Bone marrow mesenchymal stem cells transfer in patients with ST-segment elevation myocardial infarction: single-blind, randomized controlled muticentre trial

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Keywords: Mesenchymal stem cells, Bone marrow, Stem cells transplantation, Myocardial infarction

DOI: https://doi.org/10.21203/rs.3.rs-54127/v1

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Abstract

Objective: Our aimed to evaluate efficacy and safety of intracoronary autologous bone marrow mesenchymal stem cells (BM-MSCs) transplantation in patients with ST-segment elevation myocardial infarction (STEMI).

Methods: In this randomised, single-blind, controlled trial, patients with STEMI (aged 39-76 years) were enrolled at 6 centers in Beijing (the People's Liberation Army Navy General Hospital, Beijing Armed Police General Hospital, Chinese People's Liberation Army General Hospital, Beijing Huaxin Hospital, Beijing Tongren Hospital, Beijing Chaoyang Hospital West Hospital). Patients underwent optimum medical treatment and percutaneous coronary intervention, and were randomly assigned in a 1:1 ratio to BM-MSCs group or control group. The primary endpoint was change of myocardial viability at 6 months’ follow-up and left-ventricular (LV) function at 12 months’ follow-up. The secondary endpoints were incidence of cardiovascular event, total mortality and adverse event at 12 months’ follow-up. The myocardial viability assessed by single-photon emission tomography (SPECT). The left ventricular ejection fraction was used to assess LV function. All patients underwent dynamic ECG and laboratory evaluations. This trial is registered with ClinicalTrials.gov, number NCT04421274.

Results: Between March, 2008, and July, 2010, 43 patients were randomly assigned to BM-MSCs group (n=21) or control group (n=22) and followed up for 12 months. LV ejection fraction increased from baseline to 12 months in the BM-MSCs group and control group (mean baseline-adjusted BM-MSCs treatment differences in LV ejection fraction 4.8% (SD 9.0) and mean baseline-adjusted control group treatment differences in LV ejection fraction 5.8% (SD 6.04)). After 6 months of follow-up, there was no significant improvement in myocardial metabolic activity in the BM-MSCs group before and after transplantation. However, there was no statistically significant difference between the two groups in the change of LV ejection fraction (p=0.30) and myocardial metabolic activity (p>0.05). We noticed that, after 12 months of follow-up, except for 1 death and 1 coronary microvascular embolism in the BM-MSCs group, no other events occurred and Alanine transaminase (ALT) and C-reactive protein (CRP) in BM-MSCs group were significantly lower than that in control group.

Conclusions: It is unreasonable to speculate that intracoronary transfer of autologous bone marrow MSCs could augment recovery of LV function and myocardial viability after acute myocardial infarction.

Trial registration: clinicaltrials,NCT04421274. Registered 06,08,2020- Retrospectively registered, https://register.clinicaltrials.gov/NCT04421274.

Introduction

Acute myocardial infarction (AMI) is a disease in which the coronary arteries suddenly interrupt blood flow to the heart, causing acute and persistent ischemia and hypoxia in the heart, which increase the risk of death. [1] AMI is further divided into two subcategories: ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). STEMI is characterized by
persistent typical ischemic chest pain and elevated serum myocardial necrosis markers, as well as typical ST segment elevation of ECG\(^2-4\), approximately accounting for 25%-40% of AMI. Although most patients with STEMI can undergo percutaneous coronary intervention (PCI) and take the drugs recommended by the guidelines to relieve their symptoms, it cannot rescue the apoptotic and necrotic cardiomyocytes\(^5\). According to statistics, the risk of in-hospital death of AMI patients has not decreased significantly in the past 10 years\(^6\), and the number of AMI patients in China will increase to 23 million by 2030\(^7\).

An increasing evidence indicates that stem cells have the ability to multi-directional differentiation, and it is getting more and more attention that stem cell transplantation serve as a new replacement therapy in repairing damaged myocardium\(^8\). For example, pluripotent stem cells, adult tissue stem/progenitor cells including endothelial progenitor cells, skeletal muscle myoblasts, cardiac stem/progenