Clinical observation of cardiac function in patients with acute myocardial infarction complicated with heart failure undergoing stem cell transplantation: a 2-year follow-up visit

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Abstract

BACKGROUND: Many animal experiments and clinical trials have demonstrated that stem cell transplantation can improve heart function and reduce ventricular dilatation and ventricular remodeling, which has shown an incomparable superiority over traditional therapies in the treatment of myocardial infarction complicated by heart failure.

OBJECTIVE: To observe the clinical effects of single autologous peripheral blood stem cell transplantation in acute myocardial infarction patients with heart failure.

METHODS: Since 2006 August to 2010 June, 23 patients who were diagnosed to have acute ST elevation myocardial infarction complicated with heart failure were selected and divided into two groups: cell transplantation group (n=11) and control group (n=12). All patients underwent emergency coronary angiography and percutaneous coronary intervention with drug eluting stent implantation. In the stem cell transplantation group, peripheral blood stem cells positive for CD34 (about 1×10^8) were collected mobilized by granulocyte colony stimulating factor at 5 days after stent implantation, and then the cells were injected into infarcted vessels using coronary angiography method. Two-year follow-up was performed after cell transplantation to observe the cardiac function and adverse reactions in patients.

RESULTS AND CONCLUSION: After 6 months of follow-up, the cardiac function in the cell transplantation group was improved significantly compared with that before cell transplantation (P < 0.05), and the left ventricular ejection fraction was increased by (6.2±0.2)% and the left ventricular end diastolic volume was reduced by (4.7±2.9) mm. However, there was no difference in follow-up results by the end of 1 and 2 years after cell transplantation (P > 0.05), as well as no adverse reaction occurred. In the control group, after 6 months of follow-up, the left ventricular ejection fraction was reduced by (0.5±0.1)% and the left ventricular end diastolic volume was increased by (0.4±0.3) mm, which were deteriorated year after year. Percutaneous coronary intervention with autologous peripheral blood stem cell transplantation can significantly improve the left ventricular function, reduce left ventricular volume, and delay or prevent left ventricular remodeling in patients with acute myocardial infarction, which is safe and effective. But up to 2 years after cell transplantation, the cardiac function shows no further improvement.

Subject headings: myocardial infarction; heart failure; stem cell transplantation; peripheral blood stem cell transplantation; stroke volume

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INTRODUCTION

Post-infarction heart failure refers to congestive heart failure due to the large area of myocardial necrosis after acute myocardial infarction. Although coronary reperfusion therapy and long-term application of drug therapy can improve symptoms, improve quality of life and prolong life-span, the mature cardiomyocytes are difficult to regenerate and meet the needs of cardiac repair. The presence of myocardial fibrosis, ventricular remodeling and reduced heart function indicates that the long-term efficacy is still very limited.

In 2001, Orlic *et al* [1] found that autologous bone marrow stem cells transplanted in mice with heart damage could differentiate into cardiomyocytes, providing a basis for the basic and clinical research on stem cell transplantation for treatment of myocardial infarction complicated by heart failure. In

recent years, stem cell transplantation has become the hot spot in the treatment of acute myocardial infarction[2-4]. Most animal experiments and clinical trials have demonstrated that stem cell transplantation can improve cardiac function and reduce ventricular dilatation and ventricular remodeling, which has incomparable superiority over traditional treatment methods in the treatment of myocardial infarction complicated by heart failure. Currently, we can confirm the safety and preliminary effectiveness of stem cell transplantation in the treatment of myocardial infarction with heart failure through REPAIR-AMI, ASTAMI, MAGIC Cell-3-DES, BOOST and PROTECT-CAD trials[5-7].

Bone marrow stem cell transplantation has been largely reported in the treatment of myocardial infarction. Yin *et al* [8] performed the intracoronary injection of autologous bone marrow stem cells into 18 cases of acute myocardial infarction. After 6 months of follow-up, Yin and colleagues found that this therapy could improve cardiac function and reduce heart failure in patients with myocardial infarction. In another study by Wollert *et al* [9], 30 patients with acute myocardial infarction undergoing intracoronary injection of autologous bone marrow mononuclear cells showed a significant improvement in their cardiac function after 6 months, and the incidence of adverse events, such as arrhythmias, had no increase. In addition, transplantation of adipose-derived stem cells and umbilical cord blood mesenchymal stem cells has also achieved good results[10-11].

