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ORIGINAL ARTICLE

The Effects of Intracoronary Nitroglycerine Administration on Lesion Parameters, Intervention Success and 1-Year MACE in Patients with Acute Coronary Syndromes

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Abstract

Aims: Nitroglycerine (NTG) was used to relieve ischemic symptoms in patients with coronary artery disease. However, some studies demonstrated the positive effects of NTG on coronary circulation. In addition, NTG has been administrated to evaluate culprit lesion characteristics during coronary angiography. It was aimed to evaluate the effects of intracoronary NTG administration prior to percutaneous coronary intervention (PCI) on lesion severity and outcome prediction in patients with acute coronary syndrome (ACS).

Methods: A total of 312 consecutive patients diagnosed with ACS were included in the study and followed-up for 1 year. Major adverse cardiovascular events (MACE) was defined as cardiovascular death, new-onset decompensated heart failure, cerebrovascular event, sustained ventricular tachycardia and/or fibrillation within the 48 hours after the procedure.

Results: A total of 312 ACS patients (184 Unstable Angina/NSTEMI, 128 STEMI) were included in the study. A total of 212 patients were administered to the intracoronary nitroglycerin pre-PCI group (Mean ± standard deviation of age was 63 ± 12 years and 82% of patients were male) and 100 patients to the untreated group (Mean ± standard deviation of age was 61 ± 11 years and 84% of patients were male). Intracoronary NTG did not cause a significant change in lesion length. Total leukocyte count ($p = 0.005$), Hba1c level ($p = 0.031$), pre-hospital beta blocker usage ($p < 0.001$), and stent post-dilatation ($p = 0.020$) were found to be independent predictors of MACE. NTG administration changed lesion parameters and reference vessel diameters significantly.

Conclusion: Intracoronary NTG administration had no predictive value on the one-year MACE. However, it was associated with coronary perfusion parameters and severity of the coronary lesion.

Keywords

Nitroglycerine (NTG), Percutaneous coronary intervention (PCI), Acute coronary syndrome (ACS), Atherosclerosis

Introduction

Nitroglycerin (NTG) increases coronary collateral circulation and decreases preload by leading to venous dilatation and consequently reduces myocardial oxygen consumption. Therefore, NTG has been used to relieve ischemic heart pain thanks to vasodilating of the epicardial coronary arteries and increasing blood flow in myocardial tissue [1]. Moreover, NTG administration was shown to decrease contrast nephropathy, thrombocyte activation, and increase microvascular circulation [2,3].

Nowadays, percutaneous coronary intervention (PCI) is first line therapy in patients with acute coronary syndromes (ACS) including unstable angina pectoris (USAP), non-ST-elevation myocardial infarction (NSTEMI), and acute ST-elevation myocardial infarction (STEMI). Advances in intervention techniques accompanying the medical treatment improve the efficacy of PCI, outcome, and quality of life [4,5]. On

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the other hand, coronary vasospasm is involved in the etiopathogenesis of ACS and may cause a lower estimation of preferred stent size in where the stent will be placed as well as increases myocardial ischemia [6]. Thus, intracoronary NTG is frequently used during coronary angiography to identify reversible coronary vasospasm. Moreover, in some cases, complete resolution of the vasospasm by intracoronary NTG administration may prevent unnecessary stenting [7].

Although of intracoronary NTG administration is known to be favourable on decision making, its effect on lesion morphology, perfusion parameters, and major adverse cardiovascular events (MACE) in patients with ACS have not been studied before. In this study, we aimed to investigate the effects of intracoronary NTG administration on culprit lesion morphologies, coronary flow parameters, and one-year major adverse cardiovascular events (MACE) in patients with ACS.

Methods

Study population

This was a prospective observational cohort study. A total of 312 consecutive patients who were diagnosed with ACS and performed PCI between April 2017 and August 2018 were included in the study. Patients were followed-up for 1 year for MACE development.

Clinical characteristics of each patient including hypertension (HT), diabetes mellitus (DM), smoking status, family history for premature coronary artery disease (CAD), and physical examination findings were collected from each patient by experienced cardiologists and were stored in the database of the coronary angiography laboratory at our institute.

