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Effect of Intracoronary Sodium Nitroprusside Before Percutaneous Coronary Intervention on Periprocedural Myonecrosis: A Prospective Randomized Study

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ABSTRACT

The aim of this study is to evaluate the effect of pre PCI administration of intracoronary nitroprusside on post procedural myonecrosis. Myonecrosis is a prognostically important complication of PCI. Nitric oxide is a potent vasodilator in the resistance arteriolar circulation, and plays a significant role in the control of coronary blood flow through the microcirculation. nitroprussideis a direct donor of nitric oxide. A total of 62 patients were randomized into the NTP (n= 31) or control (n= 31) group. Patients who were scheduled for non-urgent PCI in de novo native coronary arteries were eligible. All patients were pretreated with statin, aspirin and clopidogrel. Myonecrosis was measured by CK-MB elevation 24 h after PCI. The NTP group received intracoronary NTP befor PCI, whereas the control group did not. All patients in NPT group received NTP for prevention of myonecrosis at a dose of at least 50 µg given intrcoronary through guiding catheter. 22 patients received 50µg,7 patients received 100µg and 3patients received 150µg. The baseline CPK-MB concentration was 16±4.89 and 16.55±6.18 in the control and NTP groups, respectively (P=0.70). The mean increase of CPK-MB concentration 24h after PCI was 20±26.64 and 10.13±14.35 in the control and NTP groups, respectively (P=0.06). Mean systolic BP before injection of NTP was 144.58±21.51mmHg and after injection of NPT was 121±21.51mmHg. Bolus administration of NTP through the guiding catheter is associated with reduction in the occurrence of myonecrosis following non-urgent PCI in patients pretreated with dual antiplatelet agents and statins.

Key words: Sodium Nitroprusside, Percutaneous Coronary Intervention, Periprocedural Myonecrosis.

INTRODUCTION

The use of percutaneous coronary intervention(PCI) to treat ischemic coronary artery disease (CAD) has expanded dramatically over the past three decades, In the absence of left main or diffuse multivessel CAD, PCI is often the preferred method of revascularization[1]. Routine measurement of creatine kinase-MB isoform (CKMB) after PCI demonstrates periprocedural elevation in up to 40% of patients,which is almost always not associated with immediate clinical manifestations[2,3]. It was generally assumed that CK-MB elevation after cardiac manipulation is expected and, thus, a clear threshold above which elevation in cardiac markers is indicative of significant damage has not been accepted[4,5]. It has been demonstrated that the risk of subsequent cardiac events (death or MI) is related to the extent of cardiac troponin or CK-MB increase[6,7].

Different strategies have been proposed and tested to prevent periprocedural MI[8,]). Several pathophysiological factors are implicated in myonecrosis but the majority of authors conclude that distal embolization of residual material of the unstable plaque during the procedure of percutaneous revascularization can result in myocardial necrosis[1]). Nitroprusside (NTP) is a direct donor of nitric oxide(NO)(11).NO is an endothelium-derived compound that has multiple vascular functions, including vasodilation, inhibition of platelet adhesion and anti-inflammatory activity[12]. Therefore we hypothesis that NTP may be efficacious for prevention of myonecrosis through its action as a NO donor, vasodilation of microvessels, antiplatelet effects and anti-inflammatory. activity.

METHODS

Trial design and randomization. This is a randomized, prospective, single-center study. Patients were randomize either to NTP and control group in a 1:1 ratio.

Patient population. From July2010 to March 2011, 62patients (age 40-79 years) with stable or unstable angina Who were scheduled to undergo non-urgent PCI of de novo native coronary lesions in a native coronary artery were randomized. Exclusion criteria included the following: complete occlusion resulting in Thrombolysis In Myocardial Infarction (TIMI) grade 0 antegrade flow, thrombus-laden lesions, significant left main coronary stenosis,balloon angioplasty without stenting, occurrence of myocardial infarction within one week, systolic BP<100mmHg, allergy to NTP, chronic renal failure, STEMI or stent thrombosis within 24h after PCI, intrastent restenosis, ostial lesion, lesions with extensive calcifications, positive biomarkers before PCI, Use of glycoprotein IIb/IIIa antagonists during PCI, fluoroscopy time >30 min,Side-branch compromised (TIMI flow<3) and any angiographic complications(see PCI procedure).

Adjunctive medications. All patients received a clopidogrel loading dose of 300 mg before the PCI (for loading dose administered more than 6 h prior to procedure), or 600 mg clopidogrel (for loading dose less than 6 h before procedure).

