Clinical Effectiveness of Intravenous Exenatide Infusion in Perioperative Glycemic Control after Coronary Artery Bypass Graft Surgery

A Phase II/III Randomized Trial

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ABSTRACT

Background: We aimed to assess the clinical effectiveness of intravenous exenatide compared to insulin in perioperative blood glucose control in coronary artery bypass grafting surgery patients.

Methods: Patients more than 18 yr old admitted for elective coronary artery bypass grafting were included in a phase II/III nonblinded randomized superiority trial. Current insulin use and creatinine clearance of less than 60 ml/min were exclusion criteria. Two groups were compared: the exenatide group, receiving exenatide (1-h bolus of 0.05 μg/min followed by a constant infusion of 0.025 μg/min), and the control group, receiving insulin therapy. The blood glucose target range was 100 to 139 mg/dl. The primary outcome was the proportion of patients who spent at least 50% of the study period within the target range. The consumption of insulin ($C_{insulin}$) and the time to start insulin ($T_{insulin}$) were compared between the two groups.

Results: In total, 53 and 51 patients were included and analyzed in the exenatide and control groups, respectively (age: 70 ± 9 *vs.* 68 ± 11 yr; diabetes mellitus: 12 [23%] *vs.* 10 [20%]). The primary outcome was observed in 38 (72%) patients in the exenatide group and in 41 (80%) patients in the control group (odds ratio [95% CI] = 0.85 [0.34 to 2.11]; $P = 0.30$). $C_{insulin}$ was significantly lower (60 [40 to 80] *vs.* 92 [63 to 121] U, $P < 0.001$), and $T_{insulin}$ was significantly longer (12 [7 to 16] *vs.* 7 [5 to 10] h, $P = 0.02$) in the exenatide group.

Conclusions: Exenatide alone at the dose used was not enough to achieve adequate blood glucose control in coronary artery bypass grafting patients, but it reduces overall consumption of insulin and increases the time to initiation of insulin.
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PERIOPERATIVE hyperglycemia is associated with an increased risk of complications in both diabetic and nondiabetic patients after cardiac surgery.[1–4] In studies performed in the early 2000s, intravenous (IV) insulin therapy was reported to achieve perioperative blood glucose control and to improve the outcome of critically ill or cardiac surgery patients.[2,5] These results have been clearly challenged by other, large randomized studies showing that the benefit of tight glycemic control could be strongly counterbalanced by the risk of severe insulin-related hypoglycemic events.[6–8] A recent network meta-analysis of 36 randomized trials comparing various insulin therapy protocols showed no mortality benefit of tight glycemic control in critically ill patients but a fivefold increase in hypoglycemia rate as compared to mild or very mild control. After cardiac surgery, both postoperative hyperglycemia and hypoglycemia were reported to be associated with an increased risk of major morbidity and mortality.[9] As a consequence, decreasing perioperative blood glucose values

What We Already Know about This Topic

- Exenatide is approved as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a biguanide, or a combination of metformin and a sulfonylurea, but have not achieved adequate glycemic control
- This study determined the clinical effectiveness of intravenous exenatide compared to insulin in perioperative blood glucose control in coronary artery bypass grafting surgery patients

What This Article Tells Us That Is New

- Exenatide alone at the dose used was not enough to achieve adequate blood glucose control in coronary artery bypass grafting patients, but it reduced overall consumption of insulin and increased the time to initiation of insulin

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below 150 mg/dl is no longer recommended, but this goal still requires both a close monitoring of blood glucose levels and multiple adaptations of insulin doses.[10] Therefore, the use of adjuvant hypoglycemic therapy able to simplify and improve glycemic control could be of great interest.

The glucagon-like peptide-1 (GLP-1) is an endocrine and paracrine incretin peptide hormone delivered by the enteroendocrine L-cells of the intestine, directly stimulated by the meal.[11] GLP-1 has insulinomimetic and insulinotropic effects, enhancing the glucose-dependent induced α-pancreatic secretion of insulin and inhibiting the β-pancreatic secretion of glucagon.[11–13] The antihyperglycemic effect of GLP-1 decreases when the blood glucose value approaches normal levels and disappears altogether when blood glucose is less than 3.9 mmol/l.[14] GLP-1 infusion could be effective in perioperative glycemic control after cardiac[15–20] and noncardiac[21] surgery and to reduce glycemic variability in critically ill patients, without hypoglycemia reported.[22] However, GLP-1 is not currently available for clinical use and remains a drug exclusively produced for experimental use.

Exenatide is a GLP-1 analog that shares the same glucose-dependent antihyperglycemic effect by acting as an agonist of the GLP-1 receptor but has a longer duration of action by resisting to degradation by dipeptidyl peptidase.[11,23] Subcutaneous exenatide, administered either as monotherapy or as a part of combination therapy with other antidiabetic agents, was reported to be effective and safe for patients with type 2 diabetes mellitus.[24–26] In a before-and-after pilot study, Abuannadi *et al.*[27] reported that IV exenatide infusion could be effective to control hyperglycemia in a cardiac intensive care unit, without any iatrogenic hypoglycemia. To date, no study has been specifically conducted to investigate the efficacy and the safety of IV exenatide in glycemic control after cardiac surgery. The ExSTRESS (exenatide for stress hyperglycemia) study was designed to test the hypothesis that IV exenatide had a higher clinical effectiveness than a validated IV insulin protocol for perioperative glycemic control after coronary artery bypass graft surgery (CABG).

Materials and Methods

Study Design

The ExSTRESS study was a single-center, nonblinded, parallel-group, phase II/III, randomized superiority trial conducted between January and December 2015 in the cardiac surgery intensive care unit of the University Hospital of Besancon (Besancon, France). The study protocol was approved by the Institutional Review Board Comité de Protection des Personnes Est-II, University Hospital of Besancon (no. 09/503, Jean-Pierre Kantelip, M.D., Ph.D.) on November 25, 2010, and by the French National Health Products Safety Agency (Agence Nationale de Sécurité du Médicament, Saint-Denis, France) on July 11, 2013. It was registered in the European Union Drug Regulating Authorities Clinical Trials (EudraCT no. 2009-009254-25 A) on January 6, 2009, and on www.ClinicalTrials.gov (identifier NCT01969149; principal investigator, Guillaume Besch, M.D.) on January 7, 2015. The study was conducted in accordance with the French bioethics law (Art. L. 1121-1 of the law no. 2004–806, August 9, 2004). This trial was overseen by an independent data safety monitoring board. The full trial protocol is available on request to the corresponding author.

