Prostaglandin E_1 Increases the Blood Flow Rate of Saphenous Vein Grafts in Patients Undergoing Off-Pump Coronary Artery Bypass Grafting

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Objective: **To compare the effects of prostaglandin E_1 (PGEl) versus placebo on blood flow rate in coronary artery bypass grafts.**

Design: **A prospective, randomized, double-blinded study.**

Setting: **A teaching hospital.**

Participants: **Forty-six patients with stable angina scheduled for isolated elective OPCAB were recruited and randomized into group PGE1 and group placebo.**

Intervention: **Following randomization, the patients in the PGE1 group (Group PGE1, n = 23) received a continuous intravenous infusion of PGEl (10 ng/kg/min) after endotracheal intubation and the placebo group (Group placebo, n = 23) received the same volume of normal saline. The infusion administration was removed after leaving the intensive care unit.**

Measurements and Main Results: **The grafts' blood flow rate was measured with a transit time flowmeter at 10 minutes and 30 minutes after coronary artery grafting. The hemodynamic parameters, including mean arterial pressure (MAP), heart rate, and SvO_2, VO_2I, DO_2I, ERO_2 monitored by a pulmonary artery catheter, were recorded. The blood flow of the saphenous vein grafts was significantly higher in the PGE1 group than the placebo group at both 10 and 30 minutes after coronary artery grafting. At the 10-minute mark, the graft flow was 54.9 ± 31.4 mL/min versus 47.3 ± 24.6 mL/min in venous nonsequential grafts to the left coronary artery for group PGE1 and placebo (p = 0.000). Corresponding values at 30 minutes were 60.1 ± 27.8 mL/min versus 48.4 ± 26.3 mL/min (p = 0.002). In the venous non-sequential grafts to the right coronary artery, a tendency of blood flow also was found to be higher in the PGE1 group than in the placebo group at 10-minutes (52.7 ± 29.4 mL/min versus 49.3 ± 23.8 mL/min, p = 0.048) and the 30-minutes (58.6 ± 26.5 mL/min, 50.9 ± 25.9 mL/min, p = 0.037). The blood flow rate of the left internal mammary artery (LIMA) grafts in group PGE1 was higher than that in the placebo group but did not reach statistical significance. The VO_2I, DO_2I, and ERO_2 in the 2 groups at the 2 time points did not reach statistical significance. The cardiac index (CI) in group PGE1 was higher than that of the placebo group at T3 and T4 (p = 0.035 and p = 0.012, respectively). The lactate (LAC) at the end of the operation (T_2), 4 hours after the operation (T_3), and 24 hours after operation (T_4) in the placebo group were higher than that of group PGE1 (p = 0.023, p = 0.015, and p = 0.043, respectively). The oxygenation saturation of the mixed venous blood (SvO_2) in the 2 groups was decreased but without significant difference.**

Conclusion: **PGE1 significantly increased the flow rate in anastomosed saphenous vein grafts, and its beneficial effects on hemodynamics and oxygen metabolism were observed.**

KEY WORDS: prostaglandin E1, coronary revascularization, off-pump, graft flow, hemodynamics, coronary blood flow

THE SAPHENOUS VEIN is the most commonly used vessel graft for off-pump coronary artery bypass graft (OPCAB) surgery. The effects of various pharmacologic agents on flow within saphenous vein grafts (SVGs) have been studied both clinically and experimentally, and a correlation between graft flow and early patency rate in SVGs has been demonstrated in previous studies.[1,2] Prostaglandin E1 (PGE1), which has strong vasodilatory and endothelial-protective effect and antiplatelet activity, is clinically used to treat ischemic diseases such as peripheral arterial occlusive diseases.[3] The vasodilatory potential of PGE1 can improve endothelial function.[4] However, to date, no studies have been published regarding the effect of PGE1 on SVG graft flow. The aim of this study was to compare the effects of PGE1 and placebo on flow in SVG after OPCAB, and the authors hypothesized that PGE1 increases graft flow in SVGs.