During catheterization, all patients received intravenous unfractionated heparin bolus 100U/Kg. Additional heparin boluses were given to maintain ACT>250 s. The ACT was measured 5 min after heparin administration. Post-procedural antiplatelet regimen consisted of aspirin 160 mg/day and clopidogrel 75 mg/day. All patients were on statins prior to PCI and were discharged on statins .

PCI procedure. Stents were implanted according to current clinical practice. Angiographic success was defined as a final angiographic residual stenosis of <20% by visual estimation. Procedural success was considered in cases of angiographic success and absence of any in-hospital major complication (acute MI, need for bypass surgery or repeat PCI, or death).The occurrence of angiographic complications during PCI was recorded. Angiographic complications included minor/major side branch compromise or occlusions, abrupt intraprocedural vessel closure, major arterial dissection, thrombus formation, transient and/or prolonged slow-no reflow, distal embolization, or coronary perforation. Patients randomized to the NTP group were given 50 μg of NTP (diluted into 5 ml normal saline) through the guiding catheter into the target coronary artery after guidewire advancement. For multi-vessel stenting, another 50 μg of NTP would be given after guidewire advancement for intervention of the subsequent vessel. Patients randomized to the control group did not receive NTP pretreatment, and the procedure was carried out in the usual manner

Hemodynamic analysis. Patients were continuously monitored during all procedures. Heart rates and blood pressures recorded before and after administration of NTP were determined. The data regarding any effects of intravessel NTP were analyzed to ascertain adverse clinical effects on cardiac hemodynamics.

Assessment

CK-MB (mass concentration) and cardiac troponin I (cTnI) were assessed before PCI using a radioimmunoassay analyzer. Abnormal baseline CK-MB and/or cTnI levels were exclusion criteria for enrollment into the study. CK-MB values were

considered abnormal if they were elevated above the upper limit of normal (ULN). This is set at 25 mg/dl by our local laboratory.

Study end point

The primary end point of the study was to evaluate the incidence of myonecrosis (any elevation of CK-MB above25 mg/dl), in patients undergoing non-urgent PCI with or without pretreatment with intracoronary NTP. The secondary end point was any effects of intracoronary NTP to ascertain adverse clinical effects on cardiac hemodynamics.

Statistical analysis

On the basis of a two-sided test size of 5% and a power of 80%, it was anticipated that a minimum of 62 patients would need to be recruited in each group to detect a difference in the incidence of myonecrosis of 20%. Continuous variables are presented as mean ± 1 SD or as median and interquartile ranges, as appropriate.Differences between groups in normally and non-normally distributed variables were assessed using the unpaired Student t test and the Mann-Whitney U test, respectively.Categorical variables were analyzed by chi-square test. All probability values were 2-tailed and a value of $p< 0.05$ was considered significant. Data were analyzed with SPSS for Windows version 16.0(SPSS Inc., Chicago,Illinois).

RESULTS

Patient characteristics

A total of 62 patients (NTP group, n=31; control group, n= 31) were recruited into this study between July2010 to March 2011. There were no significant differences in the most relevant clinical and laboratory characteristics in the 2 groups.TG,LDL and HDL cholesterol levels at the time of the procedure were similar in the 2groups.There were no differences in age, sex distribution, history of hyperlipidemia , smoking, diabetes mellitus, mean ejection fraction, hypertension, stable or unstable angina and history of Previous myocardial infarction between the 2 groups of patients. (Table1).

Angiographic and procedural characteristics. Direct stenting was performed in 38.7% of cases in the NTP group and in 48.4% in the control group ($p = 0.57$). Directional or rotational atherectomy was performed in any patients in 2 group. Drug-eluting stents were implanted in 23(74.2%) and 27 (87.1%) patients in the control and NTP groups, respectively (P=0.88). Number of treated lesions/patient were 1.29±0.46 and 1.45±0.67 in the control and NTP groups, respectively (P=0.44).DES length (mm)/patient was 24.1±19.04 and 26.16±17.09 in the control and NTP groups, respectively (P=0.66). BMS length (mm)/

Table 1 : Clinical and Biochemical charecteristics of the Patients Enrolled in the 2 Groups

	Nitroproside Group(n=31)	Control Group(n=31)	p-Value
Age (yrs)	60.29±6.09	59.55±8.1	0.68
Men	15(48.4%)	20(60)	0.2
Symptoms			
Stable angina	17(548%)	14(45.2%)	0.44
Unstable angina	14(45.2%)	17(54.8%)	0.44
Diabetes mellitus	11(35.5%)	9(29%)	0.58
Previous myocardial infarction	11(35.5%)	9(29%)	0.58
Systematic Hypertension	16(51.6%)	15(48.4%)	0.79
Active Smoker	10(32.3%)	10(32.3%)	1
Hyperlipidemia	16(51.6%)	15(48.4%)	0.79
Mean ejection fraction	50±9.39	49.52±8.69	0.93
HDL	42±7.48	40.84±10.28	0.61
LDL	100.77±32	96.8±31.69	0.62
TG	169.94±79.87	167.58±84.26	0.92

patient was 4.74±8.52and 6.03±9.04 in the control and NTP groups, respectively (P=0.54). All the other angiographic and procedural characteristics were similar in the 2 groups (Table2).

