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Effects of liraglutide on no-reflow in patients with acute ST-segment elevation myocardial infarction

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ABSTRACT

Background: The 'no-reflow' phenomenon after a percutaneous coronary intervention (PCI) in patients with acute ST-segment elevation myocardial infarction (STEMI) is a strong predictor of both short- and long-term mortality. Glucagon-like peptide-1 (GLP-1) exerts a cardioprotective effect during ischemia reperfusion injury. We planned to evaluate the effects of liraglutide on myocardial no-reflow after PCI for STEMI.

Methods: A total of 284 patients with STEMI undergoing PCI were enrolled in this study between September 2013 and March 2015. Of these, 210 patients were randomized 1:1 to receive either liraglutide or placebo 30 min before PCI (1.8 mg).

Results: The primary end point, the prevalence of no-reflow, was significantly lower in the liraglutide group than in the control group (5% vs. 15%, $P = 0.01$). Administration of liraglutide was consistently identified as a significant determinant for no-reflow ratio. There was a significant decrease in serum high-sensitivity C-reactive protein levels at 6-hour reperfusion in the liraglutide group compared to the control group (0.87 ± 0.09 mg/dL vs. 0.96 ± 0.10 mg/dL, $P < 0.001$). During a 3-month follow-up period, no difference was observed in the incidence of major adverse cardiovascular event.

Conclusions: Liraglutide may be associated with less no-reflow in STEMI, which should be confirmed by larger-scale trials.

1. Introduction

Acute ST-segment elevation myocardial infarction (STEMI) is a major cause of mortality and morbidity. Percutaneous coronary intervention (PCI) is currently the most effective treatment strategy for STEMI [1]. However, myocardial reperfusion is suboptimal in many patients, mostly because of the 'no-reflow' phenomenon. To date, however, very few drugs have been shown to reverse established no-reflow [2,3].

Elevation of blood glucose is a common metabolic disorder among patients with acute myocardial infarction (AMI) and is associated with adverse prognosis [4]. Our previous study found that plasma glucose on admission (APG) was associated with the development of no-reflow in STEMI patients [5]. The no-reflow incidence was increased as APG increased (14.6% in patients with APG < 7.8 mmol/L and 36.7% in patients with APG > 13.0 mmol/L $P = 0.009$) [6]. Glucagon-like peptide-1 (GLP-1) is an incretin hormone that regulates plasma glucose, and GLP-1 has antioxidant and anti-inflammatory properties, and may protect endothelial function [7–9]. Experimental studies have also revealed that GLP-1 or its analogs protect against reperfusion injury in pigs [10]. To date, however, there is no clinical evidence for the effects of the GLP-1 analog liraglutide on no-reflow in patients with STEMI. Therefore, the aim of this study was to evaluate the effects of liraglutide pretreatment on myocardial no-reflow of PCI in patients with STEMI.

2. Methods

2.1. Study site and ethics

This was a single-centre, prospective, interventional study conducted at the Chinese PLA General Hospital in Beijing, China. The study was approved by the Beijing Ethics Association and the Ethics Committee of the Chinese PLA General Hospital, and complied with the Helsinki Declaration. All of the subjects provided written informed consent to participate in the study. The trial was registered on ClinicalTrials.gov (registration number: NCT02507128).

2.2. Study population

The study population comprised 284 patients with STEMI who were admitted to the Chinese PLA General Hospital between September 2013 and March 2015. STEMI was defined as typical chest pain lasting >30 min within the previous 12 h, a clear ST-segment elevation of >0.1 mV in ≥2 contiguous electrocardiographic leads, and elevated blood levels of troponin T. Patients were excluded for the following reasons: unconscious at presentation; had cardiogenic shock, hypoglycemia, or diabetic ketoacidosis; had a history of myocardial infarction, stent thrombosis, or renal insufficiency; or had previously undergone coronary artery bypass surgery.

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2.3. Definitions

Anterograde coronary flow in the infarct-related artery was graded according to the thrombolysis in myocardial infarction (TIMI) grading system [11]. The myocardial blush grade was assessed as described by van't Hof et al. [12]. Angiographic no-reflow was defined as a TIMI flow grade of <3 with a myocardial blush grade of 0–1 [13]. Hypertension was defined as blood pressure ≥140/90 mmHg or a history of antihypertensive drug use. Diabetes was defined as fasting blood glucose level ≥7 mmol/L or a history of using oral hypoglycemic drugs or insulin. Hyperlipidemia was defined as the presence of at least one of the following criteria: fasting triglycerides >150 mg/dL, total cholesterol >200 mg/dL, low-density lipoprotein–cholesterol >130 mg/dL, or the use of antihyperlipidemic drugs. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [14], and renal failure was defined as an eGFR of <60 mL/min/1.73 m^2 [15]. Each patient's Killip classification was assigned on the basis of the severity of signs of heart failure at the time of hospital admission: Killip class 1 was defined by the absence of rales in the lung fields and the absence of an S_3 heart sound; Killip class 2 was defined by the presence of rales in <50% of the lung fields, or by the presence of an S_3 gallop, accompanied by elevated jugular venous pressure; Killip class 3 was defined by the presence of rales in >50% of the lung fields [16].

2.4. Revascularization procedure and medical treatment

PCI was performed by one of four operators using standard techniques. All patients also received 300 mg aspirin and 600 mg clopidogrel before the procedure. They continued to take aspirin (100 mg/d) for lifetime and clopidogrel (75 mg/d) for at least 12 months. Glycoprotein IIb/IIIa receptor antagonists were administered if there were no contraindications. Drug-eluting stents were implanted as the first-line choice of stents. TIMI flow grade and myocardial blush grade of the intervened vessel were recorded before and after stent deployment. They were estimated by at least 2 blinded, independent observers. The TIMI scores were averaged if the results were not in agreement.

2.5. Experimental treatment protocol

All patients have been informed of potential risks (hypoglycemia, pancreatitis, nausea) [17,18] associated with GLP-1 analogs and then required to submit written informed consents prior to being included in the study. Patients were randomized using a computer-generated sequence to either placebo or liraglutide at a 1:1 ratio. Investigators, participants, and other study personnel were blinded to the assigned treatment for the duration of the study. Patients in the liraglutide group were treated with subcutaneous liraglutide (Novo Nordisk, Bagsværd, Denmark) while patients in the control group were given subcutaneous placebo (Novo Nordisk). The treatment started 30 min before PCI with a dose of 1.8 mg liraglutide (the treatment was administered in the ambulance). In 50 consecutive patients, blood samples were collected at the end of the PCI procedure in order to measure the liraglutide plasma concentration in the patients randomized to liraglutide treatment (normal range 0.03 and 0.3 nmol/L) [19]. The blood sample was collected from the femoral sheath at the end of the procedure. Since the patients were treated with a drug used off label, Good Clinical Practice (GCP) training is required for all personnel involved in the trial.

2.6. Study outcomes

The primary efficacy variable was the prevalence of no-reflow assessed immediately post procedure. Secondary efficacy variables were troponin T (TnT), high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), superoxide dismutase (SOD), malondialdehyde (MDA), endothelin-1 (ET-1), and nitric oxide (NO) levels.

2.7. Laboratory tests

The lab data (hsCRP, SOD, NO, etc) were obtained at baseline (before intervention), 1-hour reperfusion and 6-hour reperfusion. TnT was measured by an enzyme-linked immunosorbent assay (ELISA) (Boehringer Mannheim, Indianapolis, intra-assay coefficient of variation [CV] 2.4%, inter-assay CV 3.5%, normal range < 0.1 ng/mL). N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) levels were determined by enzyme immunoassay (Shionoria, Osaka, Japan; intra-assay CV 2.9%, inter-assay CV 3.5%, normal range < 150 pg/mL). hsCRP levels were measured using a sandwich ELISA (R&D Systems Inc., Minneapolis, MN, USA; intra-assay CV 3.3%, inter-assay CV 3.5%, normal range < 0.8 mg/dL). Serum IL-6 concentrations were measured using an ELISA (R&D Systems Inc., Minneapolis, MN, USA; intra-assay CV 2.1%, inter-assay CV 4.0%, normal range < 8 pg/mL). SOD activity was estimated as the inhibition of a colorimetric reaction using an assay kit (Cayman

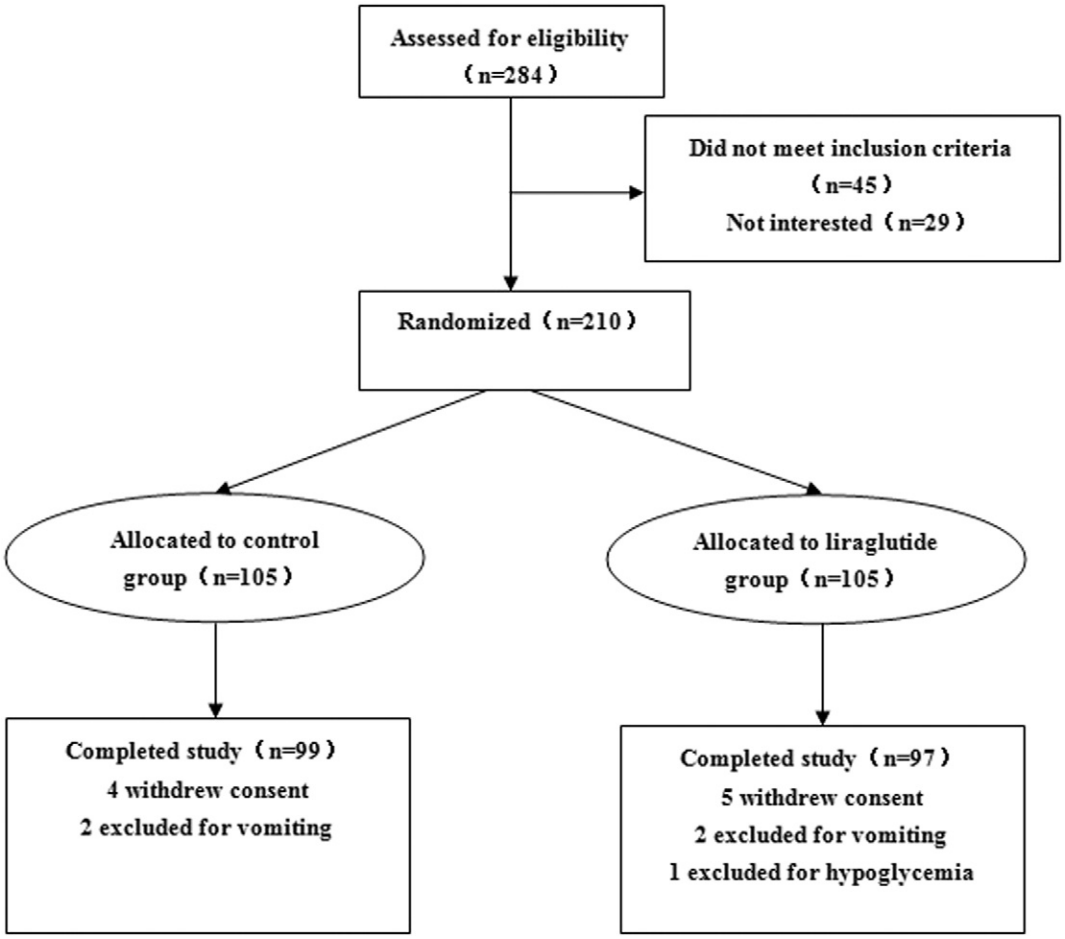

Fig. 1. Patient flow chart.