METHODS

Forty-six patients ages 40 to 65 undergoing elective primary OPCAB surgery were recruited in this prospective, randomized, double-blinded study. The study protocol was approved by the ethics committee of the institution, and written informed consent was obtained from each patient. Exclusion criteria were NYHA class 4, left ventricular ejection fraction (LVEF) less than 30%, or concurrent systemic disorders (eg, patients with severe liver dysfunction or those with chronic renal failure on hemodialysis or central nerve system diseases). Patients with arrhythmias such as atrial fibrillation or disturbances in the conduction system and those receiving treatment with acetylsalicylic acid also were excluded from this study.

The patients were divided into 2 groups, the PGE1 and placebo groups. Patients received 10 ng/kg/min of PGEl (n = 23) or placebo (n = 23) intravenous infusion following randomization. The patients received no premedication. All preoperative demographic data are shown in Table 1. The quality of the native coronary arteries was preoperatively graded according to the findings on coronary angiography.

All patients were given a standardized premedication with intramuscular morphine and scopolamine. The radial artery was cannulated under local anesthesia with a 20-gauge catheter. The bispectral index (BIS) value was observed. General anesthesia was induced with sufentanil (1 to 2 μg/kg), midazolam (0.05 mg/kg) and etomidate (0.1-0.3 mg/kg). Intubation was facilitated with intravenous rocuronium (0.9 mg/kg), and mechanical ventilation was performed to maintain normoxia and normocarbia (tidal volume 6-8 mL/kg, rate 10 to 12/min, fractional inspired oxygen concentration 0.5 [oxygen-air mixture]).

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Table 1. Comparison of Patients' Demographic Characteristics (mean ± SD)

Variables	E Group (n = 23)	C Group (n = 23)
Gender (M/F)	16/7	17/6
Age (yr)	58.6 (2.4)	61.0 (1.2)
Weight (kg)	75.2 (2.1)	74.3 (1.8)
LVEF (%)	58.1 (2.1)	59.2 (1.9)
Hb (g/dL)	13.9 (0.7)	13.2 (0.5)
History of hypertension (%)	72.2	71.3
History of MI (%)	55.3	56.4
Diabetes mellitus (%)	60.1	57.5
Duration of operation (min)	165.6 (11.9)	159.5 (12.6)
Number of patients with PID (%)	58.8	61.3

NOTE. Values are shown as mean values (standard deviation).
Abbreviations: Hb, hemoglobin; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PID, positive inotropic drug.

After intubation, a pulmonary artery catheter was inserted through the right internal jugular vein. Central venous catheterization was performed with a double-lumen catheter. Anesthesia was maintained with continuous infusion of sufentanil, 1 to 2 μg/kg/h, and hourly boluses of vecuronium and BIS were maintained between 40 to 60 by inhalation of 0.5% to 2.0% isoflurane in oxygen-air mixture. A nitroglycerin infusion was used in patients in both groups if needed. Continuous electrocardiography, end-tidal carbon dioxide, pulse oximetry, central venous pressure (CVP), nasopharyngeal temperature, urine output, intermittent arterial blood gas, and activated coagulation time were observed intraoperatively for all patients.

The patients in the PGE1 group received a continuous intravenous infusion of PGEl (a lipid emulsion of PGE1 at 10 ng/kg/min) after tracheal intubation. In the placebo group, the same volume of 0.9% NaCl was given at the same time. Intravenous fluid was administered to maintain normal CVP values.

The patients were randomized to the respective groups by opening sealed envelopes outside the operating room prior to the operation. Nurses who did not participate in the study prepared the medications. The OPCAB was performed by a senior cardiac surgical team with routine standard methods. In all patients, the saphenous vein was dissected and manually distended by using a syringe of saline to prevent spasm and possible dissection injuries of the wall. The internal mammary artery (IMA) was harvested with the aid of diathermy and hemoclips to control side branches and was dissected from the chest wall with a wide pedicle beginning at the level of the subclavian vein to immediately before its bifurcation. Five minutes after systemic heparinization (300 units/kg), the IMA was cut immediately proximal to its bifurcation.

Cardiac output (CO) was measured at the following time points: Before surgery (T1), the end of surgery (T2), 4 hours after the surgery (T3), and 24 hours after the surgery (T4). Pulmonary arterial blood samples were obtained for oxygen saturation of mixed venous blood (SvO_2). The cardiac index (CI), oxygen delivery index (DO_2I), oxygen consumption index (VO_2I), and oxygen extraction rate (O_2ER) were calculated. The content of lactate in the arterial blood (Lac) was detected as well. In the meantime, the flow in the coronary artery grafts was measured with a transit time flowmeter at 10 minutes and 30 minutes after coronary artery grafting (Transonic Company, HT313, Ithaca, NY). Heart rate (HR); mean artery pressure (MAP), and CVP were recorded synchronously during each of the flow measurements.

SPSS for Windows (Version 14.0) was used for statistical analysis. All analyses were performed on an intention-to-treat basis. Between groups, demographic and hemodynamic data, the flow in SVGs and temperature were analyzed with Student's t-test. Then, pre-existing disease, preoperative medication, and gender distribution were analyzed with Fischer's exact test. Comparison of the flows, hemodynamic parameters, and temperature within groups was performed using paired Student's t-test. The statistical tests were 2-tailed. Results are expressed as mean ± SD (range) or number (%) where appropriate. A p value < 0.05 was considered significant.

RESULTS

Preoperative data of patients in both groups are shown in Table 1. No statistically significant differences were found between groups with respect to demographics, cardiac status, pre-existing disease, and preoperative medication. The mean values of systolic artery pressure (SAP), diastolic artery pressure (DAP), and mean artery pressure (MAP) did not differ significantly between groups during the flow measurements (Table 2). The flow in the saphenous vein grafts was significantly higher in the PGE1 than the placebo group at both 10 and 30 minutes after coronary artery grafting. At the 10-minute mark, the flow was 54.9 ± 31.4 mL/min and 47.3 ± 24.6 mL/min in venous nonsequential grafts to the left coronary artery for the PGE1 and placebo groups, respectively ($p = 0.000$). Corresponding values at 30 minutes were 60.1 ± 27.8 mL/min and 48.4 ± 26.3 mL/min ($p = 0.002$). In the venous non-sequential grafts to the right coronary artery, a tendency towards higher flow also was found in the PGE1 than in the placebo group. At the 10-minute mark, the flow was 52.7 ± 29.4 mL/min and 49.3 ± 23.8 mL/min for the PGE1 and placebo groups, respectively. In addition, at the 30-minute mark the flows were 58.6 ± 26.5 mL/min and 50.9 ± 25.9 mL/min ($p = 0.037$), respectively. The flow rate of the LIMA grafts in the PGE1 group was higher than that of the placebo group but did not reach statistical significance (Table 3). The VO_2I, DO_2I and ERO_2 in the 2 groups at the different time points did not reach statistical significance. The CI in the PGE1 was higher than in the placebo group at the T3 and T4 points ($p = 0.035$ and $p = 0.012$, respectively). The LAC at T_2, T_3, and T_4 in the placebo group were higher than in the PGE1 group ($p = 0.023$, $p = 0.015$, and $p = 0.043$, respectively). The SvO_2 at T_2 and T_3 in the 2 groups were decreased, but there was no difference (Table 4).

DISCUSSION

To the authors' knowledge, the effect of PGE1 on the flow of SVG bypass in OPCAB previously has not been reported. In this study, they found that the flow in the

Table 2. Perioperative Arterial Blood Pressure (mean ± SD)

Variable (mmHg)	PGE1, Mean (SD) (n = 23)	Placebo, Mean (SD) (n = 23)	p Value
Systolic artery pressure			
10 min	97 ± 12	96 ± 11	0.256
30 min	103 ± 11	100 ± 10	0.457
Diastolic artery pressure			
10 min	56 ± 9	55 ± 10	0.103
30 min	59 ± 8	60 ± 7	0.430
Mean arterial pressure			
10 min	71 ± 8	70 ± 9	0.304
30 min	73 ± 7	72 ± 8	0.503

NOTE. 10 min: 10 minutes after coronary artery bypass grafting.
30 min: 30 minutes after coronary artery bypass grafting.