Effect of erythropoietin combined with interventional therapy on cardiac function injury and inflammation in patients with STEMI

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Objective: To explore the effect of erythropoietin combined with interventional therapy on cardiac function injury and inflammation in patients with STEMI. Methods: 58 patients with STEMI treated in our hospital between April 2012 and September 2015 were selected, the treatment methods and test results were reviewed, and then they were divided into the control group who accepted interventional therapy alone and the observation group who accepted erythropoietin combined with interventional therapy. Before and after treatment, color Doppler diasonograph was used to detect cardiac function parameters; immune scatter turbidimetry was used to determine myocardial injury marker levels in peripheral blood; ELISA was used to detect serum inflammatory factor levels. Results: Before treatment, differences in cardiac function parameter levels, myocardial injury marker contents and inflammatory factor contents were not statistically significant between two groups of patients (P>0.05). After treatment, cardiac function parameters LvEDD and LVESD levels of observation group were significantly lower than those of control group while EV and AV levels were significantly higher than those of control group (P<0.05); serum myocardial injury indexes ICTP and IMA contents of observation group were significantly lower than those of control group while CysC content was significantly higher than that of control group (P<0.05); serum inflammatory factors CRP, IL-18, IL-27 and MDC contents of observation group were significantly lower than those of control group while IL-10 content was significantly higher than that of control group (P<0.05). Conclusion: Erythropoietin combined with interventional therapy can play a positive role in myocardial protection, improve cardiac pump function, reduce myocardial cell injury and inhibit inflammatory response.

1. Introduction

ST-elevation myocardial infarction (STEMI) is sharply reduce or even disruption of coronary blood supply on the basis of coronary artery lesions, it leads to acute ischemia and even apoptosis of corresponding myocardial tissue, and 50% of deaths occur within 1 h after onset[1-2]. Interventional therapy after admission is the most reliable way for STEMI treatment, which early recanalizes target vessels and restores the myocardial blood supply in target area to protect myocardial function and suppress its irreversible apoptosis.

But with the popularity of interventional therapy, many studies have found that there is different degree of new myocardial injury early after interventional therapy, it may be related to the vascular embolism by the small embolus falling off during interventional therapy or myocardial ischemia-reperfusion injury, etc., and so many scholars put forward that other myocardial protective drugs are added on the basis of interventional therapy to furthest protect cardiac function and reduce complications[3,4]. Erythropoietin (EPO) can promote erythropoiesis, and current study has confirmed that the EPO has certain protective effect on myocardial ischemia reperfusion injury, can also reduce the infarction area and is considered as the ideal drug for auxiliary treatment of myocardial infarction[5]. In the following study, the effect of erythropoietin combined with interventional therapy on cardiac function injury and
inflammation in patients with STEMI was analyzed.

2. Materials and methods

2.1. Clinical information

58 patients with STEMI treated in our hospital between April 2012 and September 2015 were included, the treatment methods and test results were reviewed, and then they were divided into the control group (n=30) who accepted interventional therapy alone and the observation group (n=28) who accepted erythropoietin combined with interventional therapy. Control group included 17 male cases and 13 female cases, they were 49–78 years old, the course of coronary heart disease was 3–11 years, and the body mass index (BMI) was 22–29 kg/m^2 and (25.17±2.98) kg/m^2 in average; observation group included 15 male cases and 13 female cases, they were 48–76 years old, the course of coronary heart disease was 3–12 years, and the body mass index (BMI) was 22–30 kg/m^2 and (25.32±2.95) kg/m^2 in average. Two groups of patients were not statistically different in distribution of gender, age, course of coronary heart disease and BMI (P>0.05), the patients or family members learned about the research process and signed the informed consent, and the research was approved by the hospital ethics committee.

Inclusion criteria: (1) clearly diagnosed with STEMI through the emergency ultrasonography and electrocardiogram; (2) without previous medical history of STEMI; (3) with normal coagulation function. Exclusion criteria: (1) associated with systemic infectious diseases; (2) with malignant tumor diseases; (3) associated with autoimmune diseases; (4) quitting research, and with clinical data missing.

2.2. Treatment methods

Control group received interventional therapy alone, which was as follows: preoperative aspirin (Henan Fenghuang Pharmaceutical Co., LTD., approved by H41023181) 300 mg and clopidogrel (Lepu Pharmaceuticals Co., LTD., approved by H20123115) 600 mg, and intravenous injection of heparin (Shenzhen Sciprogen Bio-pharmaceutical Co., Ltd., approved by H20060191) 100 U/kg. Infarction-related artery PCI was conducted after emergency coronary angiography. Observation group of patients received erythropoietin combined with interventional therapy, which was as follows: receiving EPO (Shandong Kexing Bioproducts Co., LTD., approved by S20113007) 100 U/kg before PCI, and then received intravenous drip of 100 mL saline. PCI operation was the same as that of the control group.

