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Continuous Monitoring of Serum Tumor Necrosis Factor-α for Patients with TEMIS Treated by Nitrates Postconditioning during PCI

Mei Li[1], Dalin Song[2], Zhu Meng[2], Junquan Zhao[2*]

[1]Department of Clinical Laboratory, University of Health and Rehabilitation Sciences Qingdao Hospital & Qingdao Municipal Hospital, Qingdao, China
[2]Department of Cadre Health Care, University of Health and Rehabilitation Sciences Qingdao Hospital & Qingdao Municipal Hospital, Qingdao, China
Email: *billy_mei@126.com

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Abstract

Objective: To investigate the protective effect of nitrates postconditioning on myocardial ischemia-reperfusion injury and whether it plays a regulatory role in TNF-α in patients with STEMI during PCI. **Methods:** Patients with STEMI who underwent PCI were selected, except for obvious anemia, head trauma, cerebral hemorrhage, hypotension (systolic blood pressure less than 90 mmHg), and patients with autoimmune diseases, all kinds of acute and chronic infections and malignant tumors. They were randomly divided into PCI standardized treatment group and isosorbide dinitrate postconditioning during PCI group. The concentrations of cTnI and TNF-α in serum were detected by ELISA method in each group before PCI and after 2 hours, 1 day, 4 days and 7 days of PCI. **Results:** 1) There were no statistically significant differences in sex, age, smoking history, diabetes, hypertension and blood lipid abnormality in two groups. 2) Before operation, the concentration of cTnI in two groups was not statistically significant. The concentration of cTnI in the experimental group was lower than that of the control group after 4 days and 7 days of PCI, and $P < 0.05$, the difference was statistically significant. The concentration of cTnI reached the peak in 1 day after operation in the control group, while the experimental group was in 2 hours after operation, and the cTnI concentration in the experimental group at each time point was lower than that of the control group. 3) There was no statistical difference in the concentration of TNF-α in two groups before operation. The concentration of TNF-α in the experimental group was lower than that in the control group after 1 day, 4 days and 7 days of PCI, and $P < 0.05$, the difference was statisti-

cally significant. The peak value of TNF-α in two groups was both in 1 day after operation, and the peak level of the experimental group and the level of each time after the operation were lower than that of the control group. **Conclusion:** Nitrates postconditioning during PCI in patients with STEMI has a protective effect on myocardial ischemia-reperfusion injury. Nitrates postconditioning has an effect to reduce the level of TNF-α of patients with STEMI after PCI treatment, and may have the mechanism of alleviating the inflammatory response after myocardial ischemia and reperfusion.

Keywords

Ischemia-Reperfusion Injury (IRI), Pharmacological Postconditioning, Nitrates, TNF-α

1. Introduction

Myocardial injury caused by acute myocardial infarction includes ischemia and subsequent ischemia-reperfusion injury (IRI) [1]. In the past 30 years, medical reperfusion strategies such as intravenous thrombolysis and percutaneous coronary intervention (PCI) have been widely used in the clinic, but IRI associated with coronary revascularization has puzzled clinicians. Myocardial IRI can be manifested as serious phenomena such as malignant arrhythmia, myocardial depression, cardiac insufficiency and even death [2]. In addition, the myocardial infarction area caused by reperfusion can reach more than 50% of the final infarct area [3]. At present, drug post-treatment, as one of the therapeutic strategies to reduce reperfusion injury, is developed on the basis of myocardial ischemia post-treatment, that is, after myocardial ischemia, during or shortly before reperfusion, drugs are used to stimulate or simulate the body's own endogenous protective mechanism to achieve the protective effect of ischemic reperfusion myocardium. In recent years, it has become a research hotspot in the field of myocardial IRI protection. Our previous animal experiments showed that post-treatment with nitrate had a protective effect on myocardial IRI in rats [4]. This study was designed to confirm, using a randomized controlled trial (RCT), post-treatment with nitrate has a protective effect on patients with ST-segment elevation myocardial infarction (STEMI) treated by PCI, and one of the mechanisms of action may be to reduce inflammation.

