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Protective Effect of Nicorandil Injection on Myocardial Damage in Patients with Acute ST-Elevation Myocardial Infarction

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FL and QH conducted the experiments in this study. LL and QM contributed to the design and interpretation of the current study and wrote the article. All authors read, revised, and approved the final manuscript.

Key words
Acute ST-elevation myocardial infarction, Nicorandil injection, Myocardial damage, Myocardial infarction area, Inflammatory response

ABSTRACT

ST-elevation myocardial infarction (STEMI) is a serious cardiovascular disease. Nicorandil injection (NI) has the effect of dilating coronary artery and inhibiting calcium ion influx in myocardial cells, so it has a protective effect on myocardial damage (MD). The objective of this study was to protect NI on MD in STEMI patients. A retrospective analysis was conducted, including STEMI patients who met the inclusion criteria, and they were divided into Nicorandil group (NG) and control group (CG). The left ventricular end-systolic volume index (LVESVI), wall motion score index (WMSI), ejection fraction (EF), and clinical symptoms were compared between subjects adopting different methods following 6 weeks of intervention. The extent of myocardial infarction (MI), neutrophil lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), uric acid (UA), interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP) were analyzed. There were clear distinctions in LVESVI and WMSI between both groups. The area of MI was 14.81±4.31 percent in the NG and 18.57±4.72 in the CG, the distinction was apparent (t=-3.729). UA, NLR, and PLR in the NG were markedly lower as against the CG. The levels of IL-6, and hs-CRP in the NG were markedly better as against the CG. It was concluded that NI has an obvious protection on MD in STEMI patients, and can markedly inhibit the infarct size and inflammatory response level in patients with acute STEMI.

INTRODUCTION

Acute ST-elevation myocardial infarction (STEMI) is one of the most serious types of cardiovascular diseases (CVD), and its high incidence and high mortality have brought great challenges to public health and clinical medicine (Qian *et al*., 2022). The pathogenesis of STEMI is closely related to myocardial damage (MD). Although coronary intervention is widely used in STEMI patients, reperfusion injury caused by myocardial reperfusion is still a problem that can't be ignored (Gong *et al*., 2022; Reis, 2022). Finding an effective treatment has the clinical meaning to reduce the severity of MD in STEMI patients.

Acute myocardial infarction (AMI) is myocardial ischemic necrosis, and the pathological basis is the rupture of unstable atherosclerotic plates in the coronary artery, the local aggregation and activation of platelets (PLT), and the development of red thrombus leading to acute lumen occlusion (Rui *et al*., 2021; Nicolau, 2022). After the occurrence of AMI, myocardial cells, endothelial cells, fibroblasts, and interstitial cells are damaged and die, which leads to acute inflammatory response through immune response (Henry *et al*., 2022). Percutaneous coronary intervention (PCI) implantation of stent or balloon dilatation can also cause damage to the coronary endothelium, which inevitably causes platelet aggregation and activation, leading to micro-thrombosis. Moreover, it can damage vascular smooth muscle cells, promote local inflammatory response, and aggravate MD (Wei and Jiang, 2023; Schmitz *et al*., 2022). A few indicators in blood routine examination can be used as systemic inflammatory response, which is not only correlated with the coronary atherosclerosis (CA), but also to the severity of its lesions. These emerging serum markers are expected to predict CVD (Stark and Massberg, 2021). Among them, the increase of neutrophil (NEU) has been confirmed by many studies as an independent risk factor for adverse events of AMI, and it also has a good predictive value for the mortality of AMI patients treated with PCI, which has been widely adopted in clinical evaluation of the prognosis of AMI

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patients (Konijnenberg *et al*., 2020). Nicorandil injection (NI), as a commonly used calcium antagonist, has been adopted in the intervention of CVD. NI has antiarrhythmic effects, coronary artery dilation, and myocardial oxygen consumption reduction. The mechanism of action includes coronary artery dilation and inhibition of calcium ion influx in myocardial cells, thereby reducing myocardial ischemia and improving myocardial blood supply (Otsuka, 2021; Liu *et al*., 2021). In recent years, some studies have shown that NI may have a protective effect on MD in patients with acute STEMI (Sawuer *et al*., 2021; Wan *et al*., 2023); however, the protective effect of NI on MD in STEMI patients and its mechanism of action are still unclear.