NTP administration. All patients in NPT group received NTP for prevention of myonecrosis at a dose of at least 50 µg given intrcoronary through guiding catheter. 22 patients received 50µg,7 patients received 100µg and 3patients received 150µg.

Hemodynamic effects of NTP. Analysis of the hemodynamic data showed no evidence that NTP significantly altered patient blood pressure at the doses used (50 µg per injection).Mean systolic BP before injection of NTP was 144.58±21.51mmHg and after injection of NPT was 121±21.51mmHg

Cardiac markers increase. The baseline CPK-MB concentration was 16±4.89 and 16.55±6.18 in the control and NTP groups, respectively (P=0.70). Patients undergoing NTP pretreatment tended to have lower myonecrosis than those without NTP.The mean increase of CPK-MB concentration 24h after PCI was 20±26.64 and 10.13±14.35 in the control and NTP groups, respectively (P=0.06)(Figure 1).

DISCUSSION

This is the first randomized trial investigating the impact of NTP bolus pretreatment on the incidence of myonecrosis after non-urgent PCI. The power of this study for detecting difference between NPT and control group is 43%(á=0/05). The principle finding reported in this study was that intracoronary administration of NTP decreases the

Table 2 : Baseline angiographic and procedural characteristics of patients by treatment

			NTP Group (n=31)	Control Group (n=31)	P-Value
Type of lesion	A	0	12(38.7%)	14(45.2%)	0.58
		1	14(45.2%)	13(41.9%)	
		2	5(16.1%)	4(12.9%)	
	B	0	14(45.2%)	18(58.1%)	0.52
		1	15(48.4%)	9(29%)	
		2	2(6.5%)	4(12.9%)	
	C	0	29(93.5%)	29(93.5%)	1
		1	2(6.5%)	2(6.5%)	
Predilation		0	12(38.7%)	15(48.4%)	0.57
		1	18(58.1%)	14(45.2%)	
		2	1(3.2%)	2(6.5%)	
Postdilation		0	2(6.5%)		0.85
		1	20(64.5%)	21(67.7%)	
		2	9(29.5%)	9(29%)	
Number of BMS		0	20(64.5%)	23(74.2%)	0.37
		1	10(32.3%)	8(25.8%)	
		2	1(3.2%)	0(0%)	
Number of DES		0	4(12.9%)	8(25.8%)	0.88
		1	21(67.7%)	14(45.2%)	
		2	6(19.4%)	9(29%)	
Number of treated lesions/patient			1.45±0.67	1.29±0.46	0.44
Activated coagulating time (ACT)mean			328.39±53.83	324.10±72.90	0.79
Mean fluoroscopy time (min)			15.50±6.94	11.39±5.97	0.60

severity of myonecrosis after non-urgent PCI. Myonecrosis is a common sequel of percutaneous coronary intervention (PCI)[13]. However, the incidence (3.6% to 48.8%) and magnitude of myocardial damage after PCI is highly variable, depending on the patient's clinical, angiographic, and procedural characteristics; adjunctive pharmacotherapy; and the biomarker and thresholds applied to detect its presence[13].Possible mechanism of myonecrosis are prolonged balloon inflation ,side branch occlusion ,no reflow, distal embolization and coronary dissection[14,15,16]. Multilesion stenting, longer lesions, angulated lesion, prolonged inflation times, higher inflation pressure and number of stents are associate with increase cardiac enzyme in several studies[17-20]. Pretreatment with statin and antiplatelet agents are straregies proven to reduce post-PCI myonecrosis[21,22,23]. Briguori et al. reported the lower rate of myonecrosis after a single high (80 mg) loading dose of atorvastatin administered within 24 h before stent implantation(Naples II Trial)[23]. Patti et al. reported that loading with 600 mg of clopidogrel before PCI was associated with a significant reduction in the incidence of myonecrosis from 26 to 14%, compared with 300 mg loading(21). Chen et al. reported that despite adequate pretreatment with clopidogrel, patients with aspirin

