, in patients with PND, deficits in hippocampal insulin receptor signaling has been observed.[9-11] Furthermore, patients with Alzheimer disease also have lower cerebrospinal fluid (CSF) insulin concentration levels in addition to insulin resistance.[7,11]

Intranasal insulin (INI), a relatively novel approach to treat cognitive dysfunction,[12] bypasses the BBB and results in the sustained elevation of insulin concentrations in the CSF without entering the circulation or exerting metabolic effects systemically.[13] An INI dose of 20 to 160 IU improves the memory performance and the metabolic integrity of the brain in patients with cognitive impairment.[7,11] Some experimental studies showed that, under anesthesia and/or in a surgical setting, INI administration prevents PND. These effects are attributed to cerebral anti-inflammatory activity and a reduction in tau protein levels via the phosphoinositide 3-kinase/protein kinase B signaling cascade in the hippocampus caused by elevated insulin levels in the CSF.[11,14,15]

Although a clinical study on POD in patients undergoing laparoscopic surgery showed that perioperative INI administration significantly reduced the incidence of delirium,[16] the sample size was small. Furthermore, no clinical studies on cardiac surgery have been reported. Given the dose-dependent effects of INI on the resting-state brain activity[17] and strong inflammatory response caused by cardiopulmonary bypass (CPB),[18] the maximum safe dose of insulin should be carefully defined for patients undergoing cardiac surgery. Because the administration of 40 and 80 IU INI during cardiac surgery in a Canadian population and 160 IU INI in conscious patients[19] did not induce hypoglycemia, we hypothesized that administering 160 IU INI during cardiac surgery would not induce hypoglycemia.

Therefore, in the present study, we aimed to determine the maximum dose of INI that does not induce hypoglycemia during cardiac surgery as well as measure the amount of insulin entering the systemic circulation. Furthermore, we evaluated the incidence of POD and other postoperative complications in these patients.

METHODS
Study Design
We designed this prospective, single-center, open-label, nonrandomized, dose-titration, Phase 1, dose-escalation study to confirm the safety and tolerability of INI administration during cardiac and major vascular surgeries requiring CPB.

Ethical Approval
This study was approved by the Research Ethics Board of the University of Yamanashi Hospital (approval No. S0004) on December 28, 2020. The study was performed in accordance with the Transparent Reporting of Evaluations with Nonrandomized Design guidelines. Written informed consent for publication of study data was obtained from all patients. This trial was registered in the Japan Registry of Clinical Trials before patient enrollment on January 6, 2021 (jRCTs031230047).

Patient Population
This study was conducted at the University of Yamanashi Hospital (Yamanashi, Japan) between February 3, 2021, and September 30, 2021.
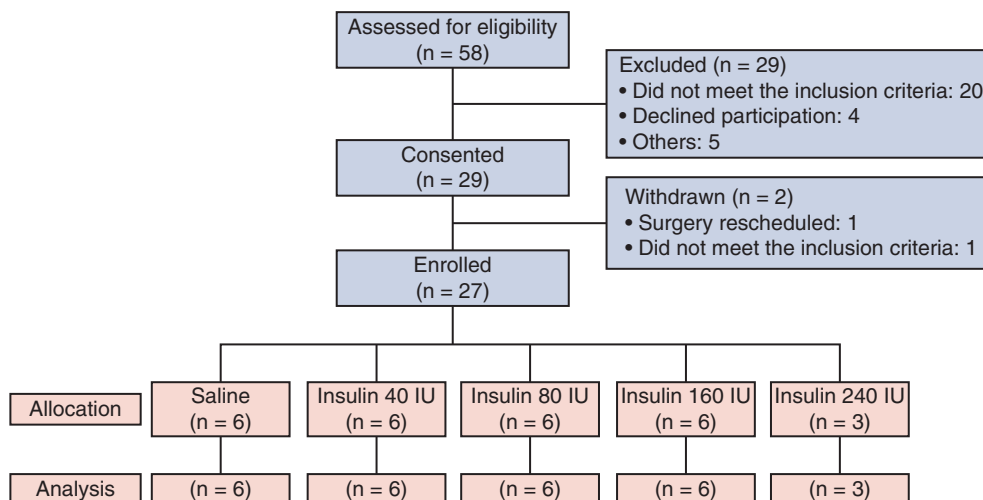
FIGURE 1. Consolidated Standards of Reporting Trials flow diagram.

Patient recruitment was performed after screening and verifying patient eligibility.

Inclusion/Exclusion Criteria

Patients aged 20 years and older who were scheduled to undergo elective cardiac surgery or major vascular surgery requiring CPB were eligible for inclusion in this study. The exclusion criteria were as follows: a history of nostril surgery, severe psychiatric disorder, liver dysfunction, infectious diseases, stroke, pituitary dysfunction, or adrenal insufficiency; a preoperative minimental state examination score[20] <24; planned use of drugs that affect glucose levels, such as insulin, steroids, glucose solution (except for crystalloid with 1% glucose continuous intravenous infusion), and epinephrine before 2 hours of entering the operating room and during the first 2 hours of surgery; allergy to insulin; serum creatinine levels of 132.6 mmol/L (>1.5 mg/dL); and baseline blood glucose concentrations <90 mg/dL (5.0 mmol/L).