This study aimed to systematically evaluate the protection of NI on MD in STEMI patients and explore its potential mechanism of action. A randomized controlled trial was conducted to compare the differences in echocardiography and clinical symptoms of STEMI patients who met the inclusion criteria. In addition, the effect of NI on the expression levels of serum inflammatory factors was evaluated to reveal its mechanism of action, providing a basis for future research, and it may provide enlightenment for the treatment of other related diseases.

MATERIALS AND METHODS

General information

A retrospective analysis of data from STEMI patients was conducted. 180 hospitalized STEMI patients who meet the requirements from Affiliated Hospital of Guizhou Medical University to Affiliated Hospital of Guizhou Medical University were randomly divided into two groups: nicorandil group (NG, n=90) and controls (CG, n=90). Patients in the NG were treated with NI, and patients in the CG were treated with conventional treatment.

Patients in both groups were eligible to join the study if they met the following inclusion criteria: (1) Age ≥18 years old and ≤75 years old; All patients in the MACE (major adverse cardiac events) group and the non-MACE group met the diagnostic criteria for acute STEMI; (2) clinically diagnosed acute STEMI; (3) patients who did not require urgent coronary angiography or intervention; (4) the onset time of myocardial infarction (MI) was within 6 h; (5) complete clinical data and relevant examination results; (6) patients could understand and cooperate with the trial process, and signed the informed consent form.

Patients who did not meet the diagnostic criteria for acute STEMI, had received coronary artery bypass grafting or PCI, other serious CVD (such as heart failure, arrhythmia, hepatic and renal insufficiency, severe organ dysfunction), with obvious bleeding tendency or receiving anticoagulant therapy, showing adverse reactions after the use of nicorandil and allergies to or contraindications to the drugs in this article, severe mental illness or cognitive impairment, and those who had participated in other interventional studies were excluded from the study.

Data collection

The clinical data mainly included: gender, age, BMI, history of hypertension, diabetes, dyslipidemia, smoking history, and drinking history. There were no statistically clear distinctions in systolic blood pressure, diastolic blood pressure, and heart rate (HR) at admission.

Routine blood analysis comprising white blood cell count (WBC), NEU absolute value, lymphocyte (LYM) absolute value, red blood cell distribution width (RDW), PLT count, neutrophile lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and Killip classification of cardiac function was done. Laboratory tests included uric acid (UA), LYM, PLT, total cholesterol, NEU, WBC, and red blood cell distribution within 24 h after admission.

Observation indicators

Range of MI

Tc-MIBI myocardial perfusion imaging was used to assess the range of MI. The equation was (area of bull's-eye region of interest/total area of bull's-eye map) ×100%= area of MI.

Echocardiography

The ventricular wall motion was evaluated according to the left ventricular segment method of echocardiography, and normal was scored as 1 point. Reduced motion was scored as 2 points. The absence of movement was recorded as 3 points. Abnormal movement was scored as 4 points, and ventricular aneurysm as 5 points. Echocardiographic parameters included left ventricular end-systolic volume index (LVESVI), wall motion score index (WMSI), and ejection fraction (EF).

Inflammatory markers

NLR, PLR, and UA of two methods were subjected to contrast following 6 weeks of intervention.

Serum inflammatory factors

The serum inflammatory factors of two methods were observed following 6 weeks of intervention. The levels of interleukin-6 (IL-6) were detected by enzyme-linked immunosorbent assay, and the level of serum high-sensitivity C-reactive protein (hs-CRP) was detected by rate nephelometry.

Statistical analysis

SPSS20.0 software was adopted to analyze the experimental data. The data following normal distribution

and homogeneity of variance were presented in the format of mean±SD ($\bar{x}\pm s$). The chi-square test was adopted to perform contrast, and the rate (n, %) was adopted to express the count data. The test level was set at 0.05, and $P<0.05$ was considered statistically significant.