The study was performed in accordance with the principles stated in the Declaration of Helsinki. The local ethics committee approved the study protocol.

Exclusion criteria

Patients who were not performed PCI, acute or chronic renal failure, malignancy, acute or chronic infectious disease, pulmonary embolism, cardiogenic shock, history of coronary artery disease (CAD) and pre-hospital nitrate recipients were excluded from the study. Patients with high thrombus burden and poor distal flow were excluded from the study. In addition, in case of acute or hyperacute instent restenosis, patients were also excluded from the study.

Selective coronary angiography and PCI procedure

Selective coronary angiography and PCI procedures of patients were performed urgently by experienced interventional cardiologist's through the femoral artery and Judkins technique. Medical treatment was given in accordance with the current guidelines to all patients. At the beginning of the procedure, 10.000 IU intravenous heparin was administered. Patients were given the loading dose of clopidogrel, ticegrelol or presugrel according to the preference of the invasive cardiologist who performed the procedure except acetyl salicylic acid loading [5]. Multiple views were obtained in all patients, with visualization of the left anterior descending (LAD) and circumflex (Cx) coronary arteries in at least four views, and the right coronary artery in at least two views. Coronary angiographies were recorded into digital media for quantitative analysis. Independent experienced cardiologists who were blinded to clinical parameters of the patients carefully reviewed coronary views during the procedure. Coronary stenting directly, or followed by balloon angioplasty, was performed where eligible. After the procedure, patients were followed in the intensive coronary unit (ICU) until stabilization.

On the first angiogram, we assessed the basal TIMI (thrombolysis in myocardial infarction) flow grade and collateral circulation of the culprit vessel. In addition, TIMI flow grades (TFGs), corrected TIMI frame count (cTFC), myocardial blush grade (MBG), and TIMI myocardial perfusion grade (TMPG) variables were obtained from the angiographic sequences immediately after PCI. Epicardial blood flow was assessed by use of either TFGs or cTFC and myocardial perfusion was assessed using TMPG [8]. Angiographic views were taken sufficiently long (> 10 s) to ensure evaluating TIMI, MBG, and TMPG flows.

Coronary artery stenoses were classified as A, B1, B2, and C type lesions according to the ACC/AHA recommendations. Lesion classification was based on 12 characteristics including lesion length, eccentricity, tortuosity, lesion angle and contour, calcification, total occlusion longer or shorter than of 3 months, presence of ostial lesion, side branch involvement, and thrombus [9].

Angiographic thrombus burden was classified as follows: Grade 0: no thrombus, Grade 1: Possible thrombus, Grade 2: the greatest dimension of thrombus is < 1/2 of the vessel diameter, Grade 3: Greatest dimension of thrombus is between > 1/2 and < 2 of vessel diameters, Grade 4: Greatest dimension of thrombus is > 2 of vessel diameters, Grade 5: total vessel occlusion due to thrombus [10].

The culprit lesion morphology was evaluated before and after NTG administration at the clearest view. The degree and length of stenosis were calculated by the software of the angiography device, automatically. Administration of intracoronary NTG during pre-dilatation of the lesion to determine the stent length and diameter or after the stent replacement was conducted upon the attending interventional cardiologist's decision. Operators generally preferred 100 or 200 micrograms NTG doses. Achievement of NTG administration was determined by the occurrence of at least 20 mmHG drops in arterial blood pressure.

Transthoracic echocardiography

Echocardiographic images were obtained from the left lateral decubitus position with using a GE-Vingmed Vivid S5 (GE-Vingmed Ultrasound AS, Horten, Norway) with a 2.5-3.5-MHz transducer by experienced cardiologists. Left atrial diameter, left ventricle end-diastolic and end-systolic diameters, interventricular septum and posterior wall thickness were measured by M-mode echocardiography. Left ventricular ejection fraction (LVEF) was measured by employing the modified Simpson's method.

