Cardioprotective effects of single oral dose of nicorandil before selective percutaneous coronary intervention

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Abstract

Objective: Nicorandil, an opener of ATP-sensitive K+ channels, was used to treat angina in patients with coronary artery disease. In this study, we aim to investigate the cardioprotective effects of single oral dose of nicorandil in patients undergoing selective percutaneous coronary intervention (PCI).

Methods: One hundred and thirty-eight patients with acute coronary syndrome undergoing PCI from July 2011 to October 2012 were randomly divided into control group (group 1, n=47), 10 mg oral nicorandil group (group 2, n=45), and 20 mg oral nicorandil group (group 3, n=46) about 2 hours before procedure, respectively. Cardiac troponin I (cTnI) levels were determined at 20 ~ 24 hours after PCI.

Results: There was a significant difference in the rate of any cTnI elevation among the three groups (group 1: 36.17%, group 2: 20.00%, group 3: 15.22%, p=0.0176). With respect to the frequency of cTnI elevation ≥3 and 5× the upper limit of normal (ULN), there also had statistical difference among the three groups (17.02% in group 1, 8.89% in group 2, and 4.35% in group 3, respectively for cTnI elevation ≥3× ULN, p=0.0428; 12.77% in group 1, 6.67% in group 2, and 2.17% in group 3, respectively, for cTnI elevation ≥5× ULN, p=0.0487). Logistic regression analysis showed that LVEF (OR=0.915, 95% CI=0.853-0.981) and the use of nicorandil (OR=0.516, 95% CI=0.267-0.996) before PCI were independent protective factors of myocardial injury.

Conclusion: Single oral dose of nicorandil (10 mg, 20 mg) 2 hours before the PCI procedure could decrease the incidence of peri-procedure myocardial injury and PCI-related myocardial infarction. *(Anatolian J Cardiol 2015; 15: 125-31)*

Key words: coronary heart disease, percutaneous coronary intervention, nicorandil, preconditioning, myocardial injury

Introduction

As an efficient method for relieving myocardial ischemia and preserving ventricular function, percutaneous coronary intervention (PCI) has been frequently applied in patients with coronary artery disease (CAD). However, PCI has been reported to be associated with reperfusion injury particularly in those with new device interventions such as stenting (1, 2). The incidence of myocardial injury demonstrated by elevated level of makers of myocardial necrosis such as cardiac troponins (cTnT or cTnI) and MB isoenzyme of creatine kinase (CKMB) in the peri-operative period ranged from 10% to 40% (3, 4). Although such patients might show no abnormalities in the electrocardiogram (ECG), and heart function (4, 5), they were reported to be associated with worse early and long-term outcomes (3, 4, 6, 7). Moreover, cTnI was a more sensitive and powerful factor for predicting the major adverse cardiac events compared with CKMB (8-10). Currently, several drugs have been used to reduce the incidence of peri-procedural myocardial injury, such as statins (11, 12), intra-coronary administration of beta receptor blocker (13), nitrates (14), glycoprotein IIb/IIIa blocker, and adenosine.

In 1986, Murry et al. (15) reported that repeated brief ischemia and reperfusion induced a powerful endogenous protective effect, known as ischemic preconditioning (IPC). Studies indicated that the opening of mitochondrial ATP-sensitive K+ (KATP) channels was crucial in initiating IPC (16-18). Nicorandil has been used as an opener of KATP channels in treating angina in patients with CAD. Previous studies reported that the cardioprotection effects of nicorandil were dependent on the opening of the KATP channel (16, 17). Nicorandil could prevent the no-flow/slow reflow phenomenon in patients undergoing primary

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Accepted Date: 10.01.2014 **Available Online Date:** 16.04.2014

DOI:10.5152/akd.2014.5207

PCI. Moreover, nicorandil had a myocardial protective effect measured by reduced ST segment elevation and less occurrence of angina during PCI in patients with unstable angina (19).

Nevertheless, in previous studies, nicorandil was administered mainly through intra-coronary or intravenous route. Few reports were available about cardioprotective effect administered with single oral dose, and measured by cardiac injury markers. In this study, the cardioprotective effects of single oral dose of nicorandil in the patients undergoing PCI were studied by determining cTnI levels at 20 ~ 24 hours after PCI.