Study Procedure

Sample size/patient allocation. Six patients were initially allocated to the saline (control) group; thereafter, 6 patients each were nonrandomly assigned to the 40, 80, 160, and 240 IU treatment groups in a sequence. Patient recruitment was terminated if hypoglycemia was observed in 2 patients in any of the treatment groups after INI administration. The investigators who collected the blood samples and assessed POD and the surgeons, anesthesiologists, and perfusionists involved in providing intraoperative clinical care were not blinded to the group allocation. The study design was based on a 3 + 3 design (3 patient cohorts) to determine the maximum tolerated dose. The number of patients per group was set to 6 because we judged that 3 patients per group were insufficient to evaluate the incidence of hypoglycemia after INI administration.[21]

Intervention and follow-up. Insulin (Humulin R) and normal saline were purchased from Eli Lilly and Terumo (Tokyo, Japan), respectively. The vials were refrigerated at 4 °C in our department. The intervention performed in this study was the administration of a single dose of INI. The investigator prepared the study drug in a spray bottle immediately before anesthetic induction.

Intraoperative care. The use of oral hypoglycemic drugs was discontinued 12 hours before the surgery. A subcutaneous sliding-scale insulin regimen was used in patients at risk of developing hyperglycemia (180 mg/dL [>10 mmol/dL]) or hypoglycemia (<70 mg/dL [<3.9 mmol/dL]) before surgery in patients with diabetes. Standard anesthesia monitors[22] were supplemented with central venous or pulmonary artery catheters and transesophageal echocardiography. Midazolam, propofol, sevoflurane, rocuronium, remifentanil, and fentanyl were administered for the induction and maintenance of anesthesia. The inhaled oxygen concentration was adjusted to range between 40% and 100% based on the surgical procedure and blood oxygen saturation. Ringer's acetate with 1% glucose and Ringer's bicarbonate were used as intravenous fluids. Systolic blood pressure was maintained at 100 mm Hg before and after CPB, with the mean arterial pressure maintained at 50 and 70 mm Hg during CPB using norepinephrine (1-10 mg/kg/hour) as a vasopressor as needed. The body temperature was maintained at 32 to 36 °C during cardiac surgery and at 22 to 32 °C during major vascular surgery and CPB. Red blood cells were administered when the hematocrit value was <25%. Heparin, the dose of which was guided by the HMS plus (Medtronic Japan), was administered intravenously before CPB, followed by additional doses, if necessary, to maintain an activated clotting time >480 seconds. Protamine, the dose of which was also guided by the HMS plus, was administered after complete separation from CPB. Subsequently, 10 to 15 mL/kg of the cardioplegia solution, 1% of glucose, 1% of sodium bicarbonate, 8.5 mEq/L potassium, and 10 mg/L adenosine were administered for the induction and maintenance of cardiac arrest.

If the blood glucose concentration was <70 mg/dL (3.9 mmol/L), 20 mL 50% glucose was administered, and a continuous glucose infusion was started at 20 mL/hour. If the blood glucose concentration was >180 mg/dL (10.0 mmol/L), insulin infusion was initiated at 2 U/hour to maintain the blood glucose concentration between 70 and 180 mg/dL (3.9-10.0 mmol/L).

Measurements and Data Handling

INI administration and glucose measurement protocol. Arterial whole-blood samples were drawn from a catheter placed in the radial artery. The baseline blood glucose concentrations were measured immediately after the placement of the arterial catheter. After tracheal intubation under general anesthesia, saline (0.4 mL) or 40 IU (0.4 mL undiluted insulin), 80 IU (0.8 mL undiluted insulin), 160 IU (1.6 mL undiluted insulin), or 240 IU insulin (2.4 mL undiluted insulin) (Humulin R) was administered via a metered nasal dispenser (AS ONE Corporation). The investigator who prepared and administered the drug was not involved in the induction or maintenance of general anesthesia.

Arterial blood samples (2.5 mL) were collected every 10 minutes during the first 60 minutes following the drug administration and every 30 minutes thereafter until the end of the surgery. Intravenous insulin was administered to correct hyperglycemia.

The glucose concentrations were analyzed immediately after blood sampling using the StatStrip Xpress glucose meter (Nova Biomedical).