Laboratory assessment

Cardiac biomarker including creatinine kinase-MB fraction (CK-MB), troponin-I (Tn-I), glucose, and inflammatory markers such as leukocytes and c-raeactive protein (CRP) were measured at admission to the hospital. The lipid and glucose samples were drawn by venipuncture to perform routine blood chemistry after at least 8 hours of fasting. Glucose, creatinine, and lipid profile were determined by standard methods. White blood cell (WBC, leukocyte) counts were obtained from an automated cell counter (Coulter Gen-S, COULTER Corp, Miami, USA). Creatine kinase-MB (CK-MB) and Tn-I levels were obtained 4 hours apart. Because above the 50 ng/ml is stated as > 50 ng/ml in our laboratory, Tn-I included as 50 ng/ml in the analysis. Delta CK-MB was calculated by following formula: Peak CK-MB minus admittion CK-MB level.

Clinical follow-up and major adverse cardiovascular outcome (MACE)

The patients were followed for an average of 1 year. The composite primary endpoint of the study was cardiovascular death, new-onset decompensated heart failure, cerebrovascular event, sustained ventricular tachycardia and/or fibrillation within the 48 hours after the procedure without recurrent ischemia/infarction, recurrent revascularization, and major bleeding after the procedure.

Major bleeding was accepted to be as any intracranial bleeding (excluding microhemorrhages, lower than 10 mm on gradient-echo MRI), clinically overt signs of hemorrhage associated with a drop in hemoglobin of 5 g/dL, and fatal bleeding (bleeding that directly results in death within 7 days) [11].

Statistical analysis

Continuous variables were given as mean ± SD; categorical variables were defined as percentage. Data were tested for normal distribution using the Kolmogorov Smirnov test. The Student t-test was used for the univariate analysis of the continuous variables and the chi square test for the categorical variables. Mean values were compared by ANOVA among different groups. Multiple logistic and linear regression analyses were used to assess multivariate relations among various variables. The effects of the various variables on MACE were calculated by univariate regression analysis. In these analyses, the variables with unadjusted $p < 0.1$ were identified as confounding factors and included in the multivariate regression analyses to determine the independent predictors of MACE. Statistical significance was defined as $p < 0.05$ and all tests of significance were two-tailed. The SPSS statistical software (SPSS 15.0 for windows, Inc., Chicago, IL, USA) was used for all statistical calculations.

Results

Demographic characteristics of patients

Patients were defined as group 1 and 2 according to whether given or not intracoronary NTG before the PCI, respectively. Of them, 212 patients were in group 1 and 100 patients were in group 2. There was no significant difference in terms of age, gender, body mass index (BMI), DM, smoking status, hyperlipidemia, family history of CAD, peripheral arterial disease (PAD), and systolic and diastolic pressures of admission between the two groups. On the other hand, waist circumference (106 ± 14 vs. 101 ± 13 cm, $p = 0.003$) was higher in group 1, whilst HT rate (61 vs. 48% $p = 0.033$) was higher in group 2 (Table 1).

In comparison of pre-hospital medical treatment, acetylsalicylic acid (34.0 vs. 20.3% $p = 0.009$), angiotensin convertin enzyme inhibitor (24 vs. 12.7% $p = 0.012$), and statin usages (21 vs. 9.4% $p = 0.005$) were higher in the group 2. Other medical treatments were similar between the two groups (Table 1).

The rate of patients with USAP/NSTEMI (66.5 vs. 43%, $p < 0.001$) was higher in the group 1 while the rate of patients with STEMI was higher in the group 2 (57 vs. 33.5%, $p < 0.001$) (Table 2).

Laboratory data

Uric acid (6.30 ± 1.93 vs. 5.79 ± 1.55 mg/dl, $p = 0.014$), serum creatinine (1.05 ± 0.4 vs. 0.97 ± 0.3), total bilirubin (0.79 ± 0.55 vs. 0.62 ± 0.30 mg/dl, $p = 0.007$), and direct bilirubin (0.26 ± 0.19 vs. 0.19 ± 0.10 mg/dl, $p = 0.005$) levels were higher in group 2 compared to group 1. There were no differences in glycosylated hemoglobin (HbA1c), blood lipid profile, WBC, hemoglobin, ALT, AST, GGT, and LDH levels between the two groups. Basal CK-MB and Troponin I levels were similar in both groups but peak CK-MB (113 ± 119 vs. 65 ± 85 ng/ml, $p < 0.001$), delta CK-MB (89 ± 111 vs. 34 ± 66 ng/ml, $p < 0.001$), peak troponin I (28 ± 22 vs. 20.4 ± 20 ng/mL, $p = 0.003$), and delta troponin levels (22 ± 21 vs. 13.6 ± 17.9 ng/mL, $p = 0.001$) were higher in the group 2 (Table 1).