Study Population

All consecutive patients undergoing elective CABG were eligible. Exclusion criteria were age less than 18 yr, inability or refusal to provide informed consent, pregnancy and/or breastfeeding, emergency surgery (defined as operation before the next working day after decision to operate), valve replacement, thoracic aortic surgery, type 1 or insulin-requiring type 2 (*e.g.*, current insulin use) diabetes mellitus, preoperative fasting blood glucose more than 300 mg/dl (16.5 mmol/l), glycosylated hemoglobin more than 8%, estimated creatinine clearance using Modification of Diet in Renal Disease formula[28] less than 60 ml/min, American Society of Anesthesiologists physical status higher than III, diabetic ketoacidosis, diabetic nonketotic hyperosmolar coma, medical history of pancreatectomy, acute or chronic pancreatitis, contraindication to insulin lispro (Lilly, France), exenatide (AstraZeneca, United Kingdom), or human serum albumin solution (LFB Biomedicaments, France). Current or previous use of an oral antidiabetic drug was not a noninclusion criterion. All oral antidiabetic drugs were discontinued on the day of surgery. The patient was approached by an investigator at the end of the anesthetic consultation performed at least 2 days before surgery to assess eligibility and gave information orally and in writing about the study. The patient was included in the study after providing written informed consent to participate. Patients were also excluded if a valve replacement and/or thoracic aortic surgery was decided during CABG.

Anesthetic Management

Preoperative fasting was started at midnight the day before surgery. Oral premedication with hydroxyzine or alprazolam was prescribed 1 h before surgery. On arrival in the operating room, standard monitoring (General Electric Healthcare, USA) was set up. An 18-gauge catheter was placed in a left forearm vein, allowing perfusion of saline. After preoxygenation with 100% oxygen *via* a face mask (expiratory oxygen fraction more than 90%), anesthesia was induced, and the patient was intubated. The anesthetic protocol used to induce and to maintain anesthesia was left to the discretion of the anesthesiologist in charge of the patient. The depth of anesthesia was adjusted to maintain the bispectral index value (BIS VISTA; Aspect Medical System, Inc., USA) between 40 and 60. A nasogastric tube, a central venous catheter, an arterial line, and a 16- or 14-gauge peripheral venous catheter were inserted after induction of anesthesia and before incision.

Prophylaxis of postoperative nausea and vomiting, based on the predictive score described by Apfel *et al.*,[29] was prescribed according to the recommendations of the French Society of Anesthesia and Intensive Care. No intravenous glucose was administered intraoperatively in the absence of hypoglycemia (defined as less than 75 mg/dl [4.1 mmol/l]). Tranexamic acid (1.5 g before incision and 1.0 g before surgical wound closure) and antibiotic prophylaxis with cefuroxime (1.50 g before incision, reinjection at priming of extracorporeal circulation, and then 0.75 g every 2 h until end of surgery) or vancomycin 15 mg/kg during 1 h in case of allergy to cefuroxime were initiated before incision.

All patients were admitted postoperatively to the cardiac surgical intensive care unit. Sedation was stopped, and the patients were extubated as soon as possible, according to usual clinical criteria (*i.e.*, free of sedation, normothermic, fulfilling specified respiratory criteria). Intravenous glucose infusion was administered at a constant rate of 4.0 to 4.5 g/h, until oral feeding could be resumed. Postoperative analgesia consisted of an association of continuous IV infusion of remifentanil 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, continuous IV infusion of nefopam 120 mg/24 h, and IV paracetamol 15 mg/kg four times a day.

Randomization and Study Drug Administration

Patients included in the study were randomly assigned the day before CABG to either the control or exenatide group using an electronic process. A computer-generated permuted-block randomization list with varying block sizes (ratio 1:1, block size of 2 and 4) was implemented on the CleanWeb web-based system (Telemedicine Technologies, France) at the beginning of the study by an independent data manager and was not modified until the end of the inclusion period. The investigator entered data online regarding each patient to allow his inclusion, and the randomized treatment assigned to the patient was immediately provided to the investigator by the CleanWeb web server. Randomization was stratified according to the presence or absence of diabetes mellitus. The investigators were unaware of the randomization block size and could not anticipate the result of the randomization process because of varying block sizes. Randomization was stratified according to the presence or absence of diabetes mellitus. Because the primary outcome was based on an objective parameter, *i.e.*, blood glucose measurement, neither the patient nor the provider was blinded to the treatment allocation. The allocated group was recorded in the patient's medical file and available to all the caregivers in charge of the patient.

In the control group, blood glucose control was managed according to a validated and published dynamic insulin therapy protocol[30] (appendix 1), adapted from Goldberg *et al.*[31] and implemented in our cardiac surgical intensive care unit since December 2005. Hourly blood glucose measurement started with the incision. All blood glucose data were obtained from glucose meter readings (Optium Xceed; Abbott Diabetes Care, United Kingdom) measured from arterial blood samples taken from the arterial line. Glucose meters were calibrated monthly according to the manufacturer's specifications. The target blood glucose level was 100 to 139 mg/dl (5.5 to 7.7 mmol/l). Insulin (insulin lispro; Lilly,) 1 U/ml in a solution of saline was prepared by the nurse in charge of the patient. The insulin infusion started with the first blood glucose value more than 139 mg/dl (7.7 mmol/l). After an initial bolus of insulin based on the blood glucose value, the infusion rate was then adjusted based on three parameters: (1) the current blood glucose value, (2) the previous blood glucose value, and (3) the current infusion rate. If a stable blood glucose level, defined as 12 consecutive blood glucose values within the blood glucose target range, was obtained, blood glucose was checked every 3 h. However, hourly blood glucose monitoring was resumed if any of the following events occurred: (1) change in infusion rate of insulin, (2) change in clinical condition, or (3) initiation or cessation of vasopressor therapy or renal replacement therapy. When hypoglycemia occurred, the insulin infusion was stopped, and IV dextrose 30% was administered (10 ml if blood glucose was between 50 and 74 mg/dl [2.7 to 4.1 mmol/l] and the patient was asymptomatic; 20 ml if blood glucose was between 50 and 74 mg/dl [2.7 to 4.1 mmol/l] and the patient is symptomatic or if blood glucose was less than 50 mg/dl [less than 2.7 mmol/l]). The blood glucose value was checked every 15 min until blood glucose was more than 100 mg/dl (more than 5.5 mmol/l). The insulin infusion was resumed 1 h after the first blood glucose value more than 100 mg/dl (more than 5.5 mmol/l) at a lower rate (75% of the original rate if blood glucose was between 50 and 74 mg/dl [2.7 to 4.1 mmol/l] and 50% of the original rate if blood glucose was less than 50 mg/dl [less than 2.7 mmol/l]).

