Research Paper

Analysis of the Relationship between Circulating NT-proBNP and Myocardial Injury, Inflammatory Response and Coronary Collateral Circulation in Acute Myocardial Infarction before Clopidogrel Treatment

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Prior to the initiation of clopidogrel treatment, this study focuses on exploring the relationship between N-terminal prohormone of brain natriuretic peptide and the severity of myocardial injury, inflammatory response markers, as well as the development of coronary collateral circulation in individuals diagnosed with acute myocardial infarction. The experimental group (n=70) included individuals with acute myocardial infarction receiving clopidogrel treatment from October 2019 to February 2022. As a comparison, during the same period 70 healthy individuals were included as the control group. The comparison included markers of myocardial injury (cardiac troponin I, creatine kinase-myocardial band, myoglobin) and inflammatory markers (tumor necrosis factor alpha, C-reactive protein, interleukin-6) along with N-terminal prohormone of brain natriuretic peptide levels. N-terminal prohormone of brain natriuretic peptide levels were also compared in different grades of cardiac function and coronary collateral circulation. This research investigated the connection between N-terminal prohormone of brain natriuretic peptide, myocardial injury, inflammatory response, and coronary collateral circulation in acute myocardial infarction patients. The experimental group exhibited remarkably increased levels of cardiac troponin I, creatine kinase-myocardial band, and myoglobin ($p<0.05$), along with elevated levels of interleukin-6, C-reactive protein, tumor necrosis factor alpha, and N-terminal prohormone of brain natriuretic peptide in comparison to the control group. Notably higher N-terminal prohormone of brain natriuretic peptide levels were found in cardiac function class IV patients compared to class III and class II ($p<0.05$). Higher N-terminal prohormone of brain natriuretic peptide levels were observed in coronary collateral circulation grade 3 patients as opposed to grade 2 and grade 1 ($p<0.05$). Serum N-terminal prohormone of brain natriuretic peptide showed positive correlation with cardiac troponin I, creatine kinase-MB, myoglobin, interleukin-6, C-reactive protein, tumor necrosis factor alpha, and cardiac function classification ($p<0.05$), and negative correlation with coronary collateral circulation ($p<0.05$). Prior to clopidogrel treatment, patients with acute myocardial infarction exhibit a notable correlation between circulating N-terminal prohormone of brain natriuretic peptide and the degree of myocardial injury, inflammatory response markers, and coronary collateral circulation.

Key words: N-terminal prohormone of brain natriuretic peptide, acute myocardial infarction, inflammatory response, coronary collateral formation

Coronary artery occlusion and disrupted blood supply lead to myocardial cell necrosis, resulting in Acute Myocardial Infarction (AMI). Typically impacting middle-aged individuals, this condition is characterized by rapid onset, rapid progression, a considerable disability rate, and a prominent fatality rate[1,2]. Since AMI progresses rapidly, timely treatment is crucial to prevent irreversible damage to the myocardium[3]. Several studies have suggested a correlation between the levels of inflammatory factors and the incidence and development of AMI[4]. Coronary collateral circulation is a protective mechanism formed during arterial perfusion of the heart, which can help maximize cardiac function[5].

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Early myocardial injury can be effectively diagnosed using N-Terminal Brain Natriuretic Peptide (NT-proBNP), which serves as a valuable index due to its sensitivity to heart damage. NT-proBNP levels have been suggested to be related to coronary collateral circulation grading for evaluating cardiac function[6]. With the aim of studying the correlation between NT-proBNP and the degree of myocardial injury, inflammatory response markers, and coronary collateral circulation in AMI patients, this research scrutinized clinical data from 70 individuals treated with clopidogrel and 70 healthy individuals during the same period.