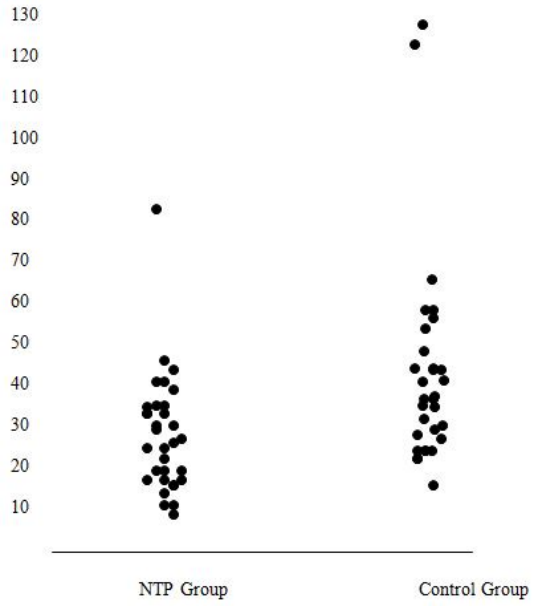

Fig. 1 : Distribution of CK-MB level after PCI in patients in the NTP and control groups

resistance as measured by a point-of-care assay have an increased risk of myonecrosis following non-urgent PCI (24). also lee et al. showed that Bolus administration of 50 mg of adenosine through the guiding catheter is associated with a 77% reduction in the occurrence of myonecrosis following non-urgent PCI in patients pretreated with dual antiplatelet agents and statins(25). Troponin is more sensitive than CK-MB in detecting smaller amounts of periprocedural myonecrosis, the prognostic implications of troponin elevation after PCI are less certain (26,27). In a study by Cavallini et al. troponin elevation was detected in 44% of patients undergoing PCI (vs. 16% CK-MB elevation) but, unlike CK-MB, did not predict 2-year mortality.

Is CK-MB elevation synonymous with myonecrosis?

Recently, magnetic resonance scans of patients with peri-PCI CK-MB elevation demonstrated discrete areas of hyperenhancement (necrosis) in the PCI territory, which did not occur in patients without CK-MB elevation(28).Nitric oxide is an endothelium-derived compound that has multiple vascular functions, including vasodilation, inhibition of platelet adhesion and anti-inflammatory activity. Nitric oxide has been shown to act as a physiological inhibitor of leukocyteendothelial cell interaction by suppressing up-regulation of several endothelial cell adhesion molecules, including P-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 (29).Nitric oxide is a potent vasodilator in the resistance arteriolar circulation (12) and plays a significant role in the control of coronary blood flow through the microcirculation (30). Although nitrates have traditionally been used as donors of nitric oxide to maximally dilate coronary arteries, significant differences between epicardial arteries and resistance arterioles have been described with respect to the metabolism of vascular wall is necessary to derive nitric oxide. However, resistance arterioles are unable to metabolize nitroglycerin to nitric oxide as do large nonresistance vessels (31), and nitroglycerin is relatively less efficacious in eliciting dilation in microvessels compared with large, epicardial vessels. On the other hand, nitroprusside (NTP) is a direct donor of nitric oxide and is reported to require no intracellular metabolism to derive nitric oxide

(11).NTP is a drug with short half-life(50 to 70 seconds)(32) and there are evidences that NTP does not significantly altered patient blood pressure and heart rate at the doses 50 to 200 µg per injection (33) Therefore we hypothesis that NTP may be efficacious and safe for prevention of myonecrosis through its action as a NO donor, vasodilation of microvessels, antiplatelet effects and anti-inflammatory activity.Yeh et al.reported that that NTP increased the caliber of both normal and stenosed coronary arteries in man and did not cause significant changes in heart rate or blood pressure(34). Parham et al. reported that intracoronary NTP (at doses up to 0.9 µg/kg) could produce coronary hyperemia (with increases in coronary blood flow) equivalent to that found with intracoronary adenosine. The hyperemic response to NTP was fast (peak coronary blood flow within 20 seconds from NTP bolus),and even more prolonged than with adenosine (up to 1 minute with NTP compared with 25seconds with adenosine)(35). Interestingly, the decrease in systemic blood pressure observed in our study was similar to or smaller than that reported in previous studies using lower NTP doses delivered through the guiding catheter (36, 37).

Study limitations

The study was not blinded. We can only speculate on the possible cardioprotective mechanisms of intracoronary NTP. The sample size is relatively small. If we had a larger sample size our result would be more significant. The Route of administration of NTP in this study was via guiding catheter. Route of administration via distal balloon delivery for selectively administrating NTP into the distal coronary bed is more reliable.

CONCLUSIONS

Bolus administration of NTP through the guiding catheter is associated with reduction in the occurrence of myonecrosis following non-urgent PCI in patients pretreated with dual antiplatelet agents and statins. Further studies are required to investigate the reduction of myonecrosis with NPT and short and long term morbidity and mortality.

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