Compared with bone marrow stem cells and adipose stem cells, peripheral blood stem cells are relatively easy to obtain and produce smaller trauma in patients. Therefore, growing studies have reported the clinical outcomes of peripheral blood stem cell transplantation in the treatment of myocardial infarction complicated by heart failure. Zhang *et al* [12] treated 23 cases of myocardial infarction complicated by cardiac insufficiency with peripheral blood stem cell transplantation, and 6 months later, echocardiographic findings confirmed that the patient's left ventricular volume and ventricular wall motion were markedly improved that the left ventricular remodeling was blocked or continued. Gu Xiang and coworkers[13] found that intracoronary injection of autologous peripheral blood stem cells for post-myocardial infarction heart failure could narrow the left ventricular end-diastolic diameter, improve the left ventricular ejection fraction, increase 6-minute walking distance, and reduce myocardial defect size in a age-independent manner. Referring to the above studies, we also used peripheral blood stem cell transplantation in the treatment of 23 patients with acute ST-segment elevation myocardial infarction complicated by heart failure, and completed the 2-year follow-up.

SUBJECTS AND METHODS

Design

Case-control study.

Time and setting

All patients with acute myocardial infarction complicated by heart failure were admitted in the Department of Cardiology, Jinqiu Hospital of Liaoning Province, China from August 2005 to September 2006.

Subjects

Twenty-three patients with acute ST-segment elevation myocardial infarction complicated by heart failure, who had undergone emergency coronary angiography and percutaneous coronary intervention with drug-eluting stent implantation, were enrolled, including 16 males and 7 females, aged 65–85 years with a mean age of (75±10) years, weighing 55.5–85.0 kg with a mean of (70±15) kg. Of the 23 patients, 13 cases had hypertension, 11 cases had diabetes, 2 cases had respiratory insufficiency, and 2 cases had renal insufficiency.

Diagnostic criteria: (1)persistent chest pain ≥ 30 minutes; (2)electrocardiogram showed 2 mm ST segment elevation in at least two adjacent or contiguous leads; (3)elevation of serum creatine kinase MB isoenzyme or troponin I; (4)presence of dyspnea, coughing, cyanosis, irritability and other symptoms of heart failure.

Inclusion criteria: (1)acute myocardial infarction complicated by heart failure; (2)cardiac function at admission ≥ grade II of Killip's classification; (3)conventional drug therapy is invalid; (4)the left ventricular ejection fraction < 45%; (5)patients and their families signed an informed consent form, and the therapeutic schedule was approved by the ethics committee of the hospital.

Exclusion criteria: (1)patients who could not receive or disagreed with percutaneous coronary intervention; (2)presence of angina and cardiogenic shock prior to transplantation; (3)with history of cancer or other fatal diseases that can impact patient's short-term survival; (4)anemia and coagulation disorders; (5)progressive hepatic failure.

According to patient's willness, the 23 patients were divided into: cell transplantation group (n=11), including 8 males and 3 females, aged 65–85 years; and control group (n=12), including 8 males and 4 females, aged 65–85 years. Baseline characteristics of the two groups were similar and comparable.

Methods

In the control group, patients were routinely given anti-platelet aggregation, crown expansion, diuretic, cardiac, and other drugs to improve the ventricular remodeling at admission, and then, received the emergency coronary angiography and percutaneous coronary intervention with drug-eluting stent implantation.

In the cell transplantation group, stem cell transplantation was conducted 5 days after percutaneous coronary intervention.