RESULTS

WBC, NEU, LYM, RDW, and PLT were collected from the venous blood of the patients at admission. Statistics were adopted to calculate the above test indicators (Table I). As displayed in Table II, there was similar in Killip classification of heart function, hypertension, diabetes, gender, and age between both groups ($P>0.05$).

Table I. Effect of nicorandil on clinical data of patients with acute ST-elevation myocardial infarction.

Items	Nicorandil group (n=90)	Control group (n=90)	Z	P
WBC	10.27±2.53	11.02±2.11	-0.235	0.509
NEU	7.49±3.18	8.03±2.87	-1.023	0.367
LYM	1.62±1.03	1.71±0.87	-1.123	0.418
RDW	12.43±1.48	11.33±1.54	-4.067	0.402
NLR	5.93±2.31	4.62±2.01	-3.054	0.538
PLR	169.43±87.65	175.32±93.45	-1.402	0.682
PLT	251.46±95.43	267.8±85.04	-1.041	0.754
NLR	8.61±3.62	4.52±3.03	-0.235	0.009*
PLR	165.36±102.54	171.43±87.49	-3.294	0.001*
UA (μmol/L)	437.62±109.43	387.8±97.61	-1.041	0.002*

*, $P<0.05$; WBC, white blood cell count; NEU, neutrophil; LYM, lymphocyte; RDW, red blood cell distribution width; NLR, neutrophile lymphocyte ratio; PLR, platelet-lymphocyte ratio; PLT, platelets; UA, uric acid.

Table II. Effect of nicorandil on clinical information of patients with acute ST-elevation myocardial infarction.

Indicators		Nicorandil group (n=90)	Control group (n=90)	χ^2/Z	P
Killip classification of cardiac function (n, %)	Grade 1	25 (27.78%)	34 (37.78%)	8.135[a]	0.508
	Grade 2	35 (38.89%)	23 (25.56%)	13.504[a]	0.714
	Grade 3	21 (23.33%)	18 (20.0%)	7.410[a]	0.911
	Grade 4	9 (20.0%)	15 (16.67%)	26.551[a]	0.573
Gender	Male	38 (42.22%)	46 (51.11%)	9.435[a]	0.645
	Female	52 (57.78%)	44 (48.89%)		
Hypertension		65 (72.22%)	47 (52.22%)	3.507[a]	0.601
Diabetes		47 (52.22%)	32 (35.56%)	4.312[a]	0.403
Age		63.27±3.42	65.78±3.07	4.132[a]	0.876

[a], chi-square test; [b], Z test.

The WMSI was 1.58±0.23 in the NG and 1.75±0.37 in the CG, and the difference had statistical meaning (t=-4.652, $P<0.05$) (Fig. 1). The LVESVI was (31.58±5.35) mL/m^2 in the NG and (35.57±6.83) mL/m^2 in the CG (t=-3.091, $P<0.05$). EF was (59.83±4.61) mL/m^2 in the NG and (56.78±5.13) mL/m^2 in the CG, and the distinction was not obvious (t=-1.817, $P>0.05$). MI area (%) measured by resting radionuclide imaging at 6 weeks after MI. MI area (%) was 14.81±4.31 in the NG and 18.57±4.72 in the CG, and the distinction had statistical meaning (t=-3.729, $P<0.05$).

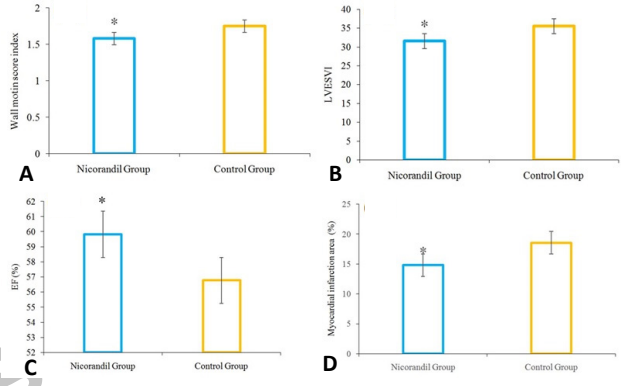

Fig. 1. Effect of nicorandil between groups. A, wall motion score index (WMSI); B, left ventricular end-systolic volume index (LVESVI); C, ejection fraction (EF); D, extent of myocardial infarction (MI) in patients with acute ST-elevation myocardial infarction.