In the exenatide group, blood glucose control management was based on continuous IV infusion of exenatide (AstraZeneca, United Kingdom). To allow IV infusion, a mix of exenatide 0.2 μg/ml and human serum albumin 2 mg/ml in a solution of saline was prepared by the nurse in charge of the patient. A human serum albumin solution was added to the exenatide solution to avoid binding of the compound to the infusion material. The target blood glucose level was the same as in the control group (100 to 139 mg/dl [5.5 to 7.7 mmol/l]), and monitoring of blood glucose values was the same as in the control group. The IV infusion of exenatide started with the first blood glucose value of more than 139 mg/ml (7.7 mmol/l). After an initial bolus of 15 ml during the first hour, continuous infusion of exenatide was kept at a constant rate of 7.5 ml/h. This therapeutic regimen is the same as that used by Abuannadi *et al.*[27] in cardiac intensive care unit patients (ClinicalTrials.gov Identifier NCT00736229; Mid America Heart Institute Saint Luke's Health System, Kansas City, Missouri). It was the only IV exenatide infusion protocol published when this study started, and it was authorized by

the French Health Authorities for off-label use in the current ExSTRESS study. If blood glucose remained at more than 139 mg/ml (7.7 mmol/l) 3 h after the beginning of the exenatide infusion (time for onset of maximal action), the infusion of exenatide was maintained at the same rate, and an insulin infusion was added to the exenatide infusion. The insulin therapy was introduced according to the rules used in the control group. Standardized management of hypoglycemia in the exenatide group was detailed in the study protocol (appendix 2). In case of hypoglycemia, the infusion of exenatide was continued, the insulin infusion was stopped, and IV dextrose 30% was administered as in the control group. If hypoglycemia persisted 15 min after IV dextrose injection and insulin infusion discontinuation, the infusion of exenatide was also stopped. Exenatide and insulin infusions were resumed 1 h after the first blood glucose value of more than 100 mg/dl (more than 5.5 mmol/l), at a rate of 7.5 ml/h without any initial bolus and at 75% of the original rate, respectively. The infusion of exenatide was discontinued in case of persistent postoperative nausea or vomiting and/or diarrhea despite a well-conducted antiemetic (intravenous droperidol 0.625 mg every 6 h and intravenous ondansetron 4 mg every 8 h) and/or antidiarrheal (oral loperamide 2 mg every 8 h) treatments.

Depending on the patient's clinical condition, oral intakes were initiated as soon as possible postoperatively. The study period ended when either oral feeding was initiated (IV exenatide and/or IV insulin replaced by subcutaneous insulin), at 48 h after the incision (IV exenatide replaced by IV insulin if necessary), or if the patient was transferred to another unit. Insulin, exenatide, and human serum albumin were specifically labeled, delivered, and recorded by the Central Pharmacy Department of the University Hospital of Besancon (Besancon, France), according to the French regulation on drug delivery for clinical research.

Data Collected and Endpoint Measures

Demographic data, past medical history, American Society of Anesthesiologists physical status, and Euroscore value were recorded at inclusion. The dosing of glycosylated hemoglobin was part of the routine preoperative assessment of patients. Intraoperative data describing the surgical procedure and the anesthetic management were obtained from the computerized anesthesia monitoring sheet.

All blood glucose values measured during the 48 h after incision were collected. If the study period ended less than 48 h after incision, only the blood glucose values measured before insulin and/or exenatide was stopped were considered.

The primary endpoint was the percentage of patients who spent more than 50% of the study period within the blood glucose target range of 100 to 139 mg/dl (5.5 to 7.7 mmol/l). This endpoint was chosen because an association between spending more than 50% of the time within the blood glucose target range and improved survival with less organ failure in intensive care unit patients has previously been suggested.[32–34] To calculate the time spent in the target range, we considered only recorded values, without any data extrapolation between two successive measurements. The blood glucose level was considered to be within the target range during the interval of time following each blood glucose measurement between 100 and 139 mg/dl. The proportion of time spent within the blood glucose target range was the ratio of the cumulative duration of time interval spent within the target range on the duration of the study period.

Secondary endpoints were the quality and safety of blood glucose control, glycemic variability, and morbidity and mortality at 30 days. The quality of blood glucose control was assessed by the percentage of time spent in the blood glucose level target range (100 to 139 mg/dl), the average blood glucose value during the study period and under treatment (insulin or exenatide), the total dose of insulin infused during the study period and under treatment, the proportion of blood glucose values within the range of 80 to 139 mg/dl during the study period, the proportion of blood glucose values within the target range of 100 to 139 mg/dl under treatment, and the time from the first measured blood glucose value to introduction of insulin infusion. Evaluation of the safety of blood glucose control was based on the incidence of serious adverse events according to the U.S. Food and Drug Administration and the incidence of moderate (blood glucose less than 60 mg/dl [3.3 mmol/l]) and severe (blood glucose less than 40 mg/dl [2.2 mmol/l]) hypoglycemia. Because exenatide was used off-label, all adverse events occurring in the exenatide group were considered serious adverse events and were specifically declared within 24 h to the Pharmacovigilance Department of the University Hospital of Besancon (Besancon, France) and analyzed by the independent data safety monitoring board. The pancreatic lipase blood level was measured preoperatively and at 7 days after CABG to specifically assess the pancreatic toxicity of intravenous exenatide. Acute pancreatitis was defined as the combination of typical acute abdominal pain with an increase in pancreatic lipase blood level greater than three times the upper normal value. Glycemic variability was evaluated by the following: the SD of blood glucose during the study period and under treatment, the mean difference between each blood glucose value and 120 mg/dl (6.6 mmol/l) under treatment, the coefficient of variability (defined as [SD of blood glucose x 100]/average value of blood glucose) during the study period and under treatment, the glycemic lability index[35] during the study period and under treatment, and the glycemic penalty index[36] during the study period and under treatment. Morbidity events considered at 30 days were the duration of invasive mechanical ventilation, new onset atrial fibrillation, ventricular tachycardia or fibrillation, stroke, acute renal failure requiring dialysis, deep wound infection, and duration of hospital stay. The reliability of all data collected was assessed by an independent data manager at the end of the study.

Statistical Analysis

In phase II of the study, a two-step analysis plan including one planned interim analysis in accordance with the procedure described by O'Brien and Fleming[37] was performed. This allows starting phase III of the trial early or stopping the study early in case of extreme results while preserving the power of the study. Two groups of patients have been included to check whether the expected rate of the primary endpoint was the same as in the study that validated the insulin therapy protocol.[30] In this study, the expected rate of the primary endpoint in the control group was 50%. An absolute difference in the primary outcome of at least 10% was required to consider that IV exenatide could provide a clinically relevant benefit in CABG patients. Considering an α risk of 0.05, a β risk of 0.10, and a loss to follow-up rate of 10%, 55 subjects were required in each group.