2.3. Observation indexes

2.3.1. Cardiac function indexes

Immediately after admission and 1 week after treatment, color Doppler diasonograph (Shenzhen SonoScape Technology Co., LTD., model SSI-5000) was used to detect the cardiac function indexes of two groups of patients, including left ventricular end-diastolic diameter (LvEDD), left ventricular end-systolic diameter (LVESD), peak velocity at early diastole (EV) and peak velocity at late diastole (AV).

2.3.2. Serum indexes

Immediately after admission and 1 week after treatment, 1.5–2.0 mL of fasting cubital venous blood was extracted from two groups of patients, immune scatter turbidimetry was used to determine the contents of myocardial injury markers in it, including carboxy-terminal telopeptide of type I collagen (ICTP), ischemia modified albumin (IMA) and cystatin C (CysC). Another 1.5–2.0 mL of fasting cubital venous blood was extracted from two groups of patients, added in sodium citrate (Changchun Terumo Medical Products Co., Ltd., approved by H22026723) for anticoagulation, then let stand at room temperature for 6 h and centrifuged at low speed to get supernatant, and enzyme-linked immunosorbent assay (ELISA) was used to determine the serum inflammatory markers C-reactive protein (CRP), interleukin-10 (IL-10), interleukin-18 (IL-18), interleukin-27 (IL-27) and macrophage-derived chemokine (MDC) contents.

2.4. Statistical analysis

Data in the study was input in SPSS18.0 and calculated, measurement data was in terms of mean ± standard deviation (x±s), comparison before and after treatment was by paired t test, comparison between two groups before and after treatment was by group t test and P<0.05 indicated statistical significance in differences.

3. Results

3.1. Cardiac function parameters

Before and after treatment, comparison of cardiac function parameters LvEDD, LVESD, EV and AV between two groups of patients was as follows: before treatment, differences in cardiac function parameters LvEDD, LVESD, EV and AV levels were not statistically significant between two groups of patients (P>0.05);
after treatment, cardiac function parameters $L_v$EDD and $L_v$ESD levels of both groups were significantly lower than those before treatment while EV and AV levels were significantly higher than those before treatment, and differences within same group were statistically significant before and after treatment ($P<0.05$). After treatment, cardiac function parameters $L_v$EDD and $L_v$ESD levels of observation group were significantly lower than those of control group while EV and AV levels were significantly higher than those of control group, and differences between groups were statistically significant after treatment ($P<0.05$), shown in Table 1.

### 3.2. Myocardial injury indexes

Before and after treatment, comparison of serum myocardial injury indexes ICTP, IMA and CysC contents between two groups of patients was as follows: before treatment, differences in serum myocardial injury indexes ICTP, IMA and CysC contents were not statistically significant between two groups of patients ($P>0.05$); after treatment, serum myocardial injury indexes ICTP and IMA contents of both groups were significantly lower than those before treatment while CysC contents were significantly higher than those before treatment, and differences within same group were statistically significant before and after treatment ($P<0.05$). After treatment, serum myocardial injury indexes ICTP and IMA contents of observation group were significantly lower than those of control group while CysC content was significantly higher than that of control group, and differences between groups were statistically significant after treatment ($P<0.05$), shown in Table 2.

### 3.3. Inflammatory factors

Before and after treatment, comparison of serum inflammatory factors CRP, IL-10, IL-18, IL-27 and MDC contents between two groups of patients was as follows: before treatment, differences in serum inflammatory factors CRP, IL-10, IL-18, IL-27 and MDC contents were not statistically significant between two groups of patients ($P>0.05$); after treatment, serum inflammatory factors CRP, IL-18, IL-27 and MDC contents of both groups were significantly lower than those before treatment while IL-10 contents were significantly higher than those before treatment, and differences within same group were statistically significant before and after treatment ($P<0.05$). After treatment, serum inflammatory factors CRP, IL-18, IL-27 and MDC contents of observation group were significantly lower than those of control group while IL-10 content was significantly higher than that of control group, and differences between groups were statistically significant after treatment ($P<0.05$), shown in Table 3.
4. Discussion

