Cardiovascular Reviews, 2023, Volume 1, Issue 1
http://ojs.bbwpublisher.com/index.php/CR

New Progress of Clinical Application of Nicorandil in the Treatment of Coronary Heart Disease

Lingbo Wang[1]*, Chengguo Wang[2]

[1]Qilu Medical University, Zibo 255300, Shandong Province, China

[2]Liaocheng Chiping District Hospital of Traditional Chinese Medicine, Liaocheng 252100, Shandong Province, China

Corresponding author: Lingbo Wang, m15263591909@163.com

Abstract: Nicorandil (NIC) is a calcium channel blocker, which has been widely used in the treatment of coronary heart disease (CHD). Although NIC has shown good efficacy and safety clinically, there are still some unresolved issues with its therapeutic mechanism and pathway of action. Studies in recent years have shown that the clinical application of NIC in the treatment of CHD has made new progress, such as being widely used in stable angina pectoris (AP), myocardial infarction, and percutaneous coronary intervention (PCI). In this article, we discuss the new progress of NIC in the treatment of CHD.

Keywords: Nicorandil; Coronary heart disease; Clinical application

Online publication: June 23, 2023

1. Introduction

Coronary heart disease (CHD) is a type of heart disease that results from ischemia and oxygen deprivation of the heart muscle due to narrowing or blockage of the coronary arteries. Nicorandil (NIC) can improve the symptoms and prognosis of CHD by inhibiting the entry of calcium ions into cardiomyocytes, reducing myocardial oxygen consumption and inhibiting myocardial contraction. NIC, which can protect the myocardium and thus inhibit the progression of CHD and reduce its complications, is now a widely used drug for CHD. Therefore, the specific use of NIC in the treatment of CHD is comprehensively analyzed in this paper.

2. Mechanism of action of nicorandil on coronary heart disease

CHD is a cardiovascular disease characterized by narrowing, blockage, and/or hardening of the walls of coronary arteries. Its pathogenesis comprises a complex process of multiple factors, including (i) endothelial cell dysfunction (endothelial cells make up a layer of cells in the blood vessel wall, secreting a series of biologically active substances that are important for maintaining vascular endothelial function and vascular tone; endothelial cell dysfunction is an early event in the pathogenesis of CHD, which can lead to vessel wall damage and inflammatory response, thereby promoting plaque formation); (ii) dyslipidemia (hyperlipidemia is an important risk factor for CHD; it can lead to vascular endothelial cell damage and inflammatory response, promoting plaque formation and development); (iii) inflammatory response (the formation and development of CHD plaques are closely related to inflammatory response; there are a large number of inflammatory cells and inflammatory mediators in plaques, such as monocytes, T lymphocytes, and inflammatory cytokines, which are involved in the formation, stability, and rupture of plaques); (iv)

oxidative stress (oxidative stress refers to the imbalance between oxygen free radicals and other oxidants inside and outside cells and antioxidant substances in cells, leading to a series of harmful reactions; in CHD, the generation of oxidative stress is closely related to intraplaque inflammatory response, dyslipidemia, and endothelial cell dysfunction).

NIC, as a calcium channel blocker with a high application rate, can block the influx of calcium ions, reduce the metabolic level of myocardial cells, and play a role in reducing myocardial ischemia and myocardial injury. NIC also has the effect of widening coronary arteries and peripheral blood vessels, reduces blood pressure and cardiac load, improves cardiac function, and reduces cardiac oxygen consumption. In addition, NIC can also inhibit the automaticity and conduction of the heart, slow down the heart rate, and reduce the oxygen demand of cardiomyocytes, thereby alleviating the onset of myocardial ischemia and angina pectoris. The drug also plays a role in the treatment of CHD through some other mechanisms of action. For example, the antioxidant and anti-inflammatory effects of NIC can inhibit the generation of oxygen free radicals and inflammatory responses, thereby alleviating myocardial ischemia and injury. As another example, NIC can inhibit platelet aggregation and thrombus formation, thus preventing the occurrence of serious consequences such as myocardial infarction caused by thrombus formation. Hu *et al*. [1] demonstrated that the intravenous pre-injection of NIC has a protective effect on the brain and can improve the neurological function and cerebral blood flow of rats after cardiopulmonary resuscitation. Shi *et al*. [2] proposed that the drug can resist the specific apoptosis process of hypoxic/reoxygenated cardiomyocytes, thereby reversing the manifestations of myocardial hypoxia.