The interim analysis was planned after the inclusion of 25 patients in each group. The threshold values of the interim analysis enabling early discontinuation of phase II for inefficiency (p_0) or sufficient clinical effectiveness (p_A) were equal to p_0 = 40% and p_A = 60%. The investigators were informed by the biostatistician whether the interim analysis could enable early discontinuation of phase II, but the value of the primary endpoint has not been communicated.

Based on the data from phase II, a reestimate of the number of subjects required for phase III was planned. On the basis of the relative values observed in each group, the demonstration of the superiority of the exenatide group compared to the control group in perioperative glycemic control appeared highly unlikely, whatever the number of patients included in a phase III. The decision to stop the study at the end of phase II for futility has been retained.

Qualitative variables are expressed as number (percentage) and continuous variables as mean ± SD unless otherwise stated. Comparisons between the control and exenatide groups were performed using the chi-square or Fisher exact tests for qualitative variables and the Student's *t* test for quantitative variables. Insulin-free survival curves were generated using the Kaplan–Meier method. Insulin-free survival was calculated as the time between the incision and the first insulin intake. The log-rank test was used to compare the two groups. According to the protocol, the time to initiation of insulin could not be less than 3 h after first intake of exenatide. Two supplementary sensitivity analyses were conducted. First, after subtracting 3 h for each patient in the exenatide group (the most conservative assumption), the insulin-free survival curves were compared again. Second, the time between the incision and the first blood glucose value above 139 mg/dl was calculated. The abnormal glycemia survival curves were compared between the two groups. The analysis was neither adjusted nor stratified on additional variables. No ancillary analysis was performed. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Inc., USA), and the significance level was fixed at 0.05.

Results

Population of the Study

In total, 297 patients were scheduled for CABG between January and December 2015, with 55 patients randomized to each group. In the control and exenatide groups, four and two patients were excluded after randomization, respectively. The reasons for exclusion are given in figure 1. These patients were not included in the analysis. In the control and exenatide groups, 51 and 53 patients, respectively, were analyzed. All these patients achieved the 48-h study period. Baseline demographic data and comorbidities were well balanced between the two groups (table 1). In the exenatide and control groups, 36 (68%) and 33 (65%) patients underwent on-pump CABG, respectively (P = 0.73). The mean duration of surgery and extracorporeal circulation was 252 ± 57 *versus* 239 ± 56 min (P = 0.25) and 81 ± 32 *versus* 72 ± 31 min (P = 0.27) in the exenatide and control groups, respectively. The mean daily glucose intake (control *vs.* exenatide: 1.62 ± 0.53 *vs.* 1.66 ± 0.57 g/kg, P = 0.70, on day 1; 1.18 ± 0.45 *vs.* 1.18 ± 0.50 g/kg, P = 0.97, on day 2) and the proportion of patients requiring the use of vasopressors (control *vs.* exenatide 20 [38%] *vs.* 19 [37%], P = 0.96, on day 1; 10 [19%] *vs.* 13 [25%], P = 0.42) did not significantly differ between the two groups during the first 48 h postsurgery. All patients requiring exenatide and/or insulin therapy were treated until 48 h after the incision.

Clinical Effectiveness of Intravenous Exenatide

In total, 2,309 and 2,174 blood glucose values were measured in the exenatide and control groups during the 48 h after incision, respectively. The time from incision to the first blood glucose value above 139 mg/dl did not differ significantly between the two groups (P = 0.24; fig. 2). In the exenatide and control groups, 38 (72%) and 41 (80%) patients achieved the target blood glucose (100 to 139 mg/dl) for at least half of the first postoperative 48 h (odds ratio [95% CI] = 0.85 [0.34 to 2.11]; P = 0.30; table 2). The percentage of time spent in the target range of 100 to 139 mg/dl did not significantly differ between the two groups (control *vs.* exenatide: 62 ± 14% [95% CI = 58 to 66] *vs.* 61 ± 14% [57 to 65], P = 0.75). Parameters reporting blood glucose control and glycemic variability during the first postoperative 48 h are presented in table 2. The proportion of blood glucose values within the target range of 80 to 139 mg/dl during the first postoperative 2 days, and the number of blood glucose values between 100 and 139 mg/dl under treatment did not significantly differ between the two groups (control *vs.* exenatide: 71 ± 15% [67 to 75] *vs.* 71 ± 14% [67 to 75], P = 0.70; and 63 ± 14% [59 to 67] *vs.* 61 ± 16% [57 to 66], P = 0.68). The number of modifications in the insulin infusion rate, reflecting the workload for the nurse, is reported in table 2. Data on insulin use in both groups are also presented in table 2. One (2%) patient in the exenatide group required neither insulin nor exenatide infusion during the study period (*vs.* 0 (0%) in the control group). Insulin-free survival

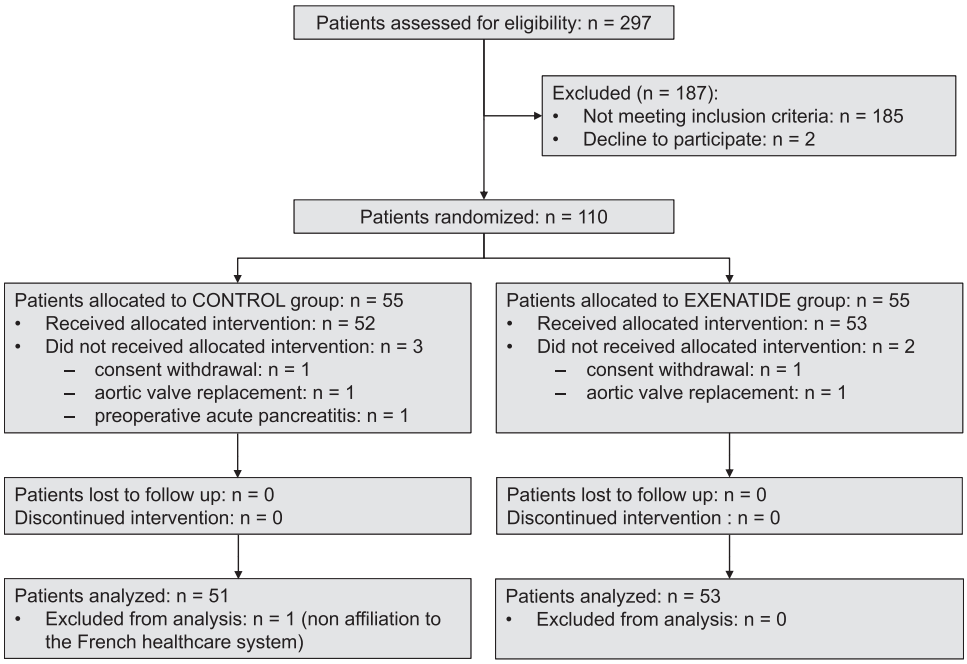

Fig. 1. Flow chart of patients' inclusions in the ExSTRESS (exenatide for stress hyperglycemia) study according to the CONSORT (Consolidated Standards of Reporting Trials) statement.