MATERIALS AND METHODS

Research objects:

70 patients treated with clopidogrel for AMI and 70 normal subjects were recruited during the period from October 2019 to February 2022. The study comprised an experimental group of 70 AMI patients and a control group of 70 normal subjects. In the experimental group, there were 39 males and 31 females, aged from 41 y to 70 y, with a mean age of (61.04±5.25) y. In Killip cardiac function class; class II 21 cases, class III 39 cases and class IV 10 cases. There were 38 cases and 32 females, aged from 41 y to 70 y old, with a mean age of (61.42±5.13) y in the control group. The data analysis showed no distinct disparities in the overall characteristics between the two groups, as the p-value exceeded 0.05.

Inclusion criteria: The experimental group comprised individuals who fulfilled the diagnostic standards for AMI as outlined in "diagnosis and treatment of AMI"[7]. These patients were treated with clopidogrel, and their AMI diagnosis was confirmed by using coronary angiography. Normal neurological function was also required.

Exclusion criteria: Patients in the experimental group were excluded if they had severe arrhythmia or electrolyte disturbance complications, malignant tumor complications, incomplete clinical data, malignant tumor coexistence, or infectious diseases.

Methods:

Serological examination: After an overnight fast, both groups underwent physical examination on the day of admission, during which 5 ml of venous blood samples were collected. The blood was separated by high-speed (3000 r/min) centrifugation for 15 min, the supernatant was sent to the laboratory. Myocardial injury markers, including Myoglobin (Mb), cardiac Troponin 1 (cTnI), and Creatine Kinase-Myocardial Band (CK-MB), were analyzed with an Enzyme-Linked Immunosorbent Assay (ELISA) kit from Jiangsu Eliza Biotechnology Co., Ltd. In the detection of inflammatory markers (C-Reactive Protein (CRP), Tumor Necrosis Factor Alpha (TNF-α), and Interleukin 6 (IL-6)), a solid-phase ELISA method was employed. The detection kit utilized for this purpose was from Wuhan Ilerite Biotechnology Co., Ltd. NT-proBNP was detected by Electrochemiluminescence immunoassay using the detection kit from Shanghai Jingkang Bioengineering Co., Ltd.

Cardiac function rating: In class I; no heart failure, but increased pulmonary capillary wedge pressure. In class II; mild heart failure, with lung wet rales <50 % in both lung fields, persistent sinus tachycardia, third heart sound galloping horse rhythm, and increased venous pressure. In class III; severe heart failure, with lung wet rales in both lung fields >50 % and associated with acute pulmonary edema and in class IV; systolic blood pressure is <90 mmHg, urine volume per hour is <20 ml, and pulse per minute is >100 times.

Coronary collateral circulation grade: Coronary angiography was performed in the experimental group, and the grade of coronary collateral circulation was evaluated according to the Rentrop method[8]. The evaluation criteria included; grade 0 means absence of filling in the non-collateral circulation channel. In grade 1, branch of collateral circulation filling lesion was observed, but it could not fill the epicardial vascular segment. In grade 2, filling vessels of collateral circulation and part of the subepicardial vascular segment were observed. And in grade 3, filling vessels of collateral circulation and the whole subepicardial vascular segment were observed.

AMI treatment: Clopidogrel hydrogen sulfate (Sanofi Winthrop Industry, Chinese medicine standard word J20180029, 75 mg) should be taken orally, each time 75 mg, once a day. Those who fail to take the drug within 12 h from the last time should take it immediately (75 mg). Conversely, those who fail to take it >12 h do not need to take it. The drug should be used for at least 6 mo.

Data collection:

Levels of NT-proBNP were compared among patients

with different grades of cardiac function and coronary collateral circulation, and its correlation with myocardial injury markers, inflammatory markers, and coronary collateral circulation formation was analyzed.

Statistical analysis:

Statistical Package for the Social Sciences (SPSS) 20.0 was utilized for analysis. For categorical data, frequency and composition ratios were used for description, and the Chi-square (χ^2) test was utilized for analysis. Numeric data were presented as mean±standard deviation, and independent sample t-tests were performed to assess statistical significance with a threshold of $p<0.05$.

