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Nitroglycerin plus clopidogrel for acute myocardial infarction and the effect on cardiac function indices

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Abstract: To evaluate the efficacy of nitroglycerin plus clopidogrel for acute myocardial infarction and the effect on the cardiac function indices. From April 2019 to April 2020, 90 patients with acute myocardial infarction enrolled in our hospital were recruited and assigned to receive either oral clopidogrel (control group) or nitroglycerin plus clopidogrel (experimental group), with 45 cases in each group. Outcome measures included clinical efficacy, inflammatory factors, cardiac function indices, myocardial enzymatic indexes, Selvester QRS score, myocardial infarction area and quality of life. Nitroglycerin plus clopidogrel resulted in significantly higher treatment efficiency versus clopidogrel alone ($P<0.05$). Patients with nitroglycerin plus clopidogrel showed significantly reduced levels of inflammatory factors, a lower ST reduction and a lower end-systolic volume index (ESVI) versus those with single clopidogrel ($P<0.05$). Nitroglycerin plus clopidogrel was associated with a shorter prothrombin time, higher end-diastolic volume index (EDVI) and SF-36 scores and lower myocardial enzymatic indexes and QRS scores versus clopidogrel ($P<0.05$). Patients with combined therapy had a smaller myocardial infarction area than those with monotherapy ($P<0.05$). Nitroglycerin plus clopidogrel ameliorates the cardiac function indices of patients with acute myocardial infarction, mitigates the inflammatory responses, and improves the patient's quality of life. Further research is required prior to clinical promotion.

Keywords: Nitroglycerin, clopidogrel, acute myocardial infarction, cardiac function index.

INTRODUCTION

As a common clinical sudden cardiovascular disease, acute myocardial infarction is mainly triggered by acute and persistent ischemia and hypoxia of the coronary artery and features a high mortality rate. This disease is characterized by rapid onset and progression, with symptoms such as irritability, fatigue, nausea and vomiting, shock, and cardiac arrhythmias. Patients may experience heart failure in severe cases, which poses a serious threat to their life safety (De Luca *et al*., 2021; Mohammad *et al*., 2020; Zhang *et al*., 2021). Thus, timely intervention for acute myocardial infarction is essential to enhance patient survival and prognosis. Nitroglycerin is a common anti-anginal drug that dilates blood vessels, to relieve blood flow resistance and promote the enrichment of blood microcirculation. However, the treatment efficiency of monotherapy with nitroglycerin for acute myocardial infarction is modest. Administration of clopidogrel to patients with myocardial infarction after percutaneous coronary intervention inhibits platelet aggregation. Clopidogrel is a selective adenosine diphosphate receptor antagonist that prevents occlusive stenosis of coronary arteries (Ahn *et al*., 2020; Gasecka *et al*., 2020; Hariri *et al*., 2020; Sabbah *et al*., 2020).

Moreover, clopidogrel may increase circulating adenosine levels and acts favorably in the coronary microcirculation. Given the action of nitroglycerin on the NO-sGC-cGMP pathway and its availability for co-administration with patients with heart failure, the present study aimed to explore the influence of nitroglycerin plus clopidogrel in patients with acute myocardial infarction.

MATERIALS AND METHODS

General information

Ninety patients with acute myocardial infarction enrolled in our hospital from April 2019 to April 2020 were recruited and assigned to the experimental group and the control group on the basis of the order of admission, with 45 cases in each group.

Inclusion criteria

(1) Patients with complete baseline data; (2) who met the diagnostic criteria of the Guidelines for the Diagnosis and therapy of Acute Myocardial Infarction; (3) both the patients and the patients' family members voluntarily joined in this research. After fully understanding the aim and process of the study, the patients signed the informed consent. This research was performed with the approval of the Medical Ethics Committee (20190899).

Exclusion criteria

(1) Patients with incomplete baseline data; (2) with allergies to the drugs applied in this research; (3) with malignant tumors and immune system diseases; (4) with cardiovascular and cerebrovascular diseases; (5) with

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liver and kidney dysfunction; (6) with psychiatric diseases and cognitive dysfunction.