Mobilization and collection of peripheral blood stem cells: granulocyte colony-stimulating factor at a dose of 300−600 μg/d was injected subcutaneously for 5 consecutive days. At day 6, peripheral blood samples were collected via cubital vein puncture. Collected blood samples were placed via a closed sterile pick device into a blood cell separator for extraction of peripheral blood stem cells. Hematopoietic stem cells were collected and stored in blood bags, and the remaining blood flowed back to the patient's body. Finally, the total amount collected was 50−100 mL. The isolated stem cells were counted by flow cytometry to collect $CD34^+$ cells (about 1×10^8).

Cell transplantation: At the day of transplantation, the femoral artery access was established under the sterile environment in the conduit room. Ischemic coronary angiography was performed to introduce a microcatheter into the guiding catheter. Then, the suspension of peripheral blood stem cells was injected *via* the microcatheter into the distal end of infarcted vessels, 2.0−3.0 mL every 3 minutes, totally 30 mL (about 1×10^8 $CD34^+$ cells). After injection, balloon occlusion was done for 3 minutes. We observed whether intraoperative arrhythmia, micro-embolism and hypotension occurred. If patients presented with chest pain, chest tightness, unbearable, or severe arrhythmia, the balloon occlusion time could be reduced appropriately.

Main outcome measures

(1)Cardiac function prior to, 6 months, 1 year, 2 years after treatment in the two groups was observed; Echocardiography (SONO7500, Philips) was used by a designated physician from the ultrasound department to evaluate the left ventricular ejection fraction and left ventricular end-diastolic volume before and after treatment. (2)Safety monitoring: we observed whether the fever, cancer and other adverse reactions occurred, and whether there were new myocardial ischemic damage, inflammation and malignant arrhythmias reactions.

Statistical analysis

Measurement data were expressed as mean±SD and statistically analyzed by SPSS 10.0 statistical software. Student's *t* test was performed between two groups, and a value of $P < 0.05$ was considered statistically different.

RESULTS

Quantitative analysis of participants

By intention-to-treat analysis, 23 patients completed the 2-year follow-up with no shedding and were all included in the result analysis.

Comparison of baseline data between two groups (**Tables 1, 2**)

Effects of stem cell transplantation on cardiac function

After 6 months of follow-up, the cardiac function in the cell transplantation group was improved significantly compared with that before cell transplantation ($P < 0.05$), and the left ventricular ejection fraction was increased by (6.2±0.2)% and the left ventricular end diastolic volume was reduced by (4.7±2.9) mm ($P < 0.05$). However, there was no difference in follow-up results by the end of 1 and 2 years after cell transplantation ($P > 0.05$). In the control group, after 6 months of follow-up, the left ventricular ejection fraction was reduced by (0.5±0.1)% and the left ventricular end diastolic volume was increased by (0.4±0.3) mm, which were deteriorated year after year (**Table 3** and **Figures 1, 2**).

Safety monitoring results

During stem cell collection, there were no serious reactions or complications. Sometimes some patients felt hand and foot numbness, dry mouth, or faint during acupuncture. No tumor, malignant arrhythmia, hemolysis, thrombocytopenia, reduced heart function, allergies, infections and other adverse reactions occurred in the cell transplantation group at 6 months, 1 year, 2 years after cell transplantation.

Table 1 Baseline data of patients in the cell transplantation group

No.	Sex	Age (year)	Body mass (kg)	Coronary heart disease	Acute myocardial infarction	Heart failure	Percutaneous coronary intervention	Hypertension	Diabetics mellitus	Respiratory insufficiency	Renal insufficiency
1	Male	65	55.5	+	+	+	+	+	+	−	−
2	Male	76	67.0	+	+	+	+	+	−	−	−
3	Male	77	74.5	+	+	+	+	−	+	+	−
4	Male	66	85.0	+	+	+	+	+	+	−	−
5	Male	75	72.5	+	+	+	+	+	−	−	−
6	Male	73	62.0	+	+	+	+	+	−	−	+
7	Female	69	65.5	+	+	+	+	−	−	−	−
8	Female	80	71.5	+	+	+	+	+	+	−	−
9	Male	85	73.0	+	+	+	+	−	−	−	−
10	Female	79	81.0	+	+	+	+	−	+	−	−
11	Male	84	68.5	+	+	+	+	−	−	−	−

Note: Baseline data in the cell transplantation group are comparable with those in the control group.