Coronary angiographic data

The most commonly responsible coronary artery of ischemia was LAD in both groups. The pre-PCI thrombus

Table 1: Baseline characteristics and clinical data of the study population according to the intracoronary nitrate administration before PCI.

Parameters	PCI with nitrate (212)	PCI without nitrate (100)	P value
Age (years)	61 ± 11	63 ± 12	NS
BMI (kg/m^2)	30.1 ± 6.0	29.5 ± 5.5	NS
Waist circumference (cm)	106 ± 14	101 ± 13	0.003
Gender (male) (%)	84	82	NS
Hypertension (%)	48	61	0.033
Diabetes mellitus (%)	33	36	NS
Smoking status (%)	48.1	54	NS
Hyperlipidemia (%)	31	36	NS
Family history of CAD (%)	41	34	NS
PAD (%)	1	3	NS
Systolic blood pressure (mmHg)	130 ± 22	129 ± 17	NS
Diastolic blood pressure (mmHg)	78 ± 13	77 ± 11	NS
Plasma blood glucose (mg/dl)	158 ± 75	146 ± 71	NS
Uric acid (mg/dl)	5.79 ± 1.55	6.30 ± 1.93	0.014
Creatinine (mg/dl)	0.97 ± 0.3	1.05 ± 0.4	0.039
Total cholesterol (mg/dl)	198 ± 43	190 ± 46	NS
LDL (mg/dl)	130 ± 39	121 ± 38	NS
HDL (mg/dl)	39 ± 8	40 ± 10	NS
Triglyceride (mg/dl)	152 ± 110	153 ± 101	NS
Leukocytes (10^3/mm^3)	10.6 ± 3.5	10.1 ± 3.1	NS
CRP (mg/dl)	0.98 ± 1.41	1.68 ± 3.92	NS
Hemoglobin (mg/dl)	14.2 ± 1.7	14.3 ± 2.0	NS
AST (U/L)	45 ± 46	38 ± 36	NS
ALT (U/L)	26 ± 16	25 ± 20	NS
GGT (U/L)	29 ± 17	31 ± 19	NS
LDH (U/L)	337 ± 152	356 ± 205	NS
Total bilirubin (mg/dL)	0.62 ± 0.30	0.79 ± 0.55	0.007
Direk bilirubin (mg/dL)	0.19 ± 0.10	0.26 ± 0.19	0.005
Aortic sclerosis (%)	49.5	60	NS
Medications			
ASA (%)	20.3	34.0	0.009
BB (%)	19.8	29	NS
CCB (%)	12.3	14	NS
Oral nitrate (%)	0.9	1	NS
ACEi (%)	12.7	24	0.012
Statin (%)	9.4	21	0.005
PPI (%)	13.7	13	NS
Clopidogrel (%)	5.2	6	NS

BMI: Body Mass Index; CAD: Coronary Artery Disease; PAD: Peripheral Arterial Disease, LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; CRP: C-Reactive Protein; AST: Aspartate Transaminase; ALT: Alanine Aminotransferase; GGT: Gama-Glutamyl Transferase; LDH: Lactate Dehydrogenase; ASA: Acetylsalicylic Acid; BB: Beta Blocker; Acei: Angiotensinogen Converting Enzyme Inhibitor; PPI: Proton Pump Inhibitor

grade (3.95 ± 1.40 vs. 2.96 ± 1.51, p < 0.001), minimum lumen diameter (1.02 ± 0.61 vs. 0.79 ± 0.53 mm, p = 0.024), maximum lumen diameter (3.20 ± 0.44 vs. 2.89 ± 0.46 mm; p < 0.001), mean lumen diameter (2.11 ± 0.44 vs. 1.84 ± 0.40 mm, p = 0.001), the proximal diameter of the reference artery (3.15 ± 0.39 vs. 2.86 ± 0.43 mm, p < 0.001), and the distal diameter of the reference artery (2.96 ± 0.48 vs. 2.57 ± 0.47 mm, p < 0.001) were higher; whereas basal TIMI flow was lower (1.19 ± 1.34 vs. 2.04 ± 1.29, p < 0.001) in group 2.