Table 1. Baseline Characteristics of Patients in the Control and Exenatide Groups

	Control Group (n = 51 patients)	Exenatide Group (n = 53 patients)	*P* Value
Age (yr)	68 ± 11	70 ± 9	0.23
Male sex	41 (80)	49 (92)	0.07
ASA physical status III	49 (96)	50 (94)	0.68
Predictive score for PONV > 2*	29 (56)	25 (48)	0.32
Medical history			
Smoking	27 (53)	30 (57)	0.71
Hypertension	36 (71)	33 (62)	0.37
Hypercholesterolemia	31 (61)	34 (64)	0.72
Obesity (BMI ≥ 30 kg/m^2)	12 (23)	9 (17)	0.41
Diabetes mellitus	10 (20)	12 (23)	0.70
Creatinine clearance (ml/min)	81 ± 12	83 ± 14	0.44
Fasting blood glucose (mg/dl)	117 ± 60	107 ± 25	0.27
Glycosylated hemoglobin (HbA1c) (%)	5.8 ± 0.6	6.1 ± 0.7	0.04
Euroscore	6.1 ± 2.7	6.4 ± 2.3	0.96
Left ventricular ejection fraction			0.13
< 30%	0 (0)	1 (2)	
30–50%	8 (16)	15 (29)	
> 50%	42 (84)	36 (69)	

Values are number (percentage) or means ± SD.

*The predictive score for postoperative nausea and vomiting is calculated according to Apfel *et al.*[29]

ASA = American Society of Anesthesiologists; BMI = body mass index (weight/height^2); PONV = postoperative nausea and vomiting.

was significantly longer in the exenatide group ($P < 0.0001$; fig. 3). This difference remained statistically different after subtracting 3 h for each patient in the exenatide group (the most conservative scenario).

Safety of Exenatide Infusion

Two (4%) patients in the exenatide group and one (2%) in the control group experienced moderate intraoperative hypoglycemia ($P = 0.58$), before the start of study drugs. No patient experienced moderate or severe hypoglycemia during IV exenatide or insulin administration (table 2).

Two patients in each group presented postoperative nausea and vomiting that disappeared after the administration of an antiemetic drug and did not require discontinuation of exenatide. Serious adverse events were declared in 5 (9%) and 5 (10%) patients in the exenatide and control groups,

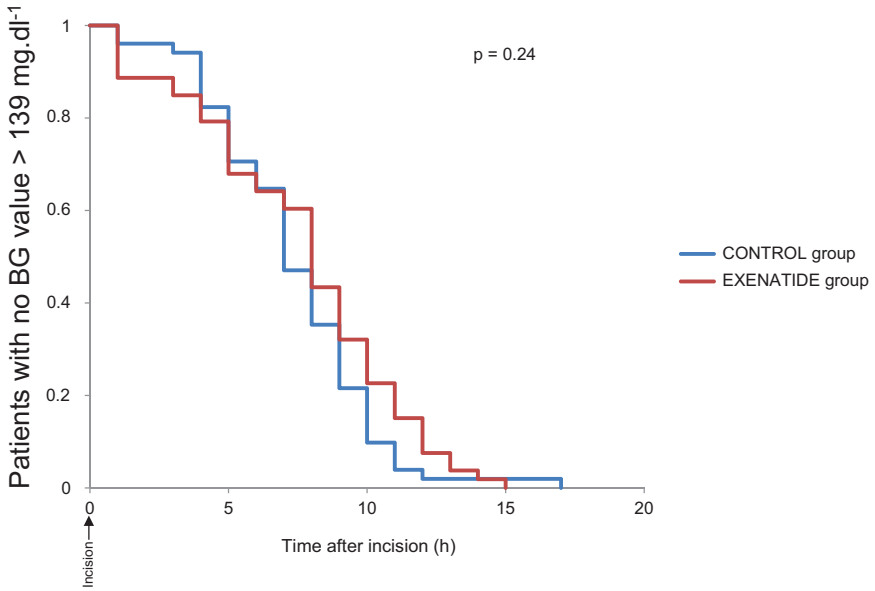

Fig. 2. Kaplan–Meier estimates of the proportion of patients with no episode of blood glucose (BG) of more than 139 mg/dl in the control and exenatide groups during the study period.

Table 2. Blood Glucose Control Parameters in the Control and Exenatide Groups

	Control Group (n = 51 patients)	Exenatide Group (n = 53 patients)	*P* Value
Primary outcome: At least 50% of study period within target glycemic range (100–139 mg/dl)	41 (80 [69; 91])	38 (72 [59; 84])	0.30
Secondary outcomes			
Quality and safety of BG control			
Mean BG value (mg/dl)*	125 ± 7 [123; 127]	125 ± 9 [123; 128]	0.93
Mean BG value under treatment (mg/dl)*	129 ± 8 [127; 132]	128 ± 9 [125; 130]	0.36
Moderate hypoglycemia†	1 (2)	2 (4)	0.58
Severe hypoglycemia§	0 (0)	0 (0)	
Glycemic variability			
SD of BG values (mg/dl)*	24 ± 7 [22; 26]	25 ± 7 [23; 27]	0.42
SD of BG values under treatment (mg/dl)*	22 ± 7 [20; 24]	24 ± 8 [22; 27]	0.18
Mean difference between each BG value and 120 mg/dl under treatment (mg/dl)*	19 ± 6 [17; 21]	21 ± 7 [19; 23]	0.36
Coefficient of variability of BG (%)*	18 ± 5 [16; 20]	20 ± 5 [18; 21]	0.36
Coefficient of variability of BG under treatment (%)*	17 ± 4 [16; 18]	19 ± 6 [17; 20]	0.08
GPI (%)*	25.6 ± 6.1 [23.9; 27.3]	25.1 ± 7.4 [23.1; 27.2]	0.74
GLI ((mmol/l)^2/h)*	0.028 ± 0.021 [0.023; 0.034]	0 028 ± 0.014 [0.024; 0.031]	0.84
GPI under treatment (%)*	28.2 ± 6.9 [26.3; 30.2]	26.4 ± 7.7 [24.2; 28.5]	0.20
GLI under treatment ((mmol/l)^2/h)*	0.023 ± 0.022 [0.017; 0.030]	0.025 ± 0.015 [0.021; 0.030]	0.62
Insulin consumption			
No insulin infusion during study period	0 (0)	5 (9)	0.06
Time to initiation of IV insulin (h)‖	7 [5–10] [7; 8]	12 [7–16] [9; 15]	0.02
Total dose of insulin infused (U)‖	92 [63–121] [81; 104]	60 [40–80] [49; 72]	< 0.001
Mean number of adjustments to the rate of insulin infusion per patient*	8 ± 4	6 ± 4	0.003

The values are numbers (proportion [95% CI]) unless otherwise indicated.