TABLE 1. Patient characteristics

Characteristic	Insulin dose (IU)				
	0	40	80	160	240
Age (y)	62 (12)	73 (11)	75 (11)	69 (10)	65 (5)
Male/female	5/1	5/1	3/3	5/1	2/1
Height (cm)	166 (4)	161 (7)	155 (10)	163 (6)	161 (7)
Weight (kg)	66 (9)	62 (21)	56 (13)	64 (16)	72 (19)
BMI	24 (3)	24 (7)	23 (4)	24 (5)	28 (8)
Hct (%)	43 (3)	39 (11)	41 (4)	41 (4)	41 (1)
ALT	25 (8)	19 (17)	23 (12)	18 (9)	18 (5)
Cr (mg/L)	0.84 (0.24)	1.05 (0.18)	1.11 (0.19)	1.03 (0.22)	0.72 (0.15)
LVEF (%)	66 (16)	59 (18)	63 (13)	62 (9)	56 (6)
Comorbidity					
DM	2	3	5	1	2
HT	2	4	5	5	1
Af	0	0	2	1	0
DLP	0	0	3	2	2
Smoking	3	2	2	4	2
COPD	0	2	2	1	0
Second operation	1	0	0	0	0
PVD	1	1	0	0	0
Procedures	6	6	6	6	3
Valve	1	2	2	3	2
CABG	1	2	2	2	1
Valve + CABG	1	1	1	1	0
Major vascular	2	1	0	0	0
Others	1	0	1	1	0
Operation time (min)	423 (110)	412 (136)	339 (58)	278 (22)	390 (21)
Anesthesia time (min)	508 (100)	492 (153)	429 (74)	373 (26)	485 (40)
CPB time (min)	246 (97)	221 (85)	149 (49)	141 (18)	216 (48)
Ao clamp time (min)	122 (26)	140 (64)	90 (43)	86 (28)	146 (40)
Estimated blood loss (mL)	3161 (1844-3656)	1001 (887-2455)	888 (803-956)	801 (386-1245)	1028 (913-1257)
Blood product transfusion (mL)	1440 (70-2960)	2080 (1900-2110)	1260 (240-2340)	1120 (260-1650)	1520 (760-2045)
RBC (mL)	840 (70-1400)	1120 (1120-1330)	660 (120-1260)	700 (140-840)	840 (420-980)
FFP (mL)	600 (0-1560)	840 (720-960)	600 (120-900)	420 (90-840)	480 (240-840)
PLT (mL)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	200 (100-225)

Values are presented as mean ± SD, median (interquartile range), or n (%). *BMI*, Body mass index; *Hct*, hematocrit; *ALT*, alanine aminotransferase; *Cr*, creatinine; *LVEF*, left ventricle ejection fraction; *DM*, diabetes mellitus; *HT*, hypertension; *Af*, atrial fibrillation; *DLP*, dyslipidemia; *COPD*, chronic obstructive pulmonary disease; *PVD*, peripheral vascular disease; *CABG*, coronary artery bypass graft; *CPB*, cardiopulmonary bypass; *Ao*, aortic; *RBC*, red blood cell; *FFP*, fresh frozen plasma; *PLT*, platelet.

The serum insulin and C-peptide levels were measured by SRL Inc. The blood samples were collected in tubes containing clotting activators for serum isolation (Venoject 2; Terumo Corporation). The tubes were centrifuged at 1500 × g for 15 minutes at 4 °C. The serum was transferred into a microtube without any additives and stored at −80 °C. A cooler box containing dry ice was used for the transportation of the tubes to the SRL Inc.

Postoperative data. Blood samples (5 mL) were collected immediately before the surgery and on postoperative days 1 and 7 to measure the concentrations of inflammatory cytokines such as interleukin (IL) 1 beta, IL-6, and tumor necrosis factor alpha (TNF-α). These parameters were also measured by SRL Inc.

Primary and secondary outcomes. The primary outcome assessed in this study was whether INI administration induces hypoglycemia