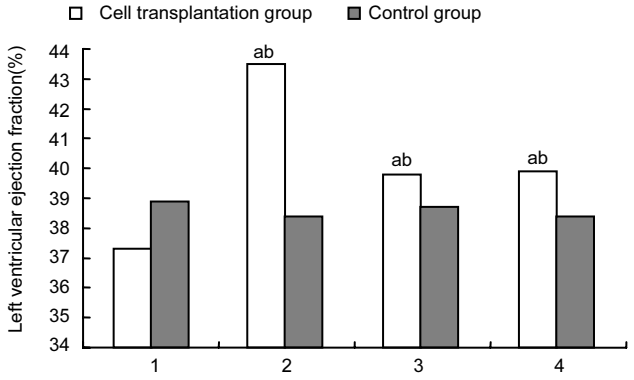

Figure 1 Comparison of left ventricular ejection fraction between two groups before treatment and during follow-up
Note: 1: Before transplantation; 2: By the end of 6-month follow-up; 3: By the end of 1-year follow-up; 4: By the end of 2-year follow-up. Data are represented as the optical absorption values at 490 nm. [a]$P < 0.05$, *vs.* ONFH femoral head group; [b]$P < 0.05$, *vs.* femoral neck fracture group. ONFH: osteonecrosis of the femoral head.

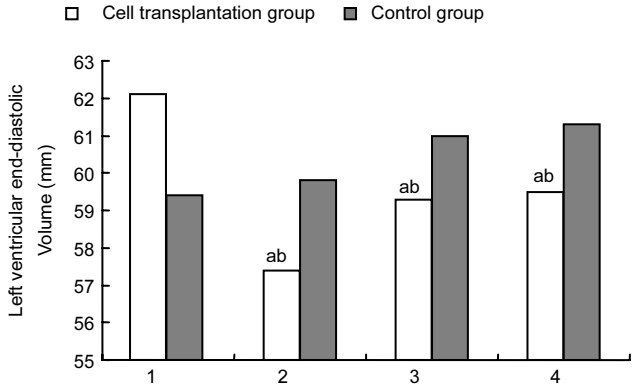

Figure 2 Comparison of left ventricular end-diastolic volume between two groups before treatment and during follow-up
Note: 1: Before transplantation; 2: By the end of 6-month follow-up; 3: By the end of 1-year follow-up; 4: By the end of 2-year follow-up. Data are represented as the optical absorption values at 490 nm. [a]$P < 0.05$, *vs.* before transplantation; [b]$P < 0.05$, *vs.* control group in the same period.

Table 2 Baseline data of patients in the control group

No.	Sex	Age (year)	Body mass (kg)	Coronary heart disease	Acute myocardial infarction	Heart failure	Percutaneous coronary intervention	Hypertension	Diabetics mellitus	Respiratory insufficiency	Renal insufficiency
1	Female	68	79.5	+	+	+	+	+	+	−	−
2	Male	73	73.0	+	+	+	+	−	+	−	+
3	Male	79	55.5	+	+	+	+	+	−	−	−
4	Male	68	68.0	+	+	+	+	+	+	−	−
5	Female	71	82.5	+	+	+	+	−	-	−	−
6	Female	77	61.0	+	+	+	+	+	+	−	−
7	Male	65	72.5	+	+	+	+	−	−	−	−
8	Male	85	69.5	+	+	+	+	−	−	−	−
9	Male	81	67.0	+	+	+	+	+	+	+	−
10	Female	72	85.0	+	+	+	+	+	−	−	−
11	Male	84	59.5	+	+	+	+	+	+	−	−
12	Male	74	70.0	+	+	+	+	−	−	−	−

Note: Baseline data in the control group are comparable with those in the cell transplantation group.