*The values are means ± SD [95% CI]. †Moderate hypoglycemia was defined as BG < 60 mg/dl. §Severe hypoglycemia was defined as BG < 40 mg/dl. ‖The values are medians [interquartile range] [95% CI].

BG = blood glucose; GLI = glycemic lability index calculated according to Ali *et al.*[35]; GPI = glycemic penalty index calculated according to Van Herpe *et al.*[36]; IV = intravenous.

respectively (odds ratio [95% CI] = 0.96 [0.21 to 4.47]; *P* = 0.95). All these events were common complications of CABG and were not related to the allocated treatment. One (2%) patient in the exenatide group and 3 (6%) in the control group had pancreatic lipase blood levels greater than three times the upper normal value (odds ratio [95% CI] = 0.31

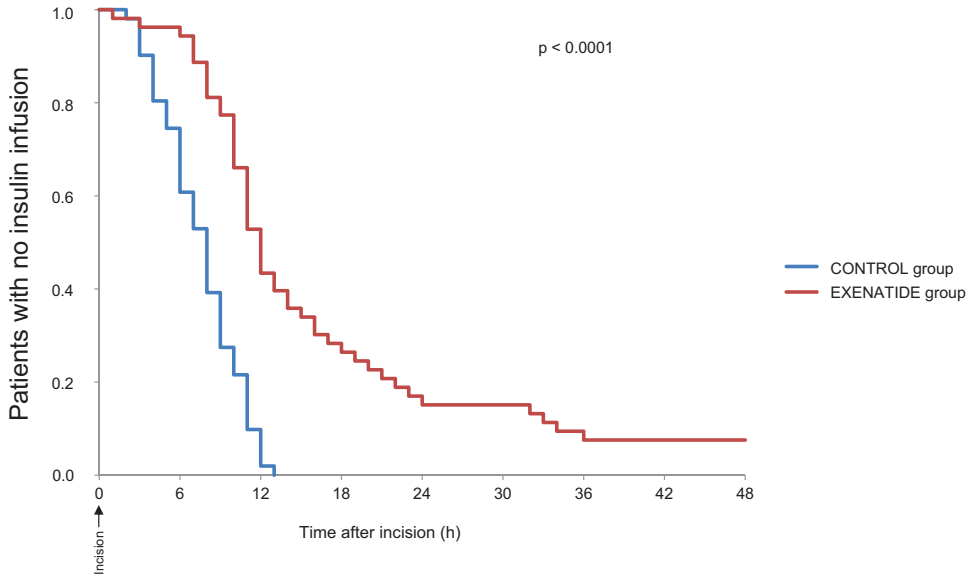

Fig. 3. Kaplan–Meier estimates of the proportion of patients who did not receive intravenous insulin infusion in the control and exenatide groups during the study period.

[0.00 to 4.03]; $P = 0.36$). None of these patients suffered from acute abdominal pain, and no case of acute pancreatitis was diagnosed. No exenatide-related adverse events were reported at 30 days. The postoperative complications and outcome at 30 days are reported in table 3.

Discussion

The results of this phase II, randomized, controlled study showed that IV exenatide provided safe but insufficiently efficient blood glucose control after CABG. Exenatide infusion reduced the total dose of insulin delivered and the number of modifications in the insulin infusion rate and delayed the start of insulin infusion. However, it did not improve the quality of blood glucose control and glycemic variability, and insulin therapy was required in most patients. The phase III study was stopped for futility.

Intravenous exenatide did not increase the percentage of patients who spent more than 50% of the study period within the target blood glucose range. The percentage of patients who spent more than 50% of the study period within the target range was considered to be the primary outcome of the present study because it has been associated with an improved outcome in intensive care unit patients.[32,33] Several reasons could explain the lack of clinical effectiveness of IV exenatide on the primary outcome in our study.

First, since blood levels of exenatide were not measured, it could not be ascertained that therapeutic concentrations of exenatide were achieved. However, IV exenatide allowed a reduction in the total dose of insulin used and delayed the initiation of insulin infusion. This suggests that the doses of exenatide we used provided a glucose-lowering effect. Furthermore, similar therapeutic regimens used in other studies resulted in exenatide concentrations efficient in lowering blood glucose levels.[14,38]

Second, the proportion of time spent within the blood glucose target range during the study period was higher in the two groups than in a previous assessment of this insulin infusion protocol.[30] In an audit of daily practices with the insulin therapy protocol in our cardiac surgical intensive care unit, conducted over the same period as the ExSTRESS trial, the proportion of patients spending at least half of the first 48 h

Table 3. Postoperative Outcomes at 30 Days in the Control and Exenatide Groups

	Control Group (n = 51 patients)	Exenatide Group (n = 53 patients)	*P* Value
Invasive mechanical ventilation (hours)*	9 ± 3 [8; 10]	10 ± 7 [8; 12]	0.26
Atrial fibrillation	10 (20 [10; 33])	12 (22 [12; 36])	0.70
Ventricular tachycardia/fibrillation	1 (2 [0; 10])	1 (2 [0; 10])	0.98
Dialysis	1 (2 [0; 10])	2 (4 [0; 12])	0.58
Stroke	0 (0)	2 (4 [0; 12])	0.16
Deep wound infection	3 (6 [1; 16])	0 (0)	0.11
Intensive care unit stay (hours)*	84 ± 33 [74; 93]	83 ± 40 [72; 94]	0.94
Hospital stay (days)*	9 ± 2 [8; 10]	10 ± 5 [8; 11]	0.56
Death	3 (6 [1; 16])	2 (4 [0; 12])	0.62

Values are numbers (proportion [95% CI]) or means ± SD [95% CI].

within the blood glucose range was 55% (unpublished data), *i.e.*, very close to the anticipated result in the control group. These data suggest a clinical trial effect that may have increased the quality of blood glucose control in the control group, thus minimizing the difference in effect between the two therapeutic strategies compared in the present study. Indeed, analysis of the control group allows stopping the study for futility at the end of phase II, even if the threshold required in the O'Brien and Fleming statistic plan analysis to conduct the phase III of the trial was reached in the exenatide group.