<3.9 mmol/L (70 mg/dL) during surgery. The secondary outcomes included the intergroup differences in changes in blood glucose concentrations 30 and 40 minutes after INI administration, because 30 minutes was the previously reported time for the peak effect of INI.[23,24] Furthermore, serum insulin and C-peptide concentrations at 10, 20, 30, and 40 minutes after INI administration; IL-1β, IL-6, and TNF-α concentrations on postoperative days 1 and 7; and the incidence of postoperative complications, including the incidence of POD, liver dysfunction (alanine aminotransferase levels 2-fold higher than the upper limit of the normal range within 7 postoperative days[25]), renal dysfunction (≥26.5 μmol/L [≥0.3 mg/dL] serum creatinine increase),[26] myocardial failure (cardiac index <1.8 L/min/m^2 and mixed venous saturation <55% despite adequate fluid replacement and high-dose inotropic support
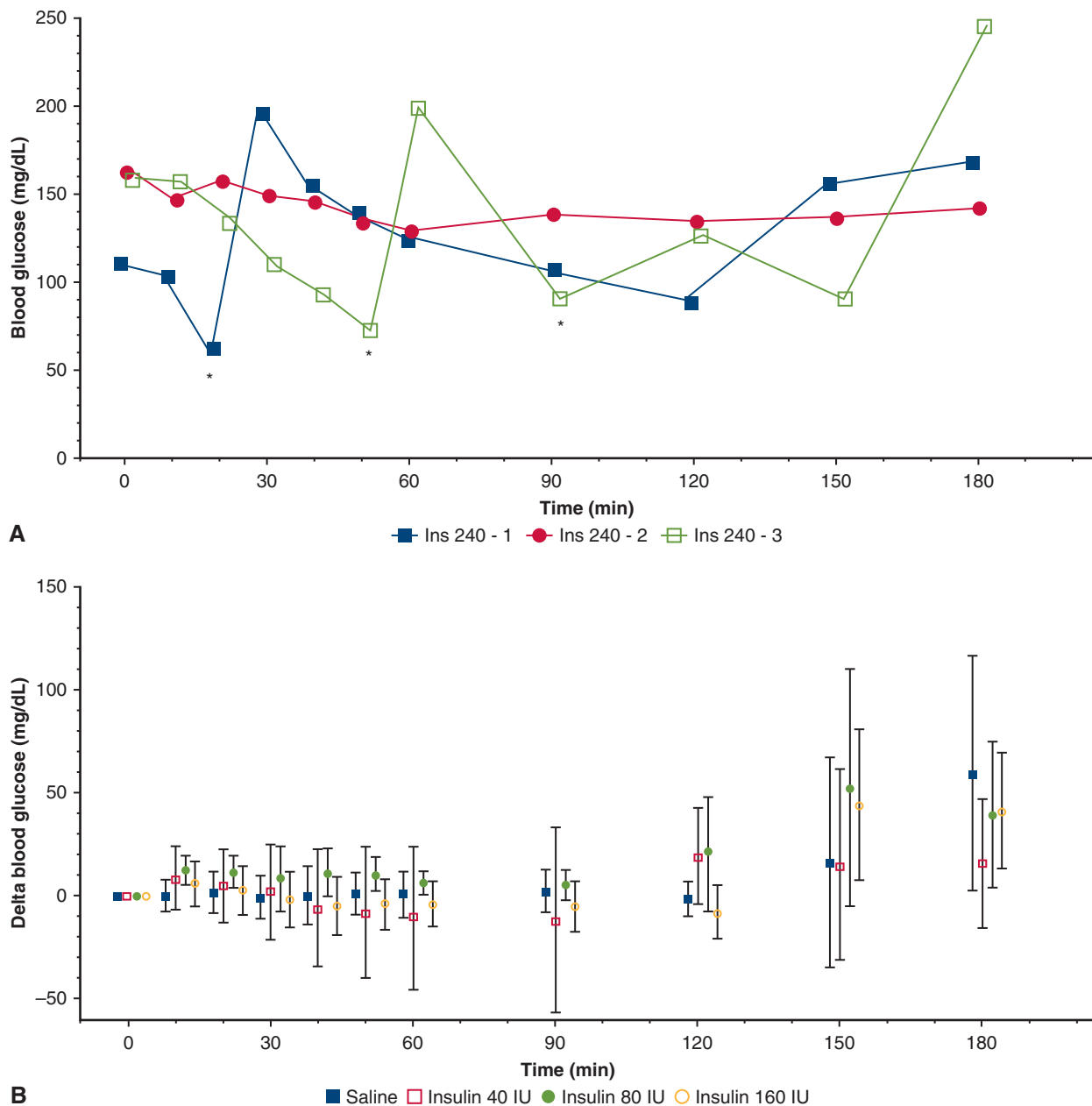
FIGURE 2. A, Blood glucose concentrations in the 240 IU insulin group. B, Changes in blood glucose concentrations. Error bars represent the SD in delta blood glucose concentrations (n = 6 in each group). *Intravenous administration of 20 mL 50% glucose.

requiring intra-aortic balloon pump, right and/or left ventricular assist device, and/or extracorporeal mechanical oxygenation after separation from CPB),[27] infection (severe sepsis, pneumonia requiring mechanical ventilation, and deep sternal wound infection),[19] and arrhythmias requiring treatment as well as death within 7 postoperative days were assessed.

Assessment of POD. POD was assessed and recorded using the Confusion Assessment Methods for the Intensive Care Unit[28] once daily for 3 postoperative days. The incidence of delirium was calculated based on the number of patients with at least 1 recorded episode of delirium.