3. Clinical application of nicorandil in stable angina pectoris

The narrowing or blockage of the coronary arteries in patients with angina predisposes them to myocardial ischemia. At this time, cardiomyocytes require more oxygen and nutrients to maintain normal function. When the myocardial oxygen supply and demand are out of balance, angina pectoris occurs. NIC can increase blood flow, improve myocardial oxygen supply, and reduce cardiac contractility and heart rate, thus reducing myocardial oxygen demand. At the same time, it can also reduce the preload and afterload of the heart, further reducing the burden on the myocardium. In a study by Gao [3], conventional therapy (control group) and NIC therapy (observation group) were used for AP patients. The results showed that the total effective rate of the observation group was 100%. The number of angina attacks, the duration of angina, and the cardiac function indexes of the observation group were better compared with the control group. It is evident that NIC can suppress the symptoms of angina pectoris and restore the relevant indexes of heart function, with a definite curative effect.

4. Clinical application of nicorandil in myocardial infarction

Myocardial infarction is often accompanied by arrhythmias. NIC can reduce the excitability of cardiomyocytes, thereby reducing the occurrence of arrhythmias. After myocardial infarction, patients are also prone to re-infarction. This drug can reduce coronary artery spasm and platelet aggregation, thereby preventing the occurrence of re-infarction. It is evident that NIC can improve the prognosis of myocardial infarction through multiple mechanisms, but it should be noted that NIC is not the only drug for the treatment of myocardial infarction. Appropriate treatment options should be selected depending on the case. Ji [4] proposed that the combined therapy of rosuvastatin and NIC should be used for acute non-ST-segment elevation myocardial infarction. The results showed that the clinical efficacy of the combination was better compared with rosuvastatin monotherapy. The levels of high-sensitivity C-reactive protein and nitric oxide also significantly improved in these patients, confirming that the combination of NIC and rosuvastatin can improve the curative effect and protect vascular endothelial function. In the research by Li *et al*. [5], nitroglycerin and NIC intracoronary injection were given before acute myocardial infarction surgery, and

the results showed that the myocardial blood perfusion and cardiac function indicators were better after NIC treatment; moreover, postoperative hypotension and anxiety were lower, without an increase in readmission or mortality rates. NIC clearly plays a role in regulating myocardial blood perfusion in patients with myocardial infarction, optimizes coronary microcirculation, does not affect blood pressure, and improves the prognosis. Zhan *et al*. [6] initiated conventional treatment (control group) and NIC treatment (observation group) for patients with acute myocardial infarction in cardiac arrest. The results showed that the left ventricular ejection fraction, vascular recanalization rate, and the one-year survival rate was higher in the observation group than in the control group; in addition, there were less complications observed in the observation group. This study confirms that NIC, other than having high safety benefits, can improve the prognosis of patients with acute myocardial infarction in cardiac arrest, improve their short-term survival rate, protect their myocardium, and optimize their heart function.

5. Clinical application of nicorandil in unstable angina pectoris

Unstable angina pectoris (UAP), a heart condition that is usually manifested by chest pain or discomfort and caused by insufficient blood supply or the lack of blood to the heart muscle, is more dangerous than stable angina because it may be a precursor to myocardial infarction. In addition, delayed treatment may aggravate the condition and cause irreversible consequences. NIC can quickly relieve the symptoms of UAP and reduce the severity of the disease. Tian *et al*. [7] treated UAP patients with conventional drugs and NIC. The results showed that the total effective rate after NIC treatment was as high as 96.08%, the improvement rate of ECG was as high as 94.12%, and the adverse event rate was only 11.76%. The frequency of angina attacks was less, and the duration was shorter. It can be seen that the drug has a good therapeutic effect on UAP patients as well as high safety and benefits. Yu [8] treated UAP patients with NIC, along with symptomatic treatment such as nitrates, plaque-stabilizing drugs, and anti-platelets. The results showed that after the combined treatment, the clinical efficacy and the symptom score of angina pectoris significantly improved. It is evident that the drug has a relatively strong effect on platelet activation and can comprehensively improve the therapeutic effect on UAP.

6. Clinical application of nicorandil in heart failure

Heart failure (HF) is caused by myocardial ischemia and hypoxia due to coronary artery disease, often resulting in decreased cardiac function and increased risk of death. Myocardial ischemia and hypoxia can lead to myocardial cell death and fibrosis, resulting in decreased myocardial contractility, impaired diastolic function, and ultimately heart failure. HF can lead to pulmonary edema and pulmonary hypertension, causing dyspnea, pneumonia, and other diseases. Myocardial electrophysiological abnormalities and cardiac structural changes, which can easily lead to arrhythmia and sudden death, may be evident in severe cases. The curative effect of NIC in the treatment of this disease is remarkable, and the manifestations of HF can be corrected as soon as possible. Li *et al*. [9] used recombinant human brain natriuretic peptide on the basis of conventional treatment to treat patients with HF (control group) and added NIC for treatment of patients in the study group. The results showed that the total effective rate of the study group was 96%. After 4 weeks of treatment, their heart function was better than that of the control group, the level of nitric oxide increased, and the content of endothelin decreased. However, the incidence of adverse reactions between the groups were similar (12% in the study group versus 10% in the control group). It is evident that NIC combined with recombinant human brain natriuretic peptide on the basis of conventional treatment can improve the curative effect of HF and protect heart function.

6. Clinical application of nicorandil in percutaneous coronary intervention

Percutaneous coronary intervention (PCI) is a commonly used cardiac interventional therapy, often in the

treatment of CHD. This procedure is effective for the dilatation of coronary artery stenosis, restoration of myocardial blood supply, and prevention of myocardial infarction and other serious consequences. In recent years, with the continuous advancements in equipment and technology, the success rate and safety of PCI have greatly improved. Compared with open surgery, PCI does not require the opening of the chest cavity, has less postoperative pain, faster recovery, and high reliability, and reduces the risk of postoperative complications. In PCI, NIC functions as follows: (i) relieve intraoperative myocardial ischemia (the operation of the equipment in PCI may compress the myocardium, resulting in intraoperative myocardial ischemia; NIC can improve myocardial ischemia and thus alleviate intraoperative myocardial ischemia); (ii) prevent postoperative myocardial ischemia (complications such as vasospasm and thrombosis caused by intravascular mechanical devices or drugs may lead to postoperative myocardial ischemia; NIC can block the massive influx of calcium ions, relieve coronary artery spasm, and prevent postoperative myocardial ischemia). In a study, Liu [10] divided patients undergoing PCI into two groups by lottery; the reference group received conventional treatment, whereas the test group received NIC. The results showed that the test group had higher partial pressure of oxygen and pH value and lower partial pressure of carbon dioxide after treatment, and the majority of patients had TIMI flow 3; the incidence of adverse reactions was similar to that of the reference group. The study suggests that NIC can correct slow blood flow during PCI, improve the blood flow and blood gas index of patients, and increase the coronary artery flow velocity, with good safety and benefits. Gong *et al*. [11] analyzed the preventive effect of NIC on contrast-induced nephropathy after PCI. The results showed that the incidence of contrast-induced nephropathy after NIC treatment was only 2%, which was lower than that of conventional treatment (14%), and the levels of urea and β2-microglobulin at different time points after PCI were lower with NIC treatment. It is evident that NIC is more preventive of contrast-induced nephropathy and can improve various physiological indicators.

7. Nicorandil safety analysis

NIC is a drug widely used in the treatment of CHD. Although NIC has relatively accurate therapeutic effect, it can result in some adverse reactions: (i) facial flushing and headache, which are the most common adverse reactions of NIC due to blood vessel dilation, but they usually disappear within hours of taking the drug, and most patients can tolerate them; (ii) gastrointestinal reactions, including nausea, vomiting, diarrhea, and other symptoms, which may lead to indigestion and loss of appetite; (iii) hypotension and bradycardia, which usually occur after starting NIC, as the drug can cause vasodilation and a drop in heart rate, resulting in hypotension and bradycardia, but they disappear or reduce after adjustment of indications and dosage; (iv) increased blood pressure, especially when NIC is used at high doses; (v) respiratory reactions, such as bronchospasm and asthma, but they are less common; (vi) central nervous system reactions, such as dizziness, headache, insomnia, *etc*.; (vii) allergic reactions, such as urticaria, rash, facial edema, angioedema, *etc*. In addition to the adverse reactions mentioned above, long-term use of NIC may also lead to edema and liver injury. When using this drug, its use should be strictly according to doctor's advice, and patients' vital signs and drug reactions should be monitored regularly. In case of discomfort, medical attention should be sought immediately.

In conclusion, the application prospect of NIC in the treatment of CHD is very broad. In future research, we should continue to explore the combination of NIC with other drugs and propose a variety of drug combinations based on the patient's underlying disease, degree of CHD, age, and treatment needs. At present, the administration routes of NIC are mainly oral and coronary injection. Although it is suitable for the treatment of most CHD patients, the dosage form is limited. Future research can consider enriching its dosage forms, such as patches, suppositories, *etc*., to adapt to the needs of different patients and treatment options. With the advancement of medical technology, individualized treatment with NIC must be emphasized. Through methods such as molecular diagnosis and biomarkers, it is possible to predict the

patient's response to NIC and formulate a corresponding individualized treatment plan.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Hu S, Zhang C, Zhang C, et al., 2017, Effects of Nicorandil Intravenous Pre-injection on Cerebral Blood Flow and Neurological Function in Cardiopulmonary Resuscitation Rats. Shandong Medicine, 57(38): 34–37.

[2] Shi X, Shi M, Peng S, 2020, Study on the Anti-Apoptotic Effect of Nicorandil on Hypoxic/Reoxygenated Cardiomyocytes Through the Phosphatidylinositol-3 Kinase Pathway. Journal of Clinical Internal Medicine, 37(11): 802–805.
Gao W, 2022, Clinical Effect and Safety Analysis of Nicorandil in the Treatment of Stable Angina Pectoris. Chinese Modern Drug Application, 16(10): 110–112.

[3] Ji Y, 2022, Observation on the Curative Effect of Rosuvastatin Combined with Nicorandil in the Treatment of Elderly Patients with Acute Non-ST-Segment Elevation Myocardial Infarction. Exploration of Rational Drug Use in China, 19(4): 49–53.

[4] Li L, Liu X, Li Q, et al., 2022, Effects of Preoperative Intracoronary Injection of Nicorandil on Postoperative Myocardial Blood Perfusion Level and Cardiac Function in Patients with Acute Myocardial Infarction. Prevention and Treatment of Cardiovascular and Cerebrovascular Diseases, 22(1): 24–28.

[5] Zhan P, Huang Q, Wang Y, et al., 2021, The Effect of Nicorandil on the Prognosis of Elderly Patients with Cardiac Arrest After Acute Myocardial Infarction. Chinese Journal of Gerontology, 41(1): 19–22.

[6] Tian W, Lian Y, 2021, The Effect of Nicorandil in the Treatment of Elderly Patients with Unstable Angina Pectoris. Chinese And Foreign Medical Research, 19(22): 25–28.

[7] Yu X, 2022, Study on the Effect of Nicorandil on the Clinical Effect and Platelet Activation of Patients with Unstable Angina Pectoris. Diabetes World, 2022(7): 134–135.

[8] Li X, Li X, Qiao X, et al., 2021, Effects of Recombinant Human Brain Natriuretic Peptide Combined with Nicorandil on Cardiac Function and Serum Levels of Nitric Oxide and Endothelin in Patients with Ischemic Heart Failure. Chinese Hospital Medicine Evaluation and Analysis, 21(1): 38–40 + 44.

[9] Liu Q, 2020, Analysis of the Improvement Effect of Intracoronary Injection of Nicorandil on Slow Blood Flow During Percutaneous Coronary Intervention. Electronic Journal of Cardiovascular Diseases of Integrated Traditional Chinese and Western Medicine, 8(12): 54–55.

[10] Gong Y, Liang M, Zhao J, et al., 2021, Effect of Intravenous Nicorandil on Contrast-Induced Nephropathy in Patients with Coronary Heart Disease After Coronary Intervention. Chinese Journal of Molecular Cardiology, 21(5): 4232–4235.