RESULTS AND DISCUSSION

The experimental group exhibited significantly elevated ($p<0.05$) levels of CK-MB, cTnI, and MB as opposed to the control group (Table 1). The experimental group exhibited notably increased serum levels of CRP, TNF-α, IL-6, and NT-proBNP as opposed to the control group ($p<0.05$) as shown in Table 2. Both the class IV group and class III group exhibited significantly higher serum NT-proBNP levels in comparison to class II group, and the IV grade group showed even higher levels as opposed to the III grade group ($p<0.05$) as shown in Table 3.

Patients with grade 2 and grade 3 coronary collateral circulation exhibited significantly elevated serum NT-proBNP levels in comparison to those with grade 1 collateral circulation, and specifically within the grade 3 group, NT-proBNP levels exhibited a significant increase in contrast to those observed in the grade 2 group ($p<0.05$) as shown in Table 4.

Based on Pearson correlation analysis, a significant positive correlation was observed between NT-proBNP and cTnI, CK-MB, MB, and cardiac function. Additionally, there was a significant negative correlation with coronary collateral circulation formation as shown in Table 5. A significant positive correlation ($p<0.05$) was observed between NT-proBNP and IL-6, CRP, and TNF-α, as determined by Pearson correlation analysis as shown in Table 6.

TABLE 1: CLINICAL INFORMATION OF THE TWO GROUPS

Group	cTnI (μg/l)	CK-MB (μg/l)	Mb (μg/l)
Experimental (n=70)	39.98±1.52	75.53±1.67	126.65±5.21
Control (n=70)	1.14±0.27	1.68±0.31	30.43±5.64
t	210.493	363.769	104.847
p	<0.001	<0.001	<0.001

TABLE 2: THE SERUM INFLAMMATORY MARKERS AND NT-proBNP LEVELS ($\bar{x}$±s)

Group	IL-6 (ng/l)	CRP (ng/l)	TNF-α (ng/l)	NT-proBNP (μg/l)
Experimental (n=70)	17.68±1.14	18.03±1.32	16.54±1.25	423.63±20.51
Control (n=70)	6.98±1.27	6.14±1.15	7.15±1.14	210.64±20.14
t	52.456	56.822	46.437	61.993
p	<0.001	<0.001	<0.001	<0.001

TABLE 3: THE NT-proBNP LEVELS IN PATIENTS WITH DIFFERENT CARDIAC FUNCTION RATING ($\bar{x}$±s)

Group	NT-proBNP (μg/l)
Class II (n=21)	399.56±21.63
Class III (n=39)	422.65±20.12$^{\#}$
Class IV (n=10)	477.99±19.67$^{\#*}$
F	49.56
p	<0.001

Note: As opposed to class II group ($^{\#}p<0.05$) and as opposed to class III group ($^{*}p<0.05$)

TABLE 4: THE NT-proBNP LEVELS IN PATIENTS WITH DIFFERENT GRADES OF CORONARY COLLATERAL CIRCULATION (x̄±s)

Group	NT-proBNP (μg/l)
Grade 1 (n=19)	387.12±21.35
Grade 2 (n=40)	431.54±20.52#
Grade 3 (n=11)	457.92±19.02#*
F	49.59
p	<0.001

Note: As opposed to grade 1 group (#p<0.05) and as opposed to grade 3 group (*p<0.05)

TABLE 5: CORRELATION ANALYSIS BETWEEN SERUM NT-proBNP AND MYOCARDIAL INJURY MARKERS, CARDIAC FUNCTION GRADE AND CORONARY COLLATERAL CIRCULATION

Variables	NT-proBNP	
	r	p
cTnI	0.41	<0.001
CK-MB	0.397	<0.001
Mb	0.433	<0.001
Cardiac function classification	0.496	<0.001
Coronary collateral circulation	-0.429	<0.001

TABLE 6: ANALYSIS OF THE RELATIONSHIP BETWEEN SERUM NT-proBNP AND INFLAMMATORY MARKERS

Variables	NT-proBNP	
	r	p
IL-6	0.414	<0.001
CRP	0.462	<0.001
TNF-α	0.427	<0.001

AMI has seen a consistent upward trend occurrence in recent years, solidifying its position as the primary catalyst for cardiovascular fatalities[3]. Despite advances in medical technology, the mortality rate of AMI is still significant, with myocardial injury, inflammatory states, and the formation of coronary collateral circulation during treatment all having a serious impact on patient prognosis[9-11]. This study utilized data from patients at our hospital to delve into the diagnosis and treatment strategies utilized for individuals with AMI, offering valuable perspectives and findings to enhance clinical practices.

NT-proBNP, produced by ventricular myocytes, exhibits high sensitivity to variations in ventricular volume. When there is ventricular pressure overload, increased volume, or increased ventricular wall pressure caused by heart failure, it causes an increase in NT-proBNP levels[12,13]. This study discovered a significant elevation in serum NT-proBNP levels within the experimental group, signifying a notable surge in NT-proBNP levels during AMI as opposed to the control group. cTnI, CK-MB, and Mb are all markers of myocardial injury. When patients have AMI, their body experiences myocardial injury, and the levels of these markers will sharply increase. In this study, the experimental group showed noticeable elevated cTnI, CK-MB, and Mb levels in comparison to the control group. Individuals with AMI suffer from myocardial hypoxia, which stimulates ventricular myocytes to produce BNP and increase the levels of NT-proBNP[14]. The study findings indicated a significant elevation in serum NT-proBNP levels in the class IV group in contrast with the class III group. This suggested that the level of NT-proBNP effectively reflects the cardiac function of patients. The findings showed that through Pearson correlation analysis, NT-proBNP is positively correlated with cTnI, CK-MB, Mb, and cardiac function, which is consistent

with previous literature results[15]. Patients with AMI cause damage to myocardial tissue and necrosis, which causes local mononuclear macrophages to gather and activate, leading to the production of IL-6 and TNF-α, and promoting hepatocyte secretion of CRP[16,17]. This study revealed a substantial increase in serum TNF-α, CRP, and IL-6 levels in the experimental group in contrast with the control group, indicating a clear inflammatory response in patients diagnosed with AMI. The findings showed that NT-proBNP was positively correlated with TNF-α, CRP, and IL-6 levels. The reason behind this is that the inflammatory response can cause the production and increase of reactive oxygen species, peroxides and proteolytic enzymes, leading to an increase in plaque load and exacerbating plaque rupture and disease, thus forming a vicious cycle with NT-proBNP[18]. Coronary collateral circulation can protect against myocardial ischemia caused by coronary artery stenosis, maximize inhibition of the infarct area, and maintain myocardial activity[19,20]. This study demonstrated that patients with grade 3 coronary collateral circulation had significantly higher serum NT-proBNP levels than those with grade 2 coronary collateral circulation. Moreover, the study findings revealed a clear negative correlation between the formation of coronary collateral circulation and NT-proBNP levels. NT-proBNP inhibitory effect on vascular smooth muscle cell proliferation and its promotive effect on atherosclerosis contribute to the hindrance of coronary collateral circulation formation. In this study, analysis of patients with AMI and normal subjects shows that NT-proBNP has high significance in the detection of AMI, which is worthy of clinical promotion and application. However, no follow-up or prognostic analysis was conducted in this study, leading to a certain degree of bias. Therefore, future studies should include follow-up and analysis of different prognoses to provide a more favorable basis for this study.

To conclude, NT-proBNP levels in patients with AMI before clopidogrel treatment have a significant correlation with myocardial injury, markers of inflammatory response, and the formation of coronary collateral circulation, suggesting its potential as an indicator of the degree of myocardial injury and inflammation.

Conflict of interests:

The authors declared no conflict of interests.

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