Statistical Analyses

The patient characteristics are presented as mean ± SD or median (interquartile range) for continuous variables and counts (percentages) for categorical variables. The mean changes in serum concentrations in the treatment and control groups were compared using the t test. The blood glucose, serum insulin, and C-peptide concentrations after INI administration were excluded from the analysis. All statistical analyses were performed using SAS version 9.4 (SAS Institute). All reported P values were 2-sided.
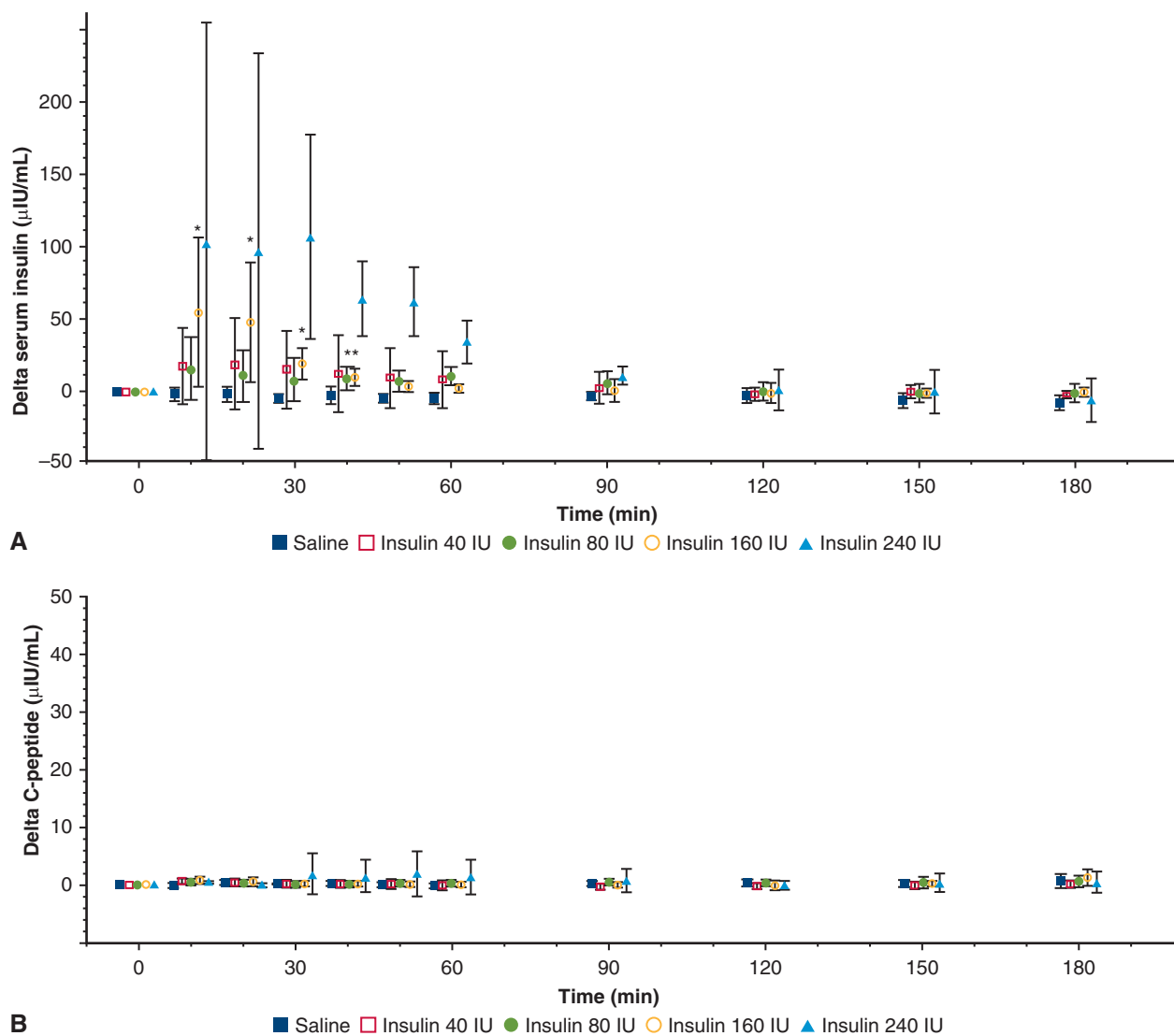
FIGURE 3. A, Changes in serum insulin concentrations. Error bars represent the SD in delta blood glucose concentrations (n = 6 in the saline, 40, 80, and 160 IU groups; n = 3 in the 240 IU group). B, Changes in serum C-peptide concentrations. Error bars represent the SD in delta blood glucose concentrations (n = 6 in the saline, 40, 80, and 160 IU groups; n = 3 in the 240 IU group). *$P < .05$ versus saline group.

RESULTS

Study Population and Primary Outcome

Of the 27 patients included in the study (Figure 1), 13 (48%) had type 2 diabetes mellitus. Patient characteristics are presented in Table 1. No patients received subcutaneous insulin infusion or glucose infusion within 2 hours before entering operating room.

Hypoglycemia was not observed following INI administration in the 40, 80, and 160 IU groups, but 2 of 3 patients in the 240 IU group developed hypoglycemia following INI administration (Figure 2, A). These patients received glucose solution intravenously at the earliest, and patient recruitment was terminated at this point, as planned.

Secondary Outcomes

For up to 160 IU INI, glucose concentrations at 30 and 40 minutes after insulin administration were not significantly lower than those after saline administration (Figure 2, B). There were time course changes in the serum insulin and C-peptide concentrations (Figure 3). The insulin concentration in the 160 IU group was significantly higher than that in the saline group (Figure 3, A); however, the changes in the C-peptide concentration were similar (Figure 3, B).