Table 2: Coronary lesion and myocardial damage parameters according to the intracoronary nitrate administration before PCI.

Infarction parameters	PCI with nitrate (212)	PCI without nitrate (100)	P value
USAP/NSTEMI (%)/STEMI (%)	66.5/33.5	43/57	< 0.001
Intracoronary nitrate (mcg)	198 ± 14	-	-
Culprit lesion artery (%)			
LAD *or branch*	49.5	33.7	NS
Cx *or branch*	21.2	40	
RCA *or branch*	29.2	26.3	
Stent type (%)			
BMS/DES	9.9/80.2	28.7/64.9	< 0.001
Pre-dilatation (%)	74.4	77	NS
Post-dilatation (%)	20.8	20.4	NS
Recurrent dilatations (%)	5.7	12.2	0.044
Lesion type (1-4) (%)			
A	0.6	1.1	NS
B1	31.9	25.3	
B2	55.2	69	
C	12.3	4.6	
CK-MB (ng/mL) (*Admission*)	31 ± 58	23 ± 54	NS
CK-MB (ng/mL) (*peak*)	65 ± 85	113 ± 119	< 0.001
CK-MB (ng/mL) (*delta*)	34 ± 66	89 ± 111	< 0.001
Troponin I (ng/mL) (*Admission*)	6.8 ± 13	5.8 ± 13	NS
Troponin I (ng/mL) (*peak*)	20.4 ± 20	28 ± 22	0.003
Troponin I (ng/mL) (*delta*)	13.6 ± 17.9	22 ± 21	0.001
Pain to balloon time (*minutes*)	76 ± 206	97 ± 302	NS
Thrombus grade	2.96 ± 1.51	3.95 ± 1.40	< 0.001
Rentrop score	0.1 ± 0.4	0.1 ± 0.3	NS
MBG	2.2 ± 0.9	1.84 ± 1.0	0.007
TFC, *pre*-PCI	18 ± 8.8	16 ± 6.7	NS
TFC, *post*-PCI	15 ± 9	16 ± 12	NS
TIMI flow, *pre*-PCI	2.04 ± 1.29	1.19 ± 1.34	< 0.001
TIMI flow, *post*-PCI	2.92 ± 0.33	2.75 ± 0.61	0.011
Deployed stent diameter (mm)	2.88 ± 0.29	3.07 ± 0.45	< 0.001
Deployed stent length (mm)	26 ± 12	25 ± 12	NS
Lesion length	17.5 ± 7.3	18.0 ± 8.6	NS
Min. LD	0.79 ± 0.53	1.02 ± 0.61	0.024
Max. LD	2.89 ± 0.46	3.20 ± 0.44	< 0.001
Mean LD	1.84 ± 0.40	2.11 ± 0.44	0.001
Proximal RD	2.86 ± 0.43	3.15 ± 0.39	< 0.001
Distal RD	2.57 ± 0.47	2.96 ± 0.48	< 0.001
Lesion severity (%)	76 ± 20	78 ± 19	NS
Number of significant vessel	1.19 ± 0.47	1.11 ± 0.39	NS

Usap: Unstable Angina Pectoris; Nstemi: Non-St Elevated Myocardial Infarction; Stemi: St-Elevated Myocardial Infarction; Lad: Left Anterior Descending Artery; Cx: Circumflex Artery; Rca: Right Coronary Artery; Bms: Bare Metal Stent; Des: Drug Eluted Stent; Ck-Mb: Creatine Kinase Myocardial Band; Mbg: Myocardial Blush Grade; Tfc: Timi Frame Count; Pci: Percutaneous Coronary Intervention; Ld: Lesion Diameter; Rd: Reference Diameter

The lesion type, length, and severity, cTFC, number of the severely stenothic artery, and collateral flow were similar in both groups. While the placed stent diameter was smaller in group 1 (2.88 ± 0.29 vs. 3.07 ± 0.45 mm, $p < 0.001$), but there was no difference in stent lengths between the two groups. In addition, the rate of drug-

Table 3: The effects of intracoronary nitrate administration on coronary lesion parameters.