Methods

Patients in both groups received conventional therapy, vital signs monitoring, oxygen therapy, analgesia, thrombolysis, anticoagulation and angina relief.

The control group received oral administration of 75mg of clopidogrel (Guodianzhi J20180029; Sanofi (Hangzhou) Pharmaceutical Co., Ltd; specification 75mg*7s) daily.

The experimental group received oral administration of clopidogrel (same administration method with the control group) and 0.5mg of nitroglycerin (GuoPharmaZenZi H23021574; Beijing Yimin Pharmaceutical Co., Ltd.; specification: 0.5mg*100s), with 5min interval between doses until the patients' pain level was relieved. Further therapy was initiated for patients immediately in case of no relief in pain level after 3 sessions of medication (Wang *et al*., 2020). The duration of treatment for both groups was 30d.

Observational indicators

The MOS 36-item short-form health survey (SF-36) Rating Scale (Lee *et al*., 2020) (SF-36) was used to evaluate patients' social functioning, physical functioning, role functioning, and cognitive functioning after therapy, with a total score of 100. The higher the score, the better the quality of life.

Clinical efficacy: The therapeutic effect was considered significant if the clinical symptoms disappeared. Treatment was considered effective if clinical symptoms were relieved. Treatment was considered ineffective if clinical symptoms did not improve. The total therapy efficacy = markedly effective rate + effective rate.

Cardiac function parameters of the patients were determined using the color Doppler echocardiography, including left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV).

Three milliliters of fasting superficial venous blood were collected from the patients and serum was isolated by centrifugation. The levels of interleukin (IL)-6, hypersensitive C-reactive protein (hs-CRP) and tumor necrosis factor (TNF)-α were determined by enzyme-linked immunosorbent assay.

The Selvester QRS scoring system was used to detect the ECG examination index values of the two selected teams of patients, and the areas of myocardial infarction of the patients were calculated and analyzed.

STATISTICAL ANALYSIS

The data of this research were processed with SPSS20.0, and GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used for image rendering. The count data was examined using the chi-square test, and the measurement data conforming to the normal distribution were analyzed using the t-test. $P<0.05$ indicates the difference was statistically significant.

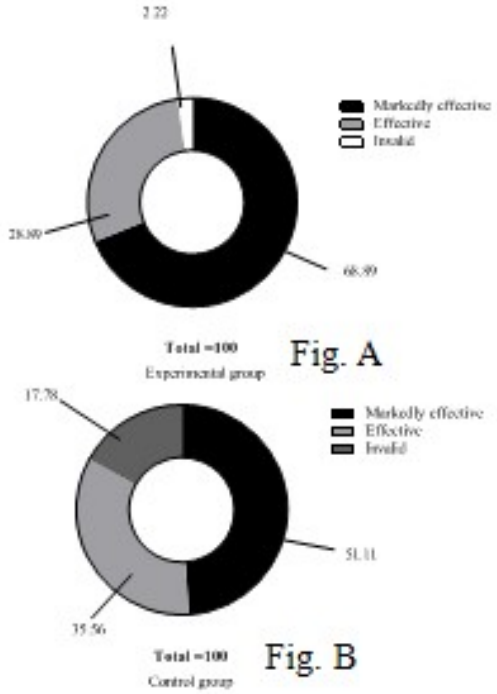
RESULTS

Comparison of baseline data

The baseline patient features between the two groups were comparable ($P>0.05$) (table 1).

Therapy Efficacy Comparison

Clopidogrel plus nitroglycerin resulted in significantly higher treatment efficacy versus clopidogrel ($P<0.05$) (fig. 1).



Note: Fig. A shows the therapy efficacy in the experimental group; Fig. B shows the therapy efficacy in the control group.

In the experimental group, the markedly effective rate was 68.89% (31/45), the effective rate was 28.89% (13/45), the ineffective rate was 2.22% (1/45) and the total therapy efficacy was 97.78% (44/45).

In the control group, the markedly effective rate was 51.11% (21/45), the effective rate was 35.56% (16/45), the ineffective rate was 17.78% (8/45), and the total therapy efficacy was 82.22% (37/45).

There was a significant difference between the two teams after therapy ($X2=6.049$, $P<0.05$).