The changes in IL-6 and TNF-α levels did not differ significantly between the treatment and saline groups (Figure 4). The changes in IL-1β concentrations were not
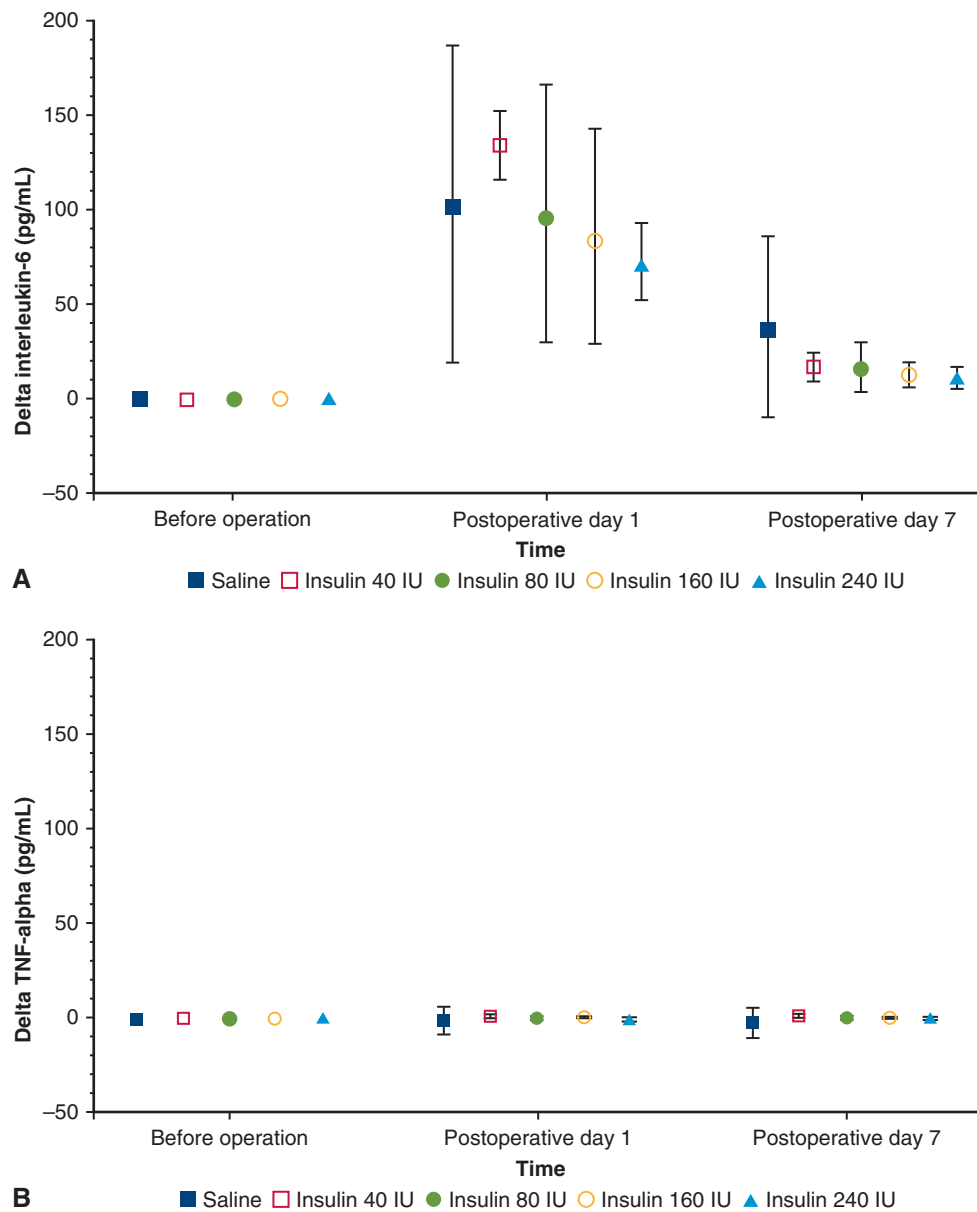
FIGURE 4. A, Changes in serum interleukin-6 concentrations. Error bars represent the SD in delta blood glucose concentrations (n = 6 in the saline, 40, 80, and 160 IU groups; n = 3 in the 240 IU group). B, Changes in serum tumor necrosis factor alpha (*TNF-α*) concentrations. Error bars represent the SD in delta blood glucose concentrations (n = 6 in the saline, 40, 80, and 160 IU groups; n = 3 in the 240 IU group).

compared between the groups because most of the IL-1β concentrations were below the detection limit.

POD was observed in 2 patients each in the saline and 160 IU insulin groups. No insulin-related complications, except for 2 cases of hypoglycemia, were observed. Table 2 presents the number of complications observed in each group. Recurrent nerve palsy, facial nerve palsy, postoperative ileus, and pulmonary hemorrhages were observed; however, causal relationships between these complications and INI administration could not be determined.

DISCUSSION

In this prospective study, intraoperative administration of 40 to 160 IU INI did not induce clinically significant hypoglycemia in patients who underwent cardiac and major vascular surgery, and this result is consistent with the findings in conscious patients (Figure 5).[12] However, hypoglycemia was observed after the administration of 240 IU INI, and this was attributed to the absorption of insulin into the bloodstream. Serum insulin concentrations were increased to approximately 50 and 100 mIU/mL at 10 minutes after administering 160 and 240 IU INI, respectively,

TABLE 2. Incidence of postoperative complications within 7 postoperative days

Complication	Insulin dose (IU)				
	0	40	80	160	240
Number	6	6	6	6	3
Liver dysfunction	1	1	4	3	3
Renal dysfunction	1	3	0	1	0
Cardiac failure	0	0	0	0	0
Infection	1	0	0	1	0
Arrhythmia	2	4	3	1	2
Death	0	0	0	0	0

without any change in the plasma C-peptide concentration (Figure 5).

In a previous clinical study, the repeated administration of 20 IU INI reduced the incidence of POD in patients undergoing laparoscopic radical colectomy (insulin group, 12.5% vs control group, 47.5%; $P = .001$).[16] In an abdominal surgery rat model, INI administration in aged rats for 3 days after surgery restored surgery-induced hippocampal neuroinflammation and hyperactivation of GSK-3β via insulin signaling and prevented cognitive impairment.[14] Similarly, INI improved cognitive function in an anesthesia exposure model.[15] Thus, the anti-inflammatory effects of the activation of insulin signaling may be effective in preventing PND. Based on the findings

of these studies, INI may prevent PND in patients undergoing cardiac surgery.