Table 3 Cardiac function of two groups before transplantation and during follow-up ($\bar{x}\pm s$)

Time	Cell transplantation group (n=11)		Control group (n=12)	
	LVEF (%)	LVDd (mm)	LVEF (%)	LVDd (mm)
Before transplantation	37.3±5.4	62.1±7.5	38.9±5.2	59.4±6.1
By the end of 6-month follow-up	43.5±5.6[ab]	57.4±4.6[ab]	38.4±5.1	59.8±6.4
By the end of 1-year follow-up	39.8±5.9[ab]	59.3±4.4[ab]	38.7±5.6	61.0±7.3
By the end of 2-year follow-up	39.9±6.0[ab]	59.5±4.2[ab]	38.4±5.4	61.3±7.8

Note: LVEF: left ventricular ejection fraction; LVDd: left ventricular end-diastolic volume. [a]$P < 0.05$, *vs.* before transplantation; [b]$P < 0.05$, *vs.* control group in the same period.

DISCUSSION

In 2001, Strauer, a physician from Dusseldorf, Germany and co-workers performed the first transplantation of autologous bone marrow stem cells in the clinical treatment of acute myocardial infarction. Autologous bone marrow stem cells at a dose of 1×10^7 were implanted via the transcatheter into the infarcted vessels during percutaneous transluminal coronary angioplasty. Ten weeks later, single photon emission computed tomography, echocardiography and radionuclide ventriculography displayed reduced myocardial infarction area, increased cardiac ejection fraction and decreased end-diastolic pressure. After cell transplantation, there was no new myocardial ischemic damage, inflammation and malignant arrhythmias. It for the first time demonstrates that intracoronary transplantation of autologous bone marrow stem cells is safe and feasible in the treatment of acute myocardial infarction.

MAGIC Cell-3-DES trial is used to evaluate the safety of stem cell therapy through granulocyte colony-stimulating factor mobilization and effect of intracoronary injection of mobilized peripheral blood stem cells on acute myocardial infarction. The trial confirms that stem cell transplantation may improve coronary flow reserves and improve the left ventricular systolic function and myocardial perfusion.

However, the application of drug-eluting stents is necessary to prevent in-stent restenosis. In our study, 23 myocardial infarction patients underwent revascularization with drug-eluting stents. Then, the peripheral blood stem cells via granulocyte colony-stimulating factor mobilization for 5 days were collected and intracoronarily injected in the cell transplantation group. By the end of 6 months after cell transplantation, the left ventricular ejection fraction was increased by (6.2±0.2)% and the left ventricular end diastolic volume was reduced by (4.7±2.9) mm, which were significant different from those before treatment ($P < 0.05$); there was also a significant difference between the cell transplantation group and control group ($P < 0.05$). Our findings indicate that based on granulocyte colony-stimulating factor mobilization, stem cell therapy cannot promote neointimal hyperplasia after drug-eluting stent implantation[14-16]. This therapy is safe and feasible to improve the left ventricular remodeling and left ventricular ejection fraction, eliminate the risk of vascular restenosis, and improve the clinical endpoint event rate in patients with acute myocardial infarction patients. The specific mechanisms of cellular physiology may be to promote neovascularization or inhibit ventricular remodeling.

Single cell transplantation garners increasing attention to whether it can bring long-term benefits for patients with acute myocardial infarction. The types of transplanted cells are no longer confined to bone marrow mononuclear cells, bone marrow mesenchymal stem cells and peripheral blood progenitor cells. In addition, numerous animal experiments have shown that the number of transplanted cells shows a linear positive relationship with the improvement in heart function. Existing transplantation methods, however, cannot successfully transfer more transplanted cells into the infarcted zone and its marginal zone. The timing and efficiency of transplantation is still a bottleneck in the widespread clinical application. Poh *et al* [17] conducted several transplantation of bone marrow mesenchymal stem cells in a swine model of myocardial infarction, which is feasible and found to improve the efficiency and safety of transplantation. The findings from the animal experiment are consistent with previous studies. Compared with the single transplantation, multiple transplantation can improve the long-term cardiac function of patients. In our study, the left ventricular ejection fraction was remarkably improved at 6 months after a single stem cell transplantation, but no further improvement was found after 2 years, indicating that multiple transplantation of stem cells are required for myocardial infarction complicated by heart failure in order to improve the long-term cardiac function.