2. Experimental Materials and Methods

2.1. Patients and Experimental Methods

STEMI patients who underwent PCI in Qingdao Haici Hospital and Qingdao Municipal Hospital from November 2017 to January 2018 were selected, excluding patients with obvious anemia, head trauma, cerebral hemorrhage, obvious hypotension (systolic blood pressure less than 90 mmHg), autoimmune diseases, various acute and chronic infections, and malignant tumors. This study was ap-

proved by the Ethics Committee of Qingdao Municipal Hospital (No. 2017-5-231). Patients meeting the above conditions were randomly divided into Group A and Group B: Group A (conventional control group) was injected 0.9% sodium chloride solution 2 mg into the ischemic coronary artery immediately after the insertion of a guide wire to open the ischemic coronary artery during routine PCI; Group B (new mode of isosorbide nitrate post-treatment experimental group) was given isosorbide nitrate 2 mg injection into the ischemic coronary artery immediately after the implantation of a guide wire to open the ischemic coronary artery during routine PCI. And neither the patient nor the doctor involved in the above procedure knew the specific type of drug given in the experiment. 5 ml of venous blood samples were collected from patients in the two groups before PCI, 2 h, 1 d, 4 d, and 7 d after PCI, and placed at room temperature, centrifuged at 1000 RPM for 20 minutes within 24 h with a high-speed centrifuge, and then the upper serum was taken and stored in a −20˚C refrigerator to avoid repeated freezing-thawing. Serum cTnI and TNF-α were detected by Elisa at each time cut-off point in the two groups (Figure 1).

2.2. Statistical Method

Statistical software SPSS 22.0 was used for data analysis. The analysis method of Chi-square test was used to express the rate of all counting data. Statistical data were presented as mean ± standard deviation ($x \pm S$). T-test was used for analysis, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Comparison of General Clinical Data between Two Groups

There were no significant differences in gender, age, smoking history, diabetes mellitus, hypertension and dyslipidemia between two groups (Table 1).

3.2. Comparison of Serum cTnI Levels between Two Groups

The preoperative cTnI content of the control group and the experimental group

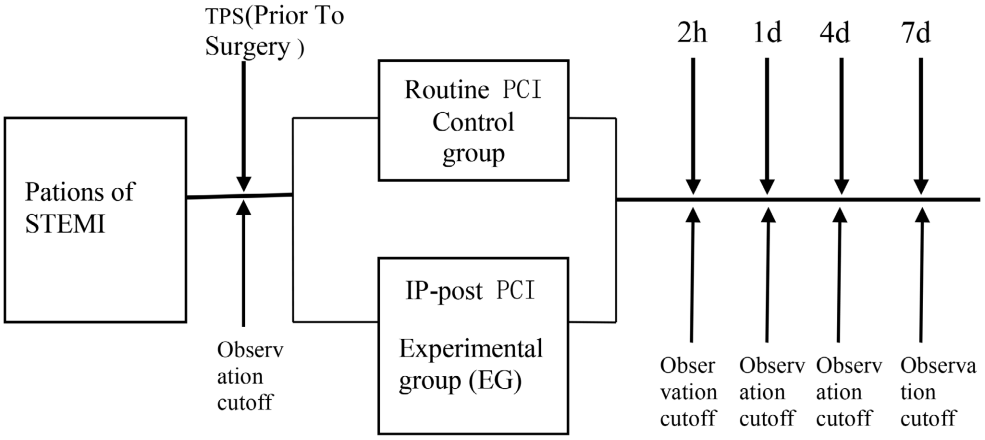

Figure 1. Flow chart of randomized double-blind study.