Studies on healthy participants indicated that CSF insulin concentrations increased within 7 minutes of INI administration, reached a peak after 30 minutes, remained high for more than 80 minutes,[11] and returned to baseline after 90 to 210 minutes.[23,24] and the systemic effects of INI are minimal[11]; 1% to 2% of insulin enters the peripheral circulation.[23] Because C-peptide is secreted in equimolar amounts in response to endogenous insulin,[29] in the present study we showed a dose-dependent increase in insulin entrance to the systemic circulation, leading to a decrease in blood glucose levels. Serum insulin concentrations after administering 160 IU INI were almost equivalent to those after administering 10 IU insulin subcutaneously, which increases the plasma insulin concentration[30] by 30 to 50 mIU/mL and decreases the blood glucose concentration by 20 to 50 mg/dL.[31,32] Thus, the risk of hypoglycemia cannot be ruled out after administration of 160 IU INI.

The amount of insulin that enters into the systemic circulation during surgery (serum insulin concentration was 15 mIU/mL at 10 to 30 minutes in the 40 and 80 IU groups, which was not significant in this study) was lower than that in conscious patients (an increase in plasma insulin concentrations of up to 25 mIU/mL 10 to 20 minutes after administering 25 IU INI); this decreased the circulating blood glucose concentration by 9 mg/dL (0.5 mmol/L) after 40 minutes.[23] The increase in BBB permeability and cerebral
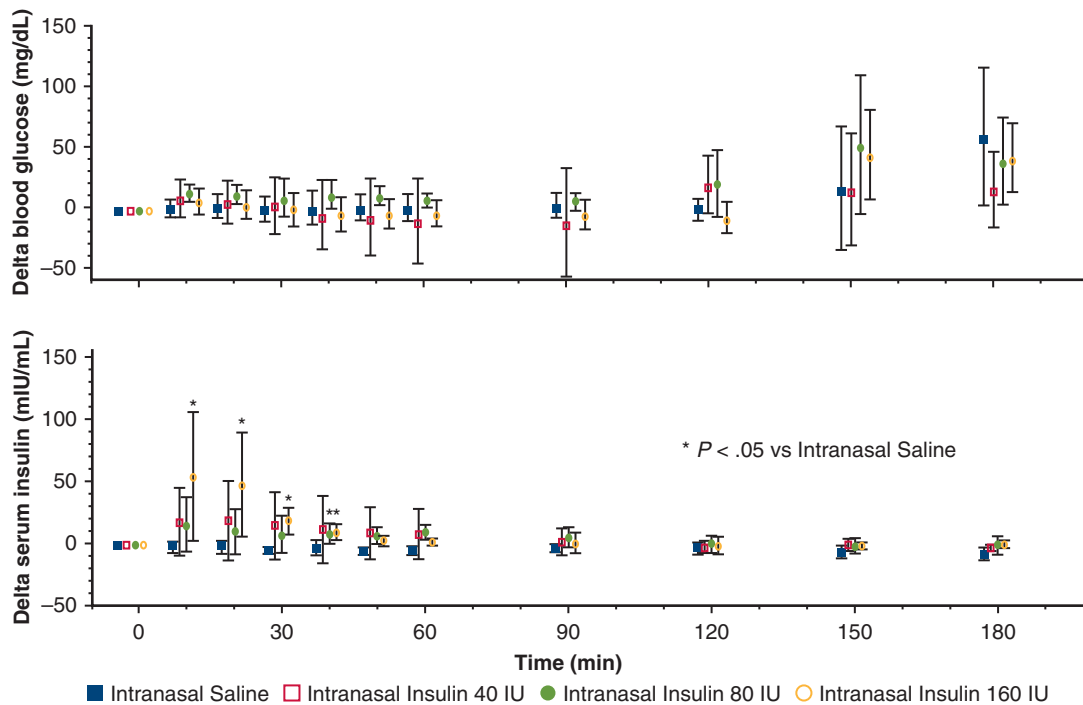