Third, although IV exenatide reduced the total dose of insulin and delayed the start of insulin infusion, most patients in the exenatide group received finally IV insulin as a rescue therapy. This may have decreased the differences in the quality of blood glucose control between the two groups. However, these results are consistent with previously published studies assessing the efficacy of GLP-1 agonists in blood glucose control in intensive care unit patients.[19,20,22,39] A sufficient antihyperglycemic effect of IV infusion of GLP-1 and exenatide alone was reported in only two studies.[21,27] In these studies, the relatively small sample size and the limitation of GLP-1 infusion to the first postoperative 8 h[21] and the inclusion of less severe patients[21,27] could partially explain the discrepancy with our results. Moreover, a rate of less than 40% of blood glucose values within the target range were reported when patients treated by exenatide were compared to those treated with insulin in the second study.[27] Although a reduction in insulin use and later initiation of insulin could have been anticipated in the exenatide group, these criteria were not chosen as primary outcomes in our study because they have not been related to major endpoints, such as morbidity or mortality.

Fourth, the perioperative period in cardiac surgery gives rise to an intense systemic inflammatory response characterized by the production of proinflammatory cytokines and tumor necrosis factor-α and high levels of endogenous cortisol. It has been suggested that hyperglycemia, interleukin-6, tumor necrosis factor-α, and high levels of endogenous cortisol could impair the function of pancreatic β-cells and alter the antihyperglycemic effect of exenatide and other GLP-1 agonists.[40–46] Approximately one third of the glucose-lowering effect of exenatide results from its capacity to delay gastric emptying, decrease splanchnic glucose uptake, and enhance postprandial glucose-stimulated insulin secretion from the pancreatic β-cells (incretin effect).[47] This mechanism of action is only exerted when patients are orally feeding and is maintained in intensive care unit patients.[17] In our study, most patients were fasting during the study period, and the infusion of exenatide was stopped when patients were orally feeding. This could have lowered the therapeutic effect of exenatide.

Because the glucose-lowering effect of exenatide depends on blood glucose, a reduction in the number and amplitude of rapid excursions in blood glucose values and a decrease in glycemic variability were anticipated in the exenatide group.[48] Increased morbidity and mortality related to glycemic variability have been reported in cardiac surgery[1,49] and critically ill patients.[35,50–53] Although a significant improvement in the coefficient of variability of blood glucose with the use of intravenous GLP-1 combined with insulin infusion in critically ill surgical patients has previously been reported,[22] we failed to confirm this hypothesis in the present study. Nonetheless, the glycemic variability observed in both groups was very close to the lowest values reported in studies assessing the clinical effectiveness of GLP-1 in reducing this parameter in critically ill patients[22] or in low-risk cardiac surgery patients.[49] This could be explained by the small proportion of diabetic patients included and by the low baseline values of glycosylated hemoglobin, since diabetes mellitus and high glycosylated hemoglobin have been reported to be the two main factors associated with an increase in glycemic variability.[54]

Finally, since the ExSTRESS trial is the first study to investigate IV exenatide in cardiac surgery patients, most of our hypotheses are based on extrapolation of the effects provided by IV GLP-1 in intensive care unit patients.[15–17,19–22] Given that GLP-1 is not available in France and equipotent doses of IV exenatide and IV GLP-1 remain unknown, IV exenatide was used off-label in the present study by following the only published and validated therapeutic regimen, approved by the French Health Authorities for clinical research. However, different results in blood glucose control may have been observed with the use of higher doses of exenatide. In this regard, results of ongoing and further studies on both clinical efficiency and safety will be interesting to consider.[55]

Furthermore, the potential benefit of IV exenatide in cardiac surgery patients could lie beyond its antihyperglycemic effect. First, IV exenatide could be a cost-effective alternative to insulin alone in blood glucose control by decreasing the nursing workload. This is suggested by the significant reduction in the number of changes in insulin infusion rate per patient observed in the exenatide group. This difference may be due in part to the delay in onset of insulin therapy in the exenatide group, but we cannot ascertain that a difference exists between the groups during insulin infusion. The change in nursing workload, if any, could not be quantified in this study, as the time to perform each action of blood glucose control was not measured. Second, postconditioning properties and intrinsic inotropic effects of exenatide have been reported in heart failure[56] and cardiac intensive care unit patients,[57–60] enhancing cardiac function and quality of life after CABG surgery. Third, neuroprotective effects of GLP-1 agonists, including exenatide, have been reported in experimental studies and have to be confirmed in ongoing trials.[55]

Limits of the Study

Because of the wide heterogeneity in the insulin therapy protocols used in cardiac surgical intensive care units, our study was conducted in a single center to ensure a homogeneous control group and in patients with relatively few comorbidities. It cannot be ascertained that different results could be observed in other patients or by using another dose and protocol of exenatide infusion. Furthermore, since measurement of the primary outcome was judged to be objective, the risk of bias was considered to be null, and no placebo was used in the control group.

Conclusions

Exenatide infused intravenously at the dose used in the present study may not spare supplemental insulin administration to efficiently manage postoperative stress hyperglycemia after CABG surgery. Intravenous exenatide reduced neither the incidence of hypoglycemia nor glycemic variability but delayed the start of insulin infusion, reduced the number of modifications in the insulin infusion rate, and could decrease the workload for nurses. Even if neither exenatide-related adverse event nor hypoglycemia have been observed, the safety of IV exenatide needs to be confirmed in larger studies. Based on the results of this randomized trial, IV exenatide cannot be considered as an alternative to insulin therapy for postoperative glycemic control after CABG surgery.

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Competing Interests

Dr. Samain had paid consultancies for the following drug companies: Takeda France SAS (Puteaux, France), Baxter (Guyancourt, France), and Leo Pharma (Voisins-le-Bretonneux, France). None of these companies were involved in the funding of the present study. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: gbesch@chu-besancon.fr. Raw data available at: gbesch@chu-besancon.fr.

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Appendix 1: Insulin Infusion Protocol

General Statements

- Target blood glucose (BG) levels: 100 to 140 mg/dl (5.5 to 7.7 mmol/l).
- Blood sampling for BG measurement: 2 ml of blood obtained *via* an indwelling arterial catheter, flushed with continuous infusion using glucose-free solution.
- BG measurement: Optium Xceed (Abbott Diabetes Care, United Kingdom).
- Preparation of insulin infusion: 1 unit (U) of regular human insulin in 1 ml of saline.
- Administrations of insulin infusion *via* infusion pump in increments of 0.5 U/h.

Initiating Insulin Infusion

Initial BG rounded to nearest 0.5 U for both bolus and initial infusion rate.