was (10.72 ± 33.63) ng/ml and (12.33 ± 22.25) ng/ml, respectively, P > 0.05, indicating that there was no statistical difference between two groups before surgery, so the data of the two groups were comparable at different time cut-off points after surgery. The concentration of cTnI in the experimental group was lower than that in the control group 2 h and 1 d after operation, but P > 0.05 showed no statistical difference. The concentration of cTnI in the experimental group was (3.88 ± 4.71) ng/ml and (0.35 ± 1.43) ng/ml on 4 and 7 days after operation, respectively, which was lower than that in the control group (10.64 ± 9.72) ng/ml (1.52 ± 2.87) ng/ml, and P < 0.05, indicating statistical significance (Table 2).

cTnI in the control group reached its highest point 1 day after surgery, and the experimental group reached its highest point 2 hours after surgery, and the cTnI level in the experimental group was lower than that in the control group at each time intercept (Figure 2).

3.3. Comparison of Serum TNF-α Levels between Two Groups

The levels of TNF-α in the control group and the experimental group were (0.145 ± 0.032) pg/ml and (0.142 ± 0.030) pg/ml, respectively, P > 0.05, with no statistical difference. Two hours after operation, the concentration of TNF-α in the experimental group was lower than that in the control group, but P > 0.05, indicating no statistical difference between two groups. The concentrations of TNF-α in the experimental group were (0.154 ± 0.023) pg/ml, (0.136 ± 0.021) pg/ml and (0.127 ± 0.023) pg/ml on day 1, 4 and 7 after operation, respectively. Compared with the control group (0.191 ± 0.057) pg/ml, (0.182 ± 0.044) pg/ml, (0.159 ± 0.042) pg/ml, and P < 0.05, indicating that the difference was statistically

Table 1. Comparison of general clinical data between two groups.

Subjects	Control group	Experimental group	P-value
Cases	16	16	
Sex (M/F)	11/5	10/6	0.710
Ages (Y)	58.63 ± 9.70	59.19 ± 11.27	0.881
Hypertensio (%)	7 (43.8)	8 (50)	0.723
DM (%)	8 (50)	6 (37.5)	0.476
Dyslipemia (%)	10 (62.5)	9 (56.3)	0.719
Smoking (%)	9 (56.3)	5 (31.3)	0.154

Table 2. Comparison of serum cTnI (ng/ml) between two groups.

Gruops	TPS of PCI	POST-OP 2 h	POST-OP 1 d	POST-OP 4 d	POST-OP 7 d
Control	10.72 ± 33.63	22.61 ± 32.40	26.65 ± 32.20	10.64 ± 9.72	1.52 ± 2.87
EG	12.33 ± 22.25	22.29 ± 28.53	19.34 ± 29.12	3.88 ± 4.71*	0.35 ± 1.43*

*Compared with the control group at the same time cut-off, P < 0.05.

significant (Table 3).

The level of TNF-α reached its peak height on the 1st day after surgery, and the level of TNF-α in the experimental group was lower than that in the control group at each time cut-off. The peak TNF-α level in the experimental group was significantly improved from the 1st day after surgery ($P < 0.05$) (Figure 3).

4. Discussion

In this study, a new mode of nitric ester drug post-treatment during PCI in

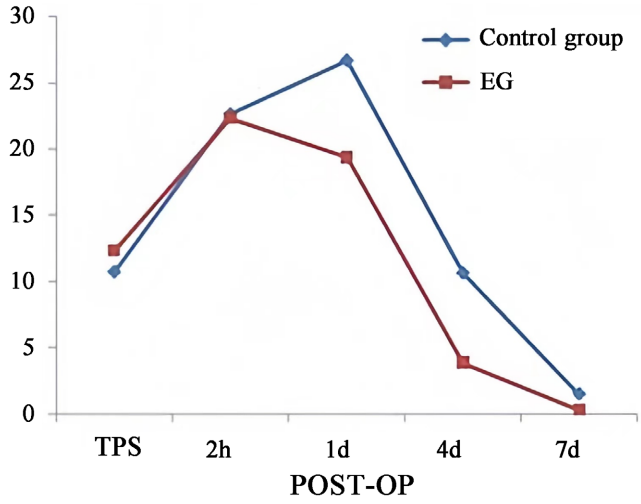

Figure 2. Comparison of serum cTnI (ng/ml) at different time cutoff points between two groups.