FIGURE 5. Changes in blood glucose and serum insulin concentrations. Error bars represent the SD in delta blood glucose concentrations (n = 6 in each group).
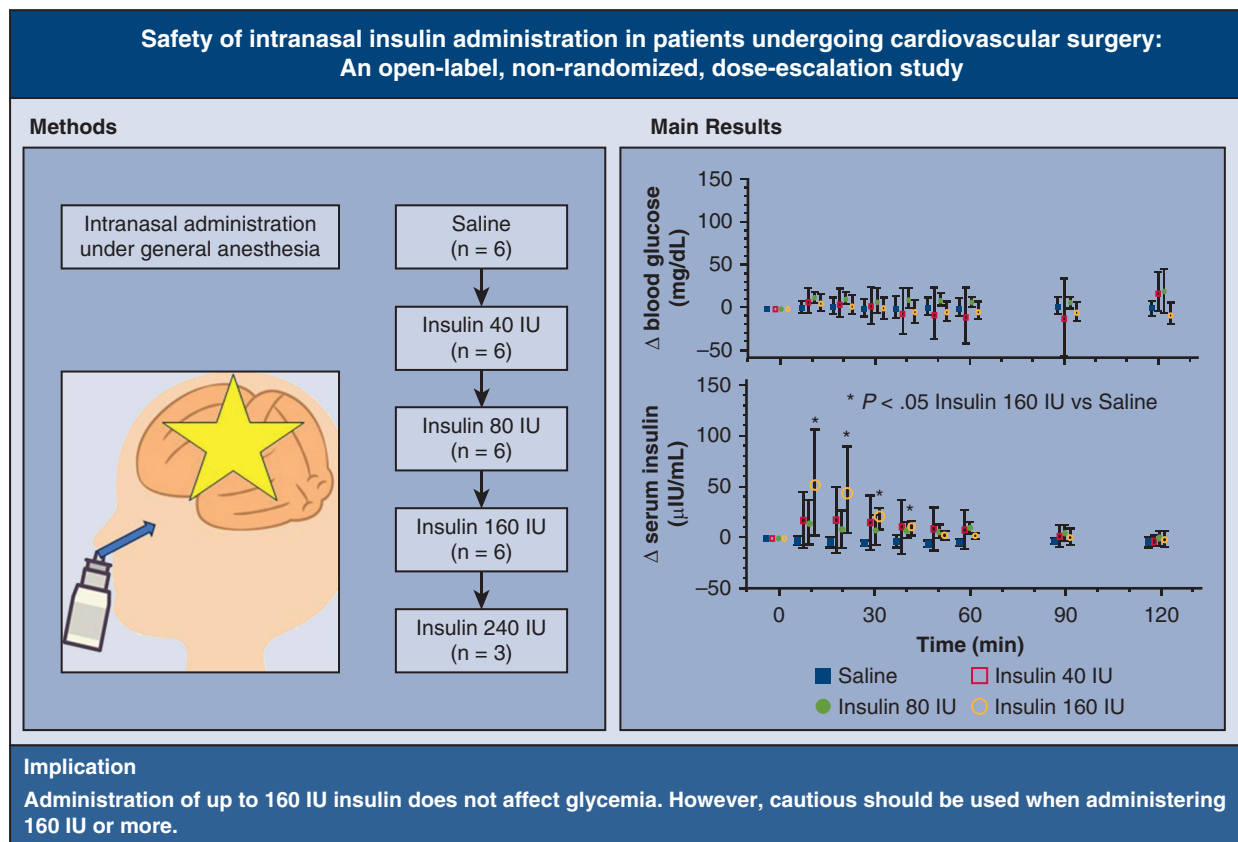
FIGURE 6. Pharmacokinetics of up to 160 intranasal insulin during cardiovascular surgery.

insulin uptake during general anesthesia may account for this discrepancy,[33] as discussed in our previous report.[19] However, the absorption of insulin into the bloodstream in Japanese patients appears to be higher than that observed in our previous study involving a Canadian population (an increase of approximately 5 mIU/mL after administering 80 IU INI to patients with diabetes).[19] This may be attributed to differences in the body surface area (1.61 ± 0.37 m^2 in the present study vs 1.93 ± 0.29 m^2 in the previous study).[19]

The differences in the postoperative inflammatory cytokine concentrations were not significant in the present study. The repeated administration of INI in patients undergoing abdominal surgery reduced the incidence of POD, indicating anti-inflammatory activity effects. However, changes in postoperative cytokine concentrations (IL-6, TNF-α, and IL-1β) in the control and insulin treatment groups were <10%.[16] A larger study is required to determine whether INI administration reduces cytokine concentrations in patients undergoing cardiac surgery. The concentrations of IL-1β in most samples were not sufficient

to be detected in this study. The IL-1 family is targeted in several conditions such as atherosclerosis and radiotherapy-induced arterial inflammation.[34] IL-1β blockers prevent the occurrence of myocardial infarction and cardiovascular death,[35] and IL-1β is considered an effective biomarker for atherosclerotic diseases. Overall, 37% of patients in this study underwent mitral valve surgery; thus, measuring the level of IL-1β may not be relevant in the present study.

This study had some limitations. First, the CSF insulin concentrations could not be measured in our patients, and it is not known whether or not insulin was taken up by the brain. However, INI dispensers, similar to those used in the present study, have been shown to be effective in delivering insulin to the brain in previous studies.[11] Second, because insulin sensitivity differs among individuals, and especially, because it is low in patients with type 2 diabetes, the difference might influence the decrease in blood glucose level. However, the average changes in blood glucose level 30 minutes after 80 IU INI intranasal saline were only −5 and 0 mg/dL, (patients without diabetes and those with

diabetes, respectively) in our previous study.[19] Third, delirium was evaluated only once daily using the Confusion Assessment Methods for the Intensive Care Unit. Although the overall incidence of POD in the present study was 33.3% (2 out of 6) and 9.5% (2 out of 21) in the saline and insulin treatment groups, respectively, the incidence has been underestimated. Detailed examination and a larger study cohort are required to detect the statistically significant effect of INI on POD. Forth, the sample size in this Phase 1 trial is too small to evaluate the occurrence of infrequent minor complications. Although the complications described in Table 2 were probably caused by the surgical stress response and not by insulin administration, a larger population is needed to determine the incidence of minor side effects such as burning sensation and epistaxis.[12]

CONCLUSIONS

The administration of INI doses of up to 160 IU before cardiac surgery does not cause significant hypoglycemia; however, its risk cannot be ruled under such conditions. It is metabolically safe to study the potential neuroprotective effects of up to 80 IU INI in patients undergoing cardiac and major vascular surgeries (Figure 6).

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling manuscripts for which they many have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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