BG Monitoring

Check BG hourly until BG is stable (12 consecutive BG values within target range). Then check BG every 3 h if:

- BG is stable
- No significant change in clinical condition
- No significant change in nutritional intake

Consider temporary resumption of hourly BG monitoring if any of the following events occurs:

- Any change in insulin infusion rate
- Significant change in clinical condition
- Initiation or cessation of pressor or steroid therapy
- Initiation, cessation, or rate change of nutritional support

Changing the Insulin Infusion Rate

If BG is less than 50 mg/dl (2.7 mmol/l):

- Stop insulin infusion, give 10 ml of intravenous (IV) dextrose 30% (D30), and recheck BG within 15 min.
- When BG is more than 100 mg/dl (5.5 mmol/l), wait for 1 h, and then resume insulin infusion at 50% of original rate.

If BG is in 50 to 74 mg/dl (2.7 to 4.1 mmol/l) range:

- Stop insulin infusion.
- If patient is symptomatic: give 10 ml of D30 IV and check BG again within 15 min.
- If patient is asymptomatic: give 5 ml of D30 IV and check BG again within 15 to 30 min.
- When BG is more than 100 mg/dl (5.5 mmol/l), wait for 1 h, and then resume insulin infusion at 75% of original rate.

If BG is more than 75 mg/dl (4.1 mmol/l):

- Step 1: Determine the current BG level. This identifies a column in table A1.1.
- Step 2: Determine the rate of change from the prior BG level. This identifies a cell in table A1.1. Then go to the right for instructions.
- Changes in infusion rate (Δ) are determined by the current rate (table A1.2).

Table A1.1. Changing in Insulin Infusion Rate Based on Current and Prior BG Levels

BG				
75–99 mg/dl	100–139 mg/dl	140–199 mg/dl	≥ 200 mg/dl	Instructions
		BG ↑ by > 50 mg · dl · h^{-1}	BG ↑	↑ infusion by 2Δ
	BG ↑ by > 25 mg · dl · h^{-1}	BG ↑ by 1–50 mg · dl · h^{-1} or BG unchanged	BG unchanged or BG ↓ by 1–25 mg · dl · h^{-1}	↑ infusion by Δ
BG ↑	BG ↑ by 1–25 mg · dl · h^{-1} or BG unchanged or BG ↓ by 1–25 mg · dl · h^{-1}	BG ↓ by 1–50 mg · dl · h^{-1}	BG ↓ by 26–75 mg · dl · h^{-1}	No infusion change
BG unchanged or BG ↓ by 1–25 mg · dl · h^{-1}	BG ↓ by 26–50 mg · dl · h^{-1}	BG ↓ by 51–75 mg · dl · h^{-1}	BG ↓ by 76–100 mg · dl · h^{-1}	↓ infusion by Δ
BG ↓ by > 25 mg · dl · h^{-1}	BG ↓ by > 50 mg · dl · h^{-1}	BG ↓ by > 75 mg · dl · h^{-1}	BG ↓ by > 75 mg · dl · h^{-1}	Hold x 30 min, then ↓ infusion by 2Δ

BG = blood glucose.

Table A1.2. Instructions in Changes in Infusion Rate

Current Rate (U/h)	Δ = Rate Change (U/h)	2Δ = 2 × Rate Change (U/h)
< 3.0	0.5	1.0
3.0–6.0	1.0	2.0
6.5–9.5	1.5	3.0
10.0–14.5	2.0	4.0
15.0–19.5	3.0	6.0
≥ 20.0	Consult M.D.	Consult M.D.

M.D. = doctor of medicine.

Appendix 2: Management of Hypoglycemia in the Exenatide Group

Definition of Hypoglycemia

Hypoglycemia was defined as blood glucose (BG) value less than 75 mg/dl (4.2 mmol/l). Hypoglycemia was symptomatic if patient presented any clinical symptom of hypoglycemia, or not. All hypoglycemia occurring in sedated patients were considered to be symptomatic.

Management of Hypoglycemia during the Intravenous Infusion of Exenatide

If Patient Did Not Receive a Coinfusion of Insulin

If hypoglycemia is asymptomatic:

- Do not stop exenatide infusion, give 5 ml of intravenous (IV) dextrose 30% (D30), and recheck BG within 15 min.
- If BG is less than 75 mg/dl (4.2 mmol/l) 15 min later, then stop exenatide infusion:
  - If hypoglycemia is asymptomatic: Give 5 ml of D30 IV, and recheck BG within 15 min.
  - If hypoglycemia is symptomatic: Give 10 ml of D30 IV, and recheck BG within 15 min.
  - When BG is more than 100 mg/dl (5.5 mmol/l), wait for 1 h, and then resume exenatide infusion at a rate of 7.5 ml/h.

If hypoglycemia is symptomatic:

- Do not stop the infusion of exenatide, give 10 ml of IV D30, and recheck BG within 15 min.
- If BG is less than 75 mg/dl (4.2 mmol/l) 15 min later, then stop exenatide infusion:
  - If hypoglycemia is asymptomatic: Give 5 ml of D30 IV, and recheck BG within 15 min.
  - If hypoglycemia is symptomatic: Give 10 ml of D30 IV, and recheck BG within 15 min.
  - When BG is more than 100 mg/dl (5.5 mmol/l), wait for 1 h, and then resume exenatide infusion at a rate of 7.5 ml/h.

If Patient Received a Coinfusion of Insulin

If hypoglycemia is asymptomatic:

- Stop insulin infusion, do not stop exenatide infusion, give 5 ml of IV D30, and recheck BG within 15 min.
- If BG is at least 5 mg/dl (4.2 mmol/l) 15 min later, wait for 1 h, and then resume insulin infusion at 25% of original rate.
- If BG is less than 75 mg/dl (4.2 mmol/l) 15 min later, then stop exenatide infusion:
  - If hypoglycemia is asymptomatic: Give 5 ml of D30 IV, and recheck BG within 15 min.
  - If hypoglycemia is symptomatic: Give 10 ml of D30 IV, and recheck BG within 15 min.
  - When BG is more than 100 mg/dl (5.5 mmol/l), wait for 1 h, and then resume exenatide infusion at a rate of 7.5 ml/h.

If hypoglycemia is symptomatic:

- Stop insulin infusion, do not stop exenatide infusion, give 10 ml of IV D30, and recheck BG within 15 min.
- If BG is at least 75 mg/dl (4.2 mmol/l) 15 min later, wait for 1 h, and then resume insulin infusion at 25% of original rate.

- If BG is less than 75 mg/dl (4.2 mmol/l) 15 min later, then stop exenatide infusion:
  - If hypoglycemia is asymptomatic: Give 5 ml of D30 IV, and recheck BG within 15 min.
  - If hypoglycemia is symptomatic: Give 10 ml of D30 IV, and recheck BG within 15 min.
  - When BG is more than 100 mg/dl (5.5 mmol/l), wait for 1 h, and then resume exenatide infusion at a rate of 7.5 ml/h.

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