Table 3. Comparison of serum TNF-α (pg/ml) between two groups.

Gruops	TPS of PCI	POST-OP 2 h	POST-OP 1 d	POST-OP 4 d	POST-OP 7 d
Control	0.145 ± 0.032	0.158 ± 0.032	0.191 ± 0.057	0.182 ± 0.044	0.159 ± 0.042
EG	0.142 ± 0.030	0.148 ± 0.032	0.154 ± 0.023*	0.136 ± 0.021*	0.127 ± 0.023*

*Compared with the control group at the same time cut-off, $P < 0.05$.

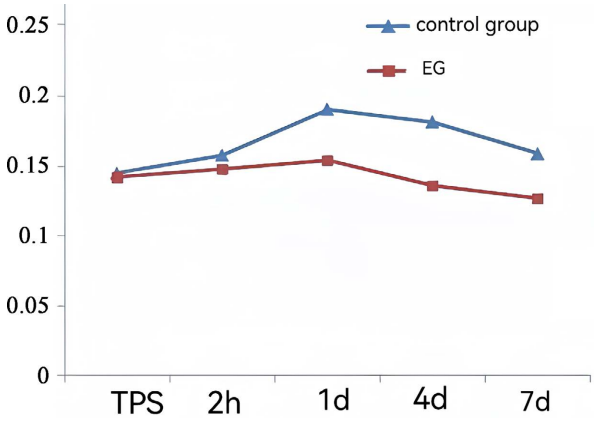

Figure 3. Comparison of serum TNF-α (pg/ml) at different time cut-off points between two groups.

STEMI patients was studied. The results of RCT indicated that the intervention mode improved myocardial reperfusion injury, and had myocardial protection and clinical application value. Serum TNF-α was detected continuously before and after PCI, and the peak height was reached on the 1st day after surgery, while the level of TNF-α in the intervention group was lower than that in the control group at each time intercept, and the peak level of TNF-α was significantly improved after the 1st day, all of which were $P < 0.05$. These results suggest that post-treatment with nitrate may have a mechanism to reduce the inflammatory response after myocardial ischemia-reperfusion.

The mechanism of myocardial IRI is very complex, including the sudden explosive production of reactive oxygen species in the early stage of reperfusion [5] [6], Ca^{2+} overload [6] and a series of inflammatory reactions [7] [8]. Inflammatory reaction runs through the whole process of myocardial ischemia and reperfusion and the later process of cardiac repair. After myocardial ischemia and reperfusion, soluble inflammatory mediators are released immediately, resulting in endothelial cell damage through the production of different types of cytokines and lipids, resulting in the destruction of the tight connections between cells, the increase of vascular permeability, and endothelial barrier dysfunction. As a result, neutrophils and other inflammatory cells migrate to damaged cardiomyocytes, resulting in increased myocardial damage [9]. During this process, various activated inflammatory cells release TNF-α and various interleukins. These cytokines and chemokines lead to vascular microcirculation disturbance, platelet aggregation and cardiomyocyte apoptosis through synergistic action, and increased IRI.