Fig. 1: Comparison of therapy efficacy between the two teams [n(%)].

Table 1: Comparison of baseline data between the two teams of patients [x±s; n(%)]

	Experimental group (n=45)	Control group (n=45)	x^2 or t	P
Age (years)			0.086	0.932
	56.75±3.32	56.69±3.29		
Gender			0.178	0.673
Male	23(51.11)	21(46.67)		
Female	22(48.89)	24(53.33)		
BMI (kg/m2)			1.119	0.266
	26.27±1.59	25.89±1.63		
Duration of disease (years)			0.300	0.765
	2.12±0.2	2.13±0.1		
Smoking			0.045	0.832
Yes	20(44.44)	21(46.67)		
No	25(55.56)	24(53.33)		
Drinking			0.178	0.673
Yes	22(48.89)	24(53.33)		
No	23(51.11)	21(46.67)		
Place of residence			0.050	0.822
Urban	31(68.89)	30(66.67)		
Rural	14(31.11)	15(33.33)		

Table 2: Comparison of electrocardiogram and cardiac function indexes between the two teams ($\bar{x}$±s)

Teams	N	ST reduction rate /mV	Prothrombin time /s	EDVI/ml	ESVI/ml
Experimental group	45	0.02±0.01	18.69±1.65	78.96±3.21	45.56±2.03
Control group	45	0.37±0.01	14.34±1.19	68.34±3.38	53.24±1.27
t		166.020	14.344	15.283	21.515
P		<0.05	<0.05	<0.05	<0.05

Table 3: Comparison of myocardial enzymatic indexes between the two teams of patients ($\bar{x}$±s)

Teams	N	BNP/ ($ng \cdot L^{-1}$)	cTnT/ ($\mu g \cdot L^{-1}$)	LDH/ ($U \cdot L^{-1}$)	CK-MB/ ($U \cdot L^{-1}$)
Experimental group	45	268.14±23.27	49.53±4.68	92.54±4.32	49.26±1.24
Control group	45	364.37±21.73	67.58±4.56	114.83±4.27	79.14±2.56
t		20.275	18.231	24.617	70.466
P		<0.05	<0.05	<0.05	<0.05

Table 4: Comparison of QRS score and myocardial infarct area between the two teams ($\bar{x}$±s)

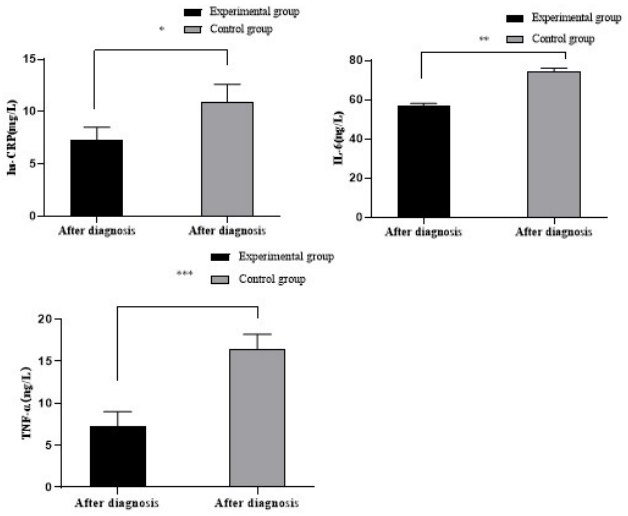
Teams	N	QRS score/points	Myocardial infarct area /%
Experimental group	45	5.14±1.27	16.23±4.61
Control group	45	6.83±1.71	18.54±4.93
t		5.322	2.296
P		<0.05	<0.05

Table 5: Comparison of SF-36 scores between the two teams ($\bar{x}$±s)

Teams	N	Cognitive functioning	Social functioning	Psychological functioning	Physical functioning	Overall functioning
Experimental group	45	81.35±6.9	83.27±6.3	82.66±7.9	83.61±8.1	82.33±9.2
Control group	45	64.31±5.3	64.12±4.9	66.11±6.3	66.22±5.8	67.25±6.8
t		13.137	16.095	10.987	11.709	8.842
P		<0.05	<0.05	<0.05	<0.05	<0.05

Inflammatory factors comparison

The levels of hs-CRP, IL-6 and TNF-α in the experimental group were lower than those in the control group (P<0.05).(fig. 2).