Lesion parameters	Before	After	P value[a]
Lesion length, pre/post-nitrate	17.5 ± 7.3	17.5 ± 7.5	NS
Delta-lesion length	0.11 ± 0.58		
Minimum LD, pre/post-nitrate	0.79 ± 0.53	0.83 ± 0.46	0.053
Delta-Min. LD	0.03 ± 0.21		
Maximum LD, pre/post-nitrate	2.89 ± 0.46	3.07 ± 0.43	< 0.001
Delta-Max. LD	0.22 ± 0.18		
Mean LD, pre/post-nitrate	1.84 ± 0.40	1.95 ± 0.36	< 0.001
Delta-Mean LD	0.11 ± 0.19		
Proximal RD, pre/post-nitrate	2.86 ± 0.43	3.04 ± 0.43	< 0.001
Delta proximal RD	0.22 ± 0.18		
Distal RD, pre/post-nitrate	2.57 ± 0.47	2.83 ± 0.40	< 0.001
Delta distal RD	0.29 ± 0.25		
Lesion severity, pre/post-nitrate (%)	76 ± 20	71 ± 18	< 0.001
Delta obstruction diameter with nitrate (%)	-4.18 ± 11.4		

LD: Lesion Diameter; RD: Reference Diameter; [a]: Paired test was used

eluted stent usage was higher (80.2 vs. 64.9%, p < 0.001) and recurrent post-dilatation was conducted more than group 2 (5.7 vs. 12.2%, p = 0.044) in group 1.

There was no difference in terms of predilatation of lesion rate and pain-to-balloon time between the two groups. MBG (2.2 ± 0.9 vs. 1.84 ± 1.0, p = 0.007) and TIMI flow (2.92 ± 0.33 vs. 2.75 ± 0.61, p = 0.011) were significantly higher in group 1 (Table 2).

Effects of intracoronary NTG administration on lesion parameters

Intracoronary NTG did not cause a significant change in lesion length, however, increased the minimum lesion diameter (0.03 ± 0.21 mm, p = 0.053), maximum lesion diameter (0.22 ± 0.18 mm, p < 0.001), mean lesion diameter (0.11 ± 0.19 mm, p < 0.001), reference coronary artery proximal diameter (0.22 ± 0.18 mm, p < 0.001), and reference coronary artery distal diameter (0.29 ± 0.25 mm, p < 0.001) whilst decreased the delta diameter of coronary lesion obstruction (4.18 ± 11.4%, p < 0.001) (Table 3).

The parameters that related to MACE

During follow-up, MACE developed in 50 of the 312 patients. The mean age was higher (65 ± 11 vs. 61 ± 12, p = 0.046) in the MACE (+) group. On the other hand, the rate of intracoronary NTG usage (51.4% vs. 69.9%, p = 0.028), NTG dose (190 ± 42 vs. 199 ± 8 mcg, p = 0.010), and the rate of patients with UA/NSTEMI (40 vs. 61%) were lower; while rate of patients with STEMI was higher (60 vs. 38%, p = 0.014) in MACE (+) group.

The proportion of patients with HT (68.6 vs. 50%; p = 0.038), admission glucose (174 ± 76 vs. 146 ± 71 mg/dl, p = 0.031), Hba1c (7.3 ± 2.2 vs. 6.6 ± 1.7 mg/dl, p = 0.027), serum creatinine (1.12 ± 0.44 vs. 0.97 ± 0.32 mg/dl, p = 0.002), delta CK-MB level (91 ± 118 vs. 47 ± 81 ng/ml; p = 0.005), and leukocyte count at admission (11.9 ± 4.77 vs. 9.98 ± 3.17 103/mm^3, p = 0.001) were significantly higher in the MACE (+) group.