Methods

Patients

This study was an investigator-initiated, open-labeled, paralleled, randomized trial. One hundred and thirty-eight patients were enrolled in this study. Prior to the PCI, enteric coated aspirin (100 mg per day), clopidogrel (75 mg per day, at least 300 mg in total), and subcutaneous injections of low molecular heparin were given to patients. Patients were randomly divided into control group (group 1, n=47, without nicorandil), 10 mg oral nicorandil group (group 2, n=45), and 20 mg oral nicorandil group (group 3, n=46) about 2 hours before the invasive procedures. The inclusion criteria were as follows: patients without medication of nicorandil within 5 days prior to the study; and those with normal levels of cardiac troponin I (cTnI) before PCI. The exclusion criteria were: patients using glibenclamide and/or glimepiride for the control of blood sugar before the PCI; those with procedure-related complications such as side-branch occlusion, coronary dissection, acute thrombosis in coronary artery, and those with no-reflow; those showed the contraindications of anti-platelet drugs.

Protocols

The study protocol was approved by The Second Hospital of Hebei Medical University Center's Ethics Committee. Informed consent was obtained before coronary angiography. Oral nicorandil were given about 2 hours prior to the invasive procedures. Peripheral blood samples were collected 20 ~ 24 hours after PCI, plasma cTnI levels were determined by Beckman coulter ACCESS 2 analyzer with chemiluminescence immunoassay method and the original reagent. PCI was performed via a transradial or femoral artery approach, and transradial approach was adopted in most patients. After PCI procedure, low molecular weight heparin was continued until discharged. What's more, clopidogrel (75 mg per day, at least one year) and enteric coated aspirin (100 mg per day, lifelong) were administrated.

Information was collected including demographic data, blood chemistry, and concurrent medications. The following PCI-related parameters were also collected including the number of diseased vessel, severity of target lesions (estimated by the Gensini coronary score), the duration and pressure of pre-balloon dilation and stent inflation, the number of stent implanted, and TIMI blood flow grade after stent implantation.

The primary endpoint was elevation of serum cTnI after PCI. Other major adverse cardiac events (MACE) and all-cause mortality during hospitalization were also recorded. MACE was defined as cardiac death, nonfatal acute myocardial infarction, nonfatal stroke, emergency bypass surgery. Bleeding events were also recorded and graded by TIMI classification.

Statistical analysis

SPSS statistical software (version 13.0 SPSS Company, Chicago, IL, USA) and MedCalc statistical software (version 9.0 MedCalc Software, Mariakerke, Belgium) were used for the data analysis. The data of normal distribution were presented as mean±standard deviation. The data of skewed distribution were presented as [M (QL, QU)]. Each set of data were underwent the normality (Kolmogorov-Smirnov) and homogeneity of variance test. If the conditions were met, one way analysis of variance (ANOVA) among the three groups was used; otherwise rank sum test (Kruskal-Wallis H test) was used. Categorical variable were expressed as frequency (%), chi-square test (chi-square for trend) were used for intergroup comparison. Stepwise, logistic regression analysis was used to screen the independent predictors of myocardial injury during the periprocedural period. A p value less than 0.05 was considered statistically significant.

Results

The baseline information in this study was summarized in Table 1 and Table 2. No statistical difference was noted in demographics and clinical variables among the three groups before PCI except the administration of statins. The use of statins was significantly higher in the group 1 than in the group 2 (p=0.007). While for angiographic features, the rate of using one stent per-patient was significantly higher in the group 1 than in the group 2 and group 3 (p=0.031 for group 1 versus group 2, p=0.013 for group 1 versus group 3, respectively). The duration of stent inflation in the group 1 lasted longer than in the group 2 and group 3 (p=0.000 for group 1 versus group 2, p=0.005 for group 1 versus group 3, respectively). The Gensini coronary score in group 1 was lower than group 2 (p=0.012). The usage of post balloon was significantly higher in the group 3 than in the group 2 (p=0.005).

There was a significant difference in the rate of any cTnI (normal: <0.100 ng/mL) elevation among the three groups (group 1: 36.17%, group 2: 20.00%, and group 3: 15.22%, p=0.0176) by chi-square for trend test, with the lowest in group 3. Moreover, with respect to the frequency of cTnI elevation ≥3 and 5× the upper limit of normal (ULN), there was also statistical trend for difference among the three groups (group 1, 17.02%; group 2, 8.89%; and group 3, 4.35%, p=0.0428, for cTnI elevation ≥3× ULN; group 1, 12.77%; group 2, 6.67%; group 3, 2.17%, p=0.0487, for cTnI elevation ≥5× ULN) by chi-square for trend test. There was also a significant difference in the rate of any cTnI elevation among the

Table 1. Baseline clinical characteristics of 3 groups (n=138)

	Groups			
	Group 1 (n=47)	**Group 2 (n=45)**	**Group 3 (n=46)**	***P***
Age, years	53.00 (49.00, 63.00)	57.00 (53.00, 64.00)	59.00 (52.75, 64.00)	0.195
Male, n (%)	31 (65.96)	31 (68.89)	27 (58.70)	0.580
BMI, kg/m^2	24.6±3.0	25.2±2.9	24.8±2.9	0.676
DM, n (%)	10 (21.28)	7 (15.56)	9 (19.57)	0.774
Hypertension, n (%)	28 (59.57)	31 (68.89)	32 (69.57)	0.527
Active smokers, n (%)	24 (51.06)	28 (62.22)	21 (45.65)	0.275
Previous PCI, n (%)	2 (4.26)	3 (6.67)	3 (6.52)	0.857
Previous MI, n (%)	3 (6.38)	2 (4.44)	2 (4.35)	0.881
AMI, n (%)	18 (38.30)	10 (22.22)	13 (28.26)	0.235
Creatinine, μmol/L	71.1±19.4	75.2±16.6	69.8±15.5	0.507
LVEF (%)	63.56 (60.12, 65.96)	65.05 (60.83, 67.72)	62.86 (60.53, 65.47)	0.630
TC, mmol/L	4.0±0.9	4.3±1.0	4.4±1.0	0.922
LDL-C, mmol/L	2.2±0.7	2.5±0.9	2.5±0.7	0.428
ACEI/ARB, n (%)	27 (57.45)	29 (64.44)	34 (73.91)	0.250
Beta blocker, n (%)	39 (82.98)	39 (86.67)	38 (82.61)	0.844
CCB, n (%)	20 (42.55)	20 (44.44)	21 (45.65)	0.955
Statin, n (%)	40 (85.10)	27 (60.00)	34 (73.91)	0.025
Tirofiban, n (%)	20 (42.55)	17 (37.78)	18 (39.13)	0.875

Values are expressed as mean±SD. The data of skewed distribution were presented as [M (QL, QU)]. Group 1 - without nicorandil; group 2 - 10 mg oral nicorandil group; group 3 - 20 mg oral nicorandil group.
ACEI - angiotensin converting enzyme inhibitor; AMI - acute myocardial infarction; ARB - angiotensin II receptor blocker; BMI - body mass index; CCB - calcium channel blocker; DM - diabetes mellitus; LDL-C - low-density lipoprotein cholesterol; LVEF - left ventricular ejection fraction; MI - myocardial infarction; PCI - percutaneous coronary intervention; TC - serum total cholesterol

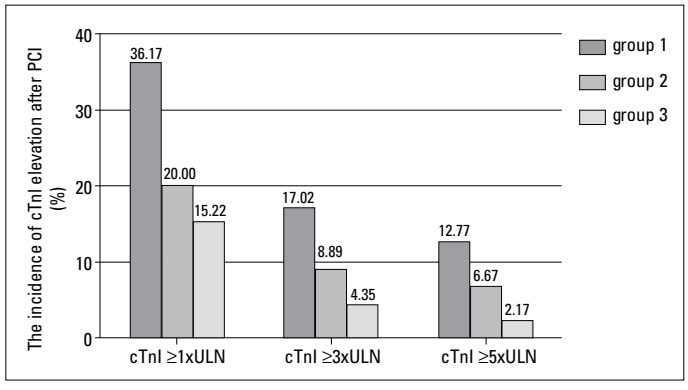

Figure 1. The incidence of cTnI elevation after PCI among 3 groups
Group 1 - without nicorandil; group 2- 10 mg oral nicorandil group; group 3-20 mg oral nicorandil group; cTnI - cardiac troponin I; PCI - percutaneous coronary intervention; ULN - upper limit of normal

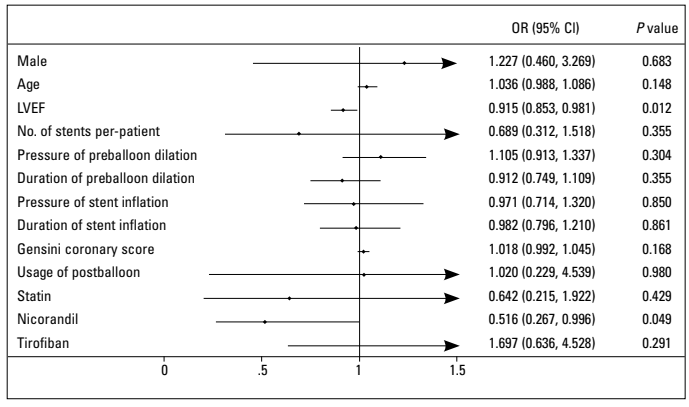

Figure 2. Multivariate logistic regression analysis: Independent predictor of peri- operation period of myocardial injury
LVEF - left ventricular ejection fraction

three groups (p=0.046) by common chi-square test. However, we failed to detect statistical difference between any two groups for cTnI elevation ≥3× ULN and 5× ULN by the common chi-square test (p=0.119, for cTnI elevation ≥3× ULN; p=0.124, for cTnI elevation ≥5× ULN) (Fig. 1).

To demonstrate whether nicorandil administration was an independent protective factor before PCI, stepwise logistic regression analysis was performed with entering baseline data [(male, age, left ventricular ejection fraction (LVEF)], PCI-related variants (NO. of stents per-patient, duration and pressure of preballoon dilation and stent inflation, severity of target lesions), and other co-medications (statin, nicorandil, tirofiban) into the model. The results indicated LVEF (OR=0.915, 95% CI=0.853-0.981, p=0.012) and the administration of nicorandil before PCI (OR=0.516, 95% CI=0.267-0.996, p=0.049) were independent protectors of peri-procedural myocardial injury (Fig. 2).

In this study, the major complications included cardiac death, nonfatal acute myocardial infarction, nonfatal stroke,

Table 2. Angiographic and interventional characteristics of 3 groups (n=138)

	Groups			*P*
	Group 1 (n=47)	**Group 2 (n=45)**	**Group 3 (n=46)**	
No. of diseased vessel, n (%)				
1	17 (36.17)	11 (24.44)	19 (41.30)	0.221
2	16 (34.04)	20 (44.44)	19 (41.30)	0.577
3	14 (29.79)	14 (31.11)	8 (17.39)	0.256
No. of stents per-patient, n (%)				
1	37 (78.72)	26 (57.78)	25 (54.35)	0.030
2	8 (17.02)	16 (35.56)	16 (34.78)	0.084
More than 3	2 (4.26)	3 (6.67)	5 (10.87)	0.462
Stent diameter, mm	3.03±0.04	2.98±0.04	3.02±0.04	0.525
Stent length, mm	18.43±0.59	20.67±0.89	17.37±0.44	0.052
Pressure of preballoon dilation, atm	9.65 (8.73, 1057)	9.45 (8.61, 10.28)	10.13 (9.38, 10.89)	0.271
Duration of preballoon dilation (s)	8.02 (7.24, 8.80)	8.91 (7.96, 9.87)	9.01 (8.27, 9.85)	0.130
Pressure of stent inflation, atm	14.30 (13.78, 14.82)	13.89 (13.50, 14.26)	13.93 (13.56, 14.31)	0.089
Duration of stent inflation (s)	9.32 (8.89, 9.97)	7.49 (6.70, 8.28)	8.41 (7.76, 9.08)	0.000
Gensini coronary score	19.23 (14.91, 23.56)	28.07 (21.95, 34.18)	21.74 (16.69, 26.79)	0.031
Usage of postballoon, n (%)	4 (8.51)	1 (2.22)	10 (21.74)	0.01
Contrast agent volume, mL	148.62±33.54	144.33±35.76	144.78±41.67	0.830

Values are expressed as mean±SD. The data of skewed distribution were presented as [M (QL, QU)].
Group 1 - without nicorandil; group 2 - 10 mg oral nicorandil group; group 3 - 20 mg oral nicorandil group

emergency bypass surgery. No complications were reported during the hospitalization period. Additionally, TIMI blood flow grade following PCI in all three groups were 3.

Discussion

The aim of this study is investigation of cardioprotective effect of nicorandil in coronary investigation.

According to the results; nicorandil before the intervention, could decreased peri-procedure myocardial injury.

PCI is currently recognized as one of the effective treatment choice for patients with CAD. However, myocardial injury after PCI has been frequently reported in these patients (1, 2). Previous studies reported that intravenous and/or intra-coronary injection nicorandil could reduce the incidence of myocardial damage after PCI (19-26). In addition, a randomized controlled study indicated that nicorandil 5 mg orally 3 times daily could reduce QT dispersion during the coronary angioplasty (27). As a hybrid of nitrate and ATP-sensitive potassium channel opener (28-30), nicorandil could increase the coronary blood flow (31-33), dilate the micro-coronary artery (34), lower the afterload, and protect the cardiac muscle by mimicing the ischemic preconditioning (15, 20, 35-39). To date, the mechanism of nicorandil in reducing the incidence of myocardial injury after PCI is still not well elucidated (40, 41).