Note: The abscissa indicates post-therapy and coordinate indicates serum indicators, respectively.

The levels of hs-CRP, IL-6, and TNF-α in the experimental group were (7.3±1.2) mg/L, (56.7±1.4) ng/L and (7.2±1.8) ng/L, respectively.

The levels of hs-CRP, IL-6, and TNF-α in the control group were (10.9±1.7) mg/L, (74.4±1.7) ng/L and (16.4±1.8) ng/L, respectively.

*indicates a significant difference in hs-CRP levels between the two teams of patients after therapy (t=11.606, P<0.05).

**indicates a significant difference in IL-6 levels between the two teams of patients after therapy (t=53.915, P<0.05).

***indicates a significant difference in TNF-α levels between the two teams of patients after therapy (t=24.244; P<0.05).

Fig. 2: Comparison of inflammatory factors between two teams of patients ($\bar{x}$±s)

Comparison of electrocardiogram and cardiac function indexes

Nitroglycerin plus clopidogrel was associated with a shorter prothrombin time, higher end-diastolic volume index (EDVI) in patients versus clopidogrel (P<0.05). (table 2).

Comparison of myocardial enzymatic indexes

Myocardial enzymatic indices in the experimental group were lower than those in the control group (P<0.05). (table 3).

Comparison of QRS score and myocardial infarct area

Nitroglycerin plus clopidogrel resulted in lower QRS scores and smaller myocardial infarct area in patients versus clopidogrel (P<0.05). (table 4)

SF-36 scores Comparison

Patients receiving combined therapy had higher SF-36 scores than those given single therapy (P<0.05). (table 5)

DISCUSSION

The rapid development of China's society and economy has led to a significant enrichment in people's living standards, which has resulted in tremendous changes in people's living and dietary habits. The occurrence of acute myocardial infarction in China has shown a dramatic increase in recent years. Acute myocardial infarction undermines the patient's myocardial oxygen supply and alters the blood flow rate, which may severely compromise patients' life quality (Altintas *et al*., 2019; Kim *et al*., 2019; Lee *et al*., 2019; Pavlovic *et al*., 2019). Acute myocardial infarction is triggered by the shedding of plaque which is characterized by fewer smooth muscle cells, thinner fibrous hairs, and more inflammatory cells, with a risk of plaque rupture. The middle-aged and elderly populations are most susceptible to acute myocardial infarction as their cardiac function degenerates with age, which may complicate the condition of patients with acute myocardial infarction given the high prevalence of organ dysfunction and multiple underlying diseases in such patients (Ibrahim *et al*., 2019; Lee *et al*., 2018; Wang *et al*., 2019; Yasuda *et al*., 2019). Symptoms of acute myocardial infarction include arrhythmia and ventricular fibrillation in the early stages of the patient's disease, and multiple complications such as hypotension, arrhythmia heart failure, and cardiogenic shock may occur after disease progression. Consequently, acute myocardial infarction features a high rate of disability and mortality, posing serious threat to patients' health and safety.

Both aspirin and clopidogrel are the most commonly used for acute myocardial infarction management. Clopidogrel features a rapid onset of action and strong antiplatelet effect, with a high safety profile that minimizes the risk of adverse reactions in patients. In addition, these drugs belong to the thiophene arsenical class of antiplatelet agents, which selectively inhibit the binding between adenosine diphosphate and platelet receptors, thereby suppressing adenosine diphosphate-mediated platelet activation. Therefore, clopidogrel is considered effective in the therapy of acute myocardial infarction (Doll *et al*., 2018; Edfors *et al*., 2018; Gong *et al*., 2018; Park *et al*., 2018). Nitroglycerin is the main clinical alternative for acute myocardial ischemia. As an anti-myocardial ischemic drug, nitroglycerin efficiently blocks platelet activity and increases blood flow in the ischemic zone, which substantially relieves angina pectoris, reduces the size of myocardial infarction, and lowers myocardial oxygen consumption.

In the present research, the levels of hs-CRP, IL-6, and TNF-α were lower in the experimental group than in the control group (P < 0.05), which was consistent with the research results by Zhang Yuqing *et al*. (Zhang *et al*., 2018). In their article, the levels of hs-CRP, IL-6 and TNF-α in the observation group were (7.5±1.8) mg/L,

(59.1±1.1) ng/L, and (7.5±1.3) ng/L, respectively; the levels of hs-CRP, IL-6, and TNF-α in the control group after therapy were (11.4±1.3) mg/L, (75.6±1.2) ng/L, and ((17.3±1.5) ng/L. The observation group showed lower levels of inflammatory factors than the control group (P<0.05). This indicates that nitroglycerin plus clopidogrel can effectively alleviate the inflammatory response. This is because IL-6 can induce the inflammatory cell adhesion and aggregation to promote inflammation, thus increasing the serum Hs-CRP level. Moreover, Hs-CRP can not only reflect the inflammatory degree, but also promote the inflammatory response and plaque rupture. The drug therapy effectively inhibited inflammation, and decreased the IL-6 and Hs-CRP levels. It not only has the effect of protecting vascular endothelial function, but also can inhibit the expression of inflammatory factors, so the intraoperative and postoperative administration of tirofiban alleviates the inflammatory degree.

Myocardial injury markers are essential in the diagnosis and therapy of myocardial infarction. Biochemical markers of myocardial injury possess high specificity and sensitivity, among which cardiac troponin T (cTnT), lactate dehydrogenase (LDH), and creatine kinase-myocardial band (CK-MB) are sensitive indicators for the diagnosis of acute myocardial infarction. CK-MB is central to the cardiac enzyme profile with a relatively short half-life. During the onset of infarction, serum concentrations of CK-MB rise with a short duration and are non-cardiac specific, which demonstrates its potential as sensitive indicators for early diagnosis of myocardial injury. Different from CK-MB, LDH has a relatively long half-life and persists in the blood, which serves to sufficient reflection of myocardial damage. The combined determination of CK-MB and LDH may potentiate the diagnostic yield (Kang *et al*., 2018; Komocsi *et al*., 2018). cTnT is the gold index for clinical diagnosis of acute myocardial infarction, as it has a wide diagnostic time window, low sensitivity in the early stage and high sensitivity and specificity in the advanced stages. In addition, brain natriuretic peptide (BNP) is a marker targeted for heart failure after myocardial infarction, which promotes nervous system excitation and inhibits the release of endothelin and pituitary pressor hormone, thereby suppressing the ventricular remodeling. BNP levels may reverse myocardial remodeling and dilate peripheral vessels to decrease volume load. The results of the present research showed that the myocardial enzyme index was lower in the experimental group. This indicates that nitroglycerin plus clopidogrel effectively reduces the levels of cTnT, LDH and CK-MB in patients. The possible explanation is that diagnostic marker enzymes LDH, and CK-MB are present plentifully in the heart. When injury to the heart occurs, these enzymes spill into blood stream. Thus, elevated levels of these enzymes released from the myocardium into blood indicate myocardial necrosis. Whereas the intervention in this study attenuated these parameters considerably. The QRS score of the experimental group was lower than the control group (P<0.05); the area of myocardial infarction in the experimental group was smaller than the control group (P<0.05), which was consistent with the results of ULVENSTAM *et al* (Ulvenstam *et al*., 2018) whose article proved that "the QRS score was (5.04±1.35) in the observation group and (6.94±1.74) in the control group, and the QRS score in the observation group was evidently lower. The area of myocardial infarction in the observation team was (17.34±3.34) % and in the control group was (18.79±3.86) %, and the area of myocardial infarction in the experimental group was significantly smaller," suggesting that the joint administration of nitroglycerin and clopidogrel effectively improves the QRS score of patients and diminishes the area of myocardial infarction with significant clinical effectiveness.

CONCLUSION

Nitroglycerin plus clopidogrel ameliorates the cardiac function indices of patients with acute myocardial infarction, mitigates the inflammatory responses, and improves the patient's quality of life. Further research is required prior to clinical promotion.

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