The rate of post-dilatation (34.3 vs. 18.5%, p = 0.029) and the usage rate of acetyl salicylic acid (42.9 vs. 22.4%, p = 0.008), beta blockers (45.7 vs. 19.9%, p = 0.001), and proton pump inhibitors (25.7% vs. 12.1%; p = 0.028) were higher in patients with MACE (Table 4).

Independent predictors of MACE

In the logistic regression analysis, admission leukocyte count (OR = 1.147, 95% CI: 1.043-1.262, p = 0.005), Hba1c level (OR = 1.230, 95% CI: 1.019-1.484, p = 0.031), the usage of pre-hospital beta blocker (OR = 4.726, 95% CI: 2.082-10.728, p < 0.001), delta CK-MB level (OR = 1.006, 95% CI: 1.002-1.009, p = 0.004), and stent post-dilatation (OR = 0.663, 95% CI: 0.292-1.503, p = 0.020) were identified as independent predictors of MACE. Whereas, intracoronary NTG administration had no statistically significant effect on MACE (Table 5).

Discussion

The NTG administration increased the diameters of lesion and reference artery, and thus changed the preferred stent size. In addition, the reperfusion parameters such as MBG and TIMI flow improved with NTG, significantly. On the other hand, the leukocyte count, HbA1c level, delta CK-MB, prior beta-blocker usage, and the post-dilatation of coronary stent were determined as independent predictors of one-year MACE.

The main aim of this study was to reveal the effects of intracoronary NTG administration on MACE prediction and coronary lesion parameters. Although intracoronary NTG increased coronary artery and lesion diameters, it did not predict one year MACE.

Table 4: The significantly differed parameters of the MACE groups in univariate analyses.

Parameters	**MACE (-)** (262)	**MACE (+)** (50)	**P value**
Age (years)	61 ± 12	65 ± 11	0.046
Intracoronary nitrate use (%)	69.9	51.4	0.028
Intracoronary nitrate (mcg)	199 ± 8	190 ± 42	0.010
USAP-NSTEMI (%)	61.8	40	0.014
STEMI (%)	38.2	60	
Hypertension (%)	50	68.6	0.038
Post-dilatation (%)	18.5	34.3	0.029
Delta CK-MB (ng/ml)	47 ± 81	91 ± 118	0.005
Peak Troponin-I (ng/ml)	21 ± 21	31 ± 21	0.011
Admission blood glucose (mg/dl)	146 ± 71	174 ± 76	0.031
Hba1c	6.6 ± 1.7	7.3 ± 2.2	0.027
Creatinine (mg/dl)	0.97 ± 0.32	1.12 ± 0.44	0.002
Leukocytes (10^3/mm^3)	9.98 ± 3.17	11.9 ± 4.77	0.001
Medications			
ASA (%)	22.4	42.9	0.008
BB (%)	19.9	45.7	0.001
PPI (%)	12.1	25.7	0.028
Pain-to-balloon time/(min)	221.77 ± 121	206.68 ± 108	0.072

USAP: Unstable Angina Pectoris; NSTEMI: Non-ST Elevated Myocardial Infarction; STEMI: ST-Elevated Myocardial Infarction; CK-MB: Creatinine Kinase Myocardial Band; ASA: Acetylsalicylic Acid; BB: Beta Blockers; PPI: Proton Pump Inhibitors

Table 5: Logistical regression analysis for prediction of MACE.