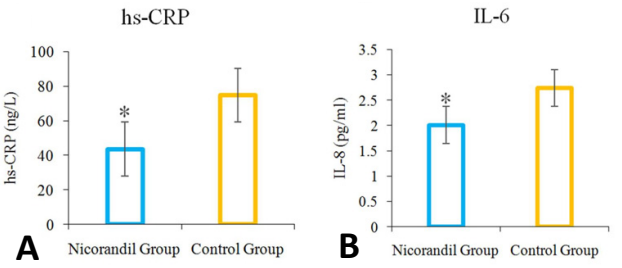

Fig. 2. Effect of nicorandil on serum interleukin-6 and high-sensitivity C-reactive protein (CRP) indicators in patients with acute ST-elevation myocardial infarction.

PLR and NLR are inflammatory markers, which are simple and reliable to reflect the degree of inflammation, and are inseparable from oxidative stress and inflammatory response in the human body. The UA, NLR, and PLR of the two groups are given in Table I. The UA, NLR, and PLR of the NG were markedly lower as against the CG ($P<0.05$).

The level of IL-6 was (2.01±0.05) in the NG and (2.74±0.13) in the CG (t=42.174, $P<0.05$). The level

of hs-CRP was (43.58±9.94) in the NG, and that was (74.82±13.83) in the CG (t=8.614, P<0.05) (Fig. 2).

DISCUSSION

Changes such as cardiac remodeling and myocardial fibrosis after MI have a continuous impact on the ventricular contraction effect, resulting in a high incidence of heart failure of 32% to 48%. Complications of MI include myocardial thickening, ventricular volume expansion and morphological changes. NI, as a commonly used calcium antagonist, can protect the ischemic myocardium, reduce the area of MI, improve stunting, simulate the myocardial protection of ischemic preconditioning, and thus improve the prognosis of the disease (Zhang *et al*., 2018). Jiang *et al*. (2020) showed that intravenous nicorandil could further reduce the area of MI in STEMI patients. Zhang *et al*. (2021) proposed that intracoronary injection of nicorandil and alprostadil had a slight outcome on blood pressure and HR. Nicorandil through targeted perfusion microcatheter can effectively improve myocardial perfusion in patients with elective PCI. This article evaluated the protection and mechanism of NI on MD in STEMI patients. Oral administration of nicorandil in patients with acute STEMI showed that patients treated with NI indicated obvious improvements in myocardial enzymes, electrocardiogram, echocardiography, and clinical symptoms relative to the CG. This suggests that NI can reduce the degree of MD and improve myocardial function, and has important application potential in the clinical treatment of STEMI patients. The area of MI measured by resting radionuclide imaging was (14.81±4.31) % in the NG and (18.57±4.72) % in the CG. These results indicate that nicorandil not only has a cardioprotective outcome on AMI patients, but also provides myocardial protection in the chronic phase and recovery phase of AMI. Lv *et al*. (2022) pointed out that nicorandil had a protective outcome on MD caused by exhaustive exercise. Wang *et al*. (2019) proposed that nicorandil exerted myocardial protection through its anti-hypoxia and anti-oxidation effects. Chen *et al*. (2021) proposed that nicorandil has a strong anti-inflammatory effect and protects the myocardium from myocardial infarction. Zhao *et al*. (2019) reported that nicorandil had an obvious effect in reducing the incidence of cardiovascular adverse events and improving cardiac function. Sharma *et al*. (2022) pointed out that nicorandil had an obvious effect on serum creatinine and blood urea nitrogen. UA is a human metabolite, and its level can be affected by a variety of factors, including inflammation and heart health status. If UA levels are reduced, it may reflect the positive effects of nicorandil on inflammation and heart health. UA was markedly higher in the NG than in the CG in this article.

The UA, NLR, and PLR of patients in the NG in this article were markedly lower as against the CG, and NLR is an indicator of inflammatory and immune status. Patients in the NG had reduced UA and NLR, meaning that there was relatively less NEU and relatively more LYM. This may imply a regulatory effect of nicorandil on inflammatory response and immune status during treatment. Reduced NLR may be associated with better suppression of inflammation and immune regulation. PLR is an indicator representing the inflammatory state and PLT activity (Hu and Yu, 2017). PLR is decreased, indicating that PLT is relatively low, while LYM count is relatively high. This may indicate that nicorandil has a certain regulatory effect on the inflammatory process and PLT aggregation. Lower PLR may be associated with reduced inflammatory response and PLT activity. Taken together with other studies related to MI patients, these findings may indicate a potential benefit of NI in improving inflammatory response, immune status, and PLT activity. These results provide some support for the use of nicorandil in the treatment of MI patients, but more clinical studies are needed to validate and further confirm the clinical significance of these findings.

Inflammatory response participates in the formation of arteriosclerosis and the onset of coronary heart disease (CHD). Hs-CRP is a representative indicator of inflammatory response and a commonly used inflammatory marker, and its elevation is often associated with the inflammatory process and increased risk of cardiovascular disease (Lin *et al*., 2022). The decrease of hs-CRP level after treatment may indicate the improvement of inflammatory state by nicorandil. Reduced hs-CRP levels may be associated with reduced inflammatory response, improved endothelial function, and reduced risk of cardiovascular disease. Some scholars pointed out that hs-CRP can predict the prognosis of CHD patients (Wen *et al*., 2023). In the process of atherosclerotic plaque formation, CRP will be deposited in the arterial wall, which can combine with lipoproteins, activate the complement system, produce a large number of inflammatory mediators, release oxygen free radicals, cause intimal damage, vasospasm, and unstable plaque detachment, aggravate atherosclerosis, and lead to AMI (Cheng *et al*., 2023). IL-6 is a cytokine involved in the regulation of inflammatory response and immune function (Cayrol and Girard, 2022). In recent years, the role of the inflammatory theory in CA has gained significant attention. All pathways converge on IL-6, which is a key cell signaling cytokine of the innate immune system (Vilotić *et al*., 2022). Li *et al*. (2022) has stated that elevated levels of IL-6 are associated with an increased risk of future myocardial infarction in apparently healthy men. This

article revealed that patients receiving nicorandil after treatment showed improvement in serum IL-6 and hs-CRP, which may imply that nicorandil has a potential role in inhibiting inflammatory response, regulating immune function, and improving cardiovascular health. These findings support the possibility of nicorandil as a treatment for CVD, but further studies are needed to validate and confirm these results. NI has potential application in the clinical management of STEMI patients, but further studies are still needed to clarify its long-term efficacy and safety, as well as the best treatment regimen.

CONCLUSION

This article aimed to investigate the protection and mechanism of NI on MD in patients with acute STEMI. The results show that NI can markedly reduce MD in STEMI patients, reduce the concentration of hs-CRP in patients with myocardial protection, but also can effectively inhibit inflammatory factors, reduce the area of MI in STEMI patients. Further studies are needed to further analyze the long-term outcomes and safety of NI. Although this article suggests that NI has a protective outcome on MD in STEMI patients in the short term, the long-term efficacy and safety of NI still need to be followed up and observed. In addition, the research on the mechanism of NI can be more in-depth and detailed. For example, the specific regulatory mechanism of NI on calcium influx in cardiomyocytes and the relationship between molecular pathways related to cardiomyocyte apoptosis, oxidative stress, and inflammatory response can be explored.

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IRB approval

This study was approved by the Advanced Studies Research Board of Affiliated Hospital of Guizhou Medical University, Guiyang 550001, Guizhou Province, China.

Ethical approval

The study was carried out in compliance with guidelines issued by ethical review board and committee of Affiliated Hospital of Guizhou Medical University, China. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

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