Currently, more attention has been paid on the mimic of ischemia preconditioning of nicorandil in the protection of myocardium. The peak plasma level of nicorandil was achieved at 0.42±0.18 hour after the single oral dose administration of 10 mg, and 0.42±0.22 hour of 20 mg (42). The plasma concentration of nicorandil decline as mean values of apparent elimination half-life was 52±13 minutes for 20 mg oral doses (42). Investigation about pharmacokinetics of nicorandil proved that nicorandil was rapidly and extensively absorbed from the gastrointestinal tract and no extensive presystemic metabolism seemed to occurred (43, 44). Additionally, IPC was believed to be transient (lasting less than 3 hours) (45). Based on these above-mentioned factors, if single oral does of 10 mg and 20 mg were used about 2 hours before selective PCI exerted cardioprotective effects by initiating IPC, IPC could last through the entire PCI procedure. It has been reported that a 3-fold elevation of cTnI after successful elective PCI is predictive of future cardiac events, especially the need for early repeat revascularization (46, 47). According to the Universal Definition of Myocardial Infarction (48), percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTnI values (>5× 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTnI values >20% if the baseline values are elevated and are stable or falling. Our results showed that there were significant differences in the rate of any cTnI elevation among the three groups (p=0.0176), cTnI ≥3× ULN (p=0.0428) and 5× ULN (p=0.0487). The analysis of chi-square for trend does not provide the difference among variables, but show the tendency about variables. Although there had no statistical difference between

any two groups respectively for cTnI elevation ≥3× ULN and 5× ULN by the common chi-square test, we did demonstrate that there was a statistical trend for difference among the 3 groups by the more powerful chi-square for trend test. This might be further explained by the relative small sample size of our study. In 2003, Sugimoto et al. (49) designed a retrospective study to assess whether intravenous nicorandil in conjunction with PCI improve the long-term prognosis in patients with acute myocardial infarction. The study showed that the frequency of cardiac events was significantly lower in the nicorandil group, and the use of nicorandil was derived as a potential factor related to freedom of cardiac events by multiple regression analysis (OR=0.27, p<0.01). Similarly, in our study we also showed that administration of nicorandil was a protective factor of myocardial damage, and nicorandil caused a dose-dependent decrease in myocardial damage rate (OR=0.516, p=0.049). Those with increased LVEF showed lower incidence of cTnI elevation, demonstrating LVEF might be a protective factor for the myocardial damage (OR=0.915, p=0.012). So we assumed that the incidence of cTnI elevation may lower by improving the LVEF before selective PCI. Based on these facts, we speculated that the myocardial damage-limiting effects of nicorandil in the perioperative stage were through mimicking the IPC.

Study limitations

Our study has several limitations. Firstly, only cTnI was selected as the measurement of myocardial injury. However, many studies demonstrated cardiac troponins are more sensitive and powerful factor for predicting the major adverse cardiac events compared with CKMB. What is more, the third universal definition of myocardial infarction also used cardiac troponins as the most important measurement, in which PCI-related myocardial infarction was only defined by elevation of cardiac troponins instead of CKMB. Secondly, the sample size of our study was relatively small. This may be one of the reasons why chi-square test and chi-square for trend test have different statistical conclusion for comparison of cTnI elevation≥ 3× ULN and 5× ULN among the 3 groups. Thirdly, our study wasn't a double-blind, placebo-controlled study, and the follow-up period was restricted for only during the hospitalization. So the conclusion derived from our study should be further confirmed by larger scale and longer follow-up studies.

Conclusion

Single oral dose of nicorandil (10 mg, 20 mg) 2 hours before the PCI procedure could decrease the incidence of peri-procedure myocardial injury and the incidence of peri-procedure myocardial infarction.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - W.C.; Design - J.Y., J.Z., W.C.; Supervision - F.L., R.X.; Resource - X.Y., G.G.; Data collection &/or processing - H.Z., J.L.; Analysis &/or interpretation - X.Y., G.Z.; Literature search - Q.W., X.G.; Writing - J.Y., J.Z.; Critical review - W.C.

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