Variables	**P value**	**OR (95% CI)**
Leukocyte count (10^3/mm^3)	0.005	1.147 (1.043-1.262)
Hba1c	0.031	1.230 (1.019-1.484)
Prior beta-blocker usage	< 0.001	4.726 (2.082-10.728)
Delta-CK MB (ng/mL)	0.004	1.006 (1.002-1.009)
Post-dilatation of stent	0.020	2.705 (1.170-6.253)
NTG administration	0.325	0.663 (0.292-1.503)
Constant	< 0.001	0.002

NTG: Nitroglycerine

Whereas, MBG and TIMI flow has improved with NTG administration. We think one of the possible causes is that NTG may not increase tissue-level reperfusion and myocardial viability. In order to evaluate the efficacy of intracoronary NTG administration at the tissue level, more specific techniques such as positron emission tomography (PET), myocardial perfusion scintigraphy (MPS), or cardiac magnetic resonance imaging (MRI) could be used [12-15]. In addition, reperfusion markers were interpreted by the naked eye without quantitative tools. Moreover, NTG was preferred in the smaller coronary arteries (proximal reference diameter: 2.86 ± 0.43 vs. 3.04 ± 0.43 mm, $p < 0.001$; distal RD: 2.57 ± 0.47 vs. 2.96 ± 0.48 $p < 0.001$), mostly. Thus, it was seen high interobserver variabilities and unequal distribution among groups. As a result, we think that a double-blind controlled study would give more accurate results regarding NTG and MACE relation.

The secondary consequences of this study were also noteworthy. Beta-blocker usage before the hospital admission increased one-year MACE, significantly. However, it was suggested to be given beta-blockers prior to the reperfusion of coronary occlusion in some previous studies, but there were also conflicting results [16,17]. Some studies revealed that beta-blocker use did not affect survival in patients with ACS who was treated with thrombolysis [18,19]. Chen ZM, et al. reported that early use of oral metoprolol did not have any effect on death, cardiac arrest, and reinfarction in patients with acute myocardial infarction (MI). It was even found to increase the prevalence of cardiogenic shock on the first day of admission. However, it was beneficial in preventing ventricular arrhythmias [20]. And also, some previous meta-analyses showed no significant mortality benefit of beta-blockers during short-term follow-up in patients with ACS [21,22]. We think it is still required further studies evaluating the effectivity of beta-blocker

usage in high risk patients for CAD.

Another remarkable finding of this study was post-dilatation of the placed stent was found to predict one year MACE. Zhi-Jiang Zhang, et al. also reported that post-dilatation of the stent in patients with acute MI increased the risk of death and recurrent MI at one-year follow-up. In addition, they found no benefit of post-dilatation on recurrent revascularization in all CAD patients [23]. On the other hand, HbA1c is well established predictor of MACE in both diabetic and non-diabetic individuals [24,25]. Although DM presence was not associated with, HbA1c was found to be an independent predictor of MACE in this study. Besides, the leukocyte count was another independent predictor of MACE. This finding was also demonstrated by TACTICS-TIMI 18 study, in which the six-month mortality rate was higher in those with higher leukocyte levels in patients with UA/NSTEMI [26]. In addition, Julio Núñez, et al. showed that the level of leukocyte was an independent predictor of long-term mortality in patients with acute MI [27].

Delta CK-MB was shown to be a marker of the magnitude of the myocardial damage in previous studies. Since it has prognostic significance it was used in clinical practice to modify treatment options in patients with CAD, frequently [28,29]. We also found that delta CK-MB was one of the independent predictors of MACE in this study. We think because the troponin-I level above 50 ng/ml is stated as > 50 ng/ml in our laboratory, it was not found to be a predictor of MACE. Indeed, intracoronary NTG was found to be associated with delta CK-MB, but it was not a predictor of MACE. The relationship between intracoronary NTG administration and MACE deserves to be examined with further studies with larger patient populations.

Limitations

There was limited number of patients included in our study and longer follow-up period is required. Secondly, randomization of patients, between the groups was deficient. Since we did not have the opportunity to use IVUS in our clinic, only angiographic evaluation could be performed. We think that a double-blind randomized-controlled study would give more accurate results. More detailed and sophisticated test such as MRI, PET, and MPS could be more beneficial identifying myocardial viability and damage size.

Conclusion

Intracoronary NTG administration increased lesion diameters and thus bring change in the choice of stent size in patients with ACS. However, NTG administration was not a predictor of MACE, it was related to coronary reperfusion parameters such as TIMI flow and MBG. In addition, leukocyte count, HbA1c level, delta CK-MB, beta-blocker usage, and the post-dilatation of coronary stent were independent predictors of one-year MACE.

Conflicts of Interest

None.

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