Stem cell therapy is safe and feasible for treatment of myocardial infarction complicated by heart failure. Large-sample, large-scale, multi-center long-term randomized controlled studies are required in the further to further evaluate the efficacy and risk[18].

A 6-month follow-up shows that the single intracoronary transplantation of autologous peripheral blood stem cells can significantly improve the left ventricular function, reduce the left ventricular volume, prevent or delay left ventricular remodeling in patients with acute myocardial infarction, which is safe and effective. Multiple transplantations are suggested to continuously improve the left ventricular function, but large-scale multi-center clinical randomized controlled studies are necessary to verify the safety and feasibility.

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干细胞移植急性心肌梗死合并心力衰竭患者的心功能变化：2 年随访

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文章亮点：

1 干细胞移植治疗心肌梗死的报道中，大多移植的是骨髓干细胞，与骨髓干细胞相比，外周血干细胞获得相对容易，且对患者的创伤小，本文报道了用外周血干细胞治疗心肌梗死合并心衰的临床效果。

2 本试验单次注射外周血干细胞，移植后 6 个月左室射血分数明显改善，但随访至 2 年心功能无进一步的改善，说明心梗合并心衰干细胞治疗需多次注射干细胞，方能长期改善心功能。因此建议多次移植，希望能持续改善左室功能，但其安全性、可行性仍需大规模多中心临床随机对照研究验证。

关键词：
干细胞；移植；外周血干细胞；急性心肌梗死；心衰；干细胞移植；心功能；安全性
主题词：
心肌梗塞；心力衰竭；干细胞移植；外周血干细胞移植；每搏输出量

摘要

背景：很多动物实验和临床试验均证实，干细胞移植可改善心脏功能，减少心室扩张及心室重构，在治疗心肌梗死合并心衰方面已经表现出传统治疗方法所无可比拟的优越性。

目的：观察单次自体外周血干细胞移植在急性心肌梗死后心衰患者中的临床疗效。

方法：选择 2005 年 8 月至 2006 年 9 月收治的急性 ST 段抬高心肌梗死合并心衰患者 23 例，将入选者分成两组，细胞移植组 11 例，对照组 12 例，均急诊行冠状动脉造影及药物洗脱支架置入(PCI)。细胞移植组于支架置入后 5 d，采集经粒细胞集落刺激因子动员 5 d 的外周血干细胞(CD34+细胞，大约 1×10^8)，用冠脉造影注射法注入梗死相关血管。细胞移植后随访 2 年，观察患者心功能变化及不良反应。

结果与结论：细胞移植组移植前与随访至 6 个月时相比，心功能明显改善($P < 0.05$)，左室射血分数提高(6.2±0.2)%，左室舒张末期容积减少(4.7±2.9) mm，而移植后随访至 1 年、2 年时结果并无明显区别($P > 0.05$)，未发现细胞移植的不良反应。对照组随访至 6 个月时，左室射血分数下降(0.5±0.1)%，左室舒张末期容积增大(0.4±0.3) mm，并且逐年恶化。证实经皮经冠状动脉内自体外周血干细胞单次移植 6 个月时，能明显改善急性心肌梗死患者的左室功能，减小左室容量，阻止或延缓左室重构，且安全有效，但随访至 2 年，心功能没有得到进一步的改善。

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利益冲突：文章及内容不涉及相关利益冲突。

伦理要求：所有患者及家属均签署知情同意书。辽宁省金秋医院有进行外周血干细胞移植治疗的资质。

学术术语：外周血干细胞-干细胞由骨髓大量生成，其中少量的干细胞被释放到血液中，这就是外周血干细胞。 通过使用重组人粒细胞集落刺激因子能够增加释放到血液中的干细胞数量，从而有可能直接从血液中采集到干细胞移植所需要的足量的干细胞。

作者声明：文章为原创作品，无抄袭剽窃，无泄密及署名和专利争议，内容及数据真实，文责自负。

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