In order to reduce IRI, scholars have proposed ischemic preconditioning, ischemic post-treatment and drug post-treatment. Although ischemic preconditioning is currently recognized as the most powerful protective mechanism, its clinical application is greatly limited due to the uncertainty of ischemic time in acute myocardial infarction. The subsequent ischemic post-treatment, which is implemented after ischemia, solves the problem of intervention time limitation and makes its clinical application possible. However, ischemic post-treatment requires multiple cycles of ischemia/reperfusion through mechanical operation, which is an invasive operation. In addition, ischemic post-treatment was performed on 700 STEMI patients undergoing PCI in a study. It was found that the infarct size of the myocardia was not improved [10]. Therefore, the efficacy of ischemic post-treatment in saving ischemic myocardia and myocardial infarction size still needs to be further clarified. Drug after treatment, that is, the addition of rational drugs to reduce IRI shortly before or during reperfusion, has been a research focus in the field of myocardial IRI protection for more than two decades because of its easy and safer operation. A variety of drugs have been used for drug after treatment, such as adenosine, minocycline, edaravone, nicoradil, statins, etc. However, the results are controversial [11]-[16].

Nitric ester is an exogenous nitric oxide (NO) donor. It has a wide range of action mechanisms, such as dilating vascular smooth muscle, inhibiting platelet

aggregation and inhibiting inflammation. In recent years, a large number of experimental studies have shown that NO is involved in myocardial IRI, myocardial ischemia-reperfusion can directly mediate the specific interaction between neutrophils and endothelial cell adhesion molecules, recruit neutrophils to gather in vascular endothelial cells, resulting in endothelial cell dysfunction, and NO can inhibit the activation of endothelial cell adhesion molecules. The specific binding of neutrophils to vascular endothelial cell adhesion molecules is weakened to reduce endothelial damage, thereby reducing myocardial systolic dysfunction, cell edema and apoptosis [17]. In this experiment, the levels of cTnI in the nitrate post-treatment group were lower than those in the control group at 4 d and 7 d after surgery, and the difference was statistically significant, indicating that nitrate post-treatment had a protective effect on myocardial IRI in STEMI patients.

In 2015, the Journal of the American College of Cardiology published a study on IRI [18]. Through a nuclear magnetic scan of the heart, it was found that myocardial edema presented a bipeak pattern in the first week after ischemia/reperfusion, that is, myocardial cell edema appeared rapidly at the beginning of reperfusion and almost disappeared 24 hours later, while delayed wave edema appeared a few days after ischemia/reperfusion. The maximum was reached on day 7 after reperfusion. Further studies [19] showed that the first wave of edema may be caused by reperfusion itself, and the second wave of edema may be caused by the inflammatory response caused by immune cells' phagocytosis of necrotic substances during tissue healing. TNF-α is an inflammatory factor released by macrophages. A study of [20] has shown that the level of TNF-α in myocarocytes increases during ischemia, and the content of TNF-α in myocarocytes increases again after reperfusion compared with that before reperfusion. The reperfusion process promotes the rapid accumulation of white blood cells in the myocardium, and the accumulated white blood cells simultaneously produce a large amount of TNF-α, which leads to direct myocardial injury and even myocardial cell apoptosis [21]. Therefore, the content of TNF-α can better reflect the inflammatory response of myocardial ischemia-reperfusion. In this experiment, the level of TNF-α in the nitrate-treated group was lower than that in the control group, and the difference was statistically significant at 1 d, 4 d and 7 d after surgery, indicating that nitrate-treated group can reduce TNF-α and may have a mechanism of action to alleviate the inflammatory response after myocardial ischemia-reperfusion.

However, this experiment also has some limitations. First of all, due to the small number of cases in this experiment, the convincing results are relatively weak. Secondly, because this study was administered in accordance with conventional dosing, it is not clear what is the optimal dose of myocardial IRI protection, or even what dose range of isosorbide nitrate has myocardial protective effect, and whether it has negative results beyond this range. These are all questions worthy of further investigation.

5. Conclusion

In the PCI treatment of STEMI patients, a certain dose of nitrates given during the surgical opening of occlusive vessels may reduce the IRI of STEMI patients, and may have a mechanism of action to reduce the inflammatory response after myocardial ischemia-reperfusion. Further research should improve the pattern of drug administration and blood sample acquisition, and expand the sample size.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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