STEMI is a clinical common type of myocardial infarction, and early PCI therapy helps recanalize infarction-related vessels and restore the myocardial blood and oxygen supply in infarction area. But the reperfusion injury occurs frequently in patients with myocardial infarction after PCI, patients are mainly characterized by transient sinus bradycardia, atrioventricular block, burst ventricular tachycardia and so on, the incidence rate is as high as 50%–80%, and so preventive medication is extremely necessary[6]. The mechanisms of reperfusion arrhythmia include oxygen free radical onset, myocyte calcium overload and uneven recovery after intracellular potassium loss, etc., and triggered activity and reentrant excitation are the recognized root causes of arrhythmia. It has been confirmed in the rat models with acute myocardial infarction that EPO treatment before ischemia can reduce the incidence of ventricular arrhythmias. The anti-arrhythmic mechanisms of EPO mainly include the following: (1) the EPO is combined with myocardial cell surface receptor (EPO) to activate phosphatidylinositol-3-kinase and other anti-apoptotic signaling pathways, up-regulate the expression of all sorts of anti-apoptotic proteins and inhibit myocardial cell apoptosis; (2) through the anti-apoptotic molecules such as Bcl-2 and Bcl-XL, it reduces intracellular calcium overload after myocardial cell reperfusion, and maintains intracellular calcium ion and PH stability; (3) it reduces the oxygen free radical generation in myocardial cells and inhibits cellular electrophysiological disorder caused by oxygen free radicals[7,8]. In view of the myocardial protective effects of EPO, it was introduced in the treatment of patients with STEMI in the study and elaborated from cardiac injury and inflammation.

Percutaneous coronary intervention (PCI) can early recanalize infarction-related vessels and restore blood flow in myocardial cells, but because of the secondary injury, ventricular remodeling and so on caused by reperfusion, patients may be with significantly declined cardiac function early after operation, and severe cases may even develop heart failure[9,10]. In the study, observation group accepted EPO 100 U/kg before PCI and received echocardiography early after operation to evaluate cardiac function parameters, and it was found that compared with control group, the observation group were with lower LvEDD and LVESD levels, and higher EV and AV levels 3 d after operation. LvEDD and LVESD can objectively reflect the ventricular diameter, and their levels are negatively correlated with ventricular contractility; EV and AV levels represent the mitral blood flow velocity, and the greater the flow velocity, the more complete the coronary artery recanalization, and the more the myocardial blood supply[11]. Above results indicate that EPO combined with interventional therapy can more effectively optimize patients’ postoperative cardiac function parameters, and it is mainly because that EPO is combined with the EPO receptor on ventricular cells to exert protective effect on ischemic injury.

Myocardial injury is directly characterized by cardiac dysfunction, and the contents of a series of factors in circulating blood may also change[12]. ICTP is a newly discovered myocardial injury-specific factor, its level increase may indicate atheromatous plaque instability, and it belongs to the noninvasive myocardial injury predictor[13]. IMA is an ideal ischemia modified albumin, the oxygen free radicals damage the amino acid sequences of serum albumin when ischemia reperfusion occurs and change its transition metal ability, the damaged albumin is called IMA, and its content is consistent with the degree of myocardial injury[14]. CysC belongs to cysteine protease inhibitors, and study has confirmed that homocysteine (Hcy) is an independent risk factor for coronary heart disease, the occurrence risk of coronary heart disease increases with the increase of Hcy levels, CysC, as Hey inhibitor, has myocardial protective effect, and CysC content is negatively correlated with the risk of myocardial infarction[15]. In the study, the contents of above myocardial injury markers were detected, and it was found that compared with control group, the observation group were with lower ICTP and IMA contents, and higher CysC content in peripheral blood after treatment. This further confirms that EPO application before PCI can exert myocardial protective effect.

Many studies confirm that atherosclerosis is due to excessive activation of inflammation, and systemic inflammatory response is throughout the course of coronary heart disease and myocardial infarction[16]. From the perspective of inflammation, CRP, IL-18, IL-27 and other pro-inflammatory factors can locally recruit mononuclear macrophages, accelerate atherosclerosis plaque rupture and increase the risk of myocardial infarction. Macrophage-derived chemokine is the strongest chemokine that can locally recruit mononuclear macrophages, and it can further prompt the release of inflammatory mediators, enhance the systemic inflammatory response in patients with coronary heart disease or myocardial infarction, and increase myocardial damage[17,18]. IL-10, as an anti-inflammatory factor, belongs to the myocardial injury-protecting factor and can fight against the pro-inflammatory factors and reduce their serum levels, but patients with coronary artery disease are mostly with low levels of IL-10, which is associated with the IL-10 neutralization by a large amount of pro-inflammatory factors. EPO can significantly reduce neutrophil infiltration, decrease nuclear factor α B activation caused by ischemia-reperfusion, reduce the generation of pro-inflammatory factors such as IL-6 and TNF-α, eventually reduce myocardial cell inflammation and inhibit cardiac remodeling after myocardial infarction[19,20]. In the study, the serum levels of above inflammatory markers were detected, and it was found that compared with control group, the observation group were with lower serum CRP, IL-18, IL-27 and MDC contents, and higher IL-10 content after treatment, confirming that preoperative EPO...
application can play a positive role in resisting inflammation and balancing the pro-inflammatory/anti-inflammatory factor balance.

To sum up, it is concluded as follows: EPO combined with PCI can exert positive myocardial protective effect and reduce systemic inflammatory response, and it is worth popularization and application in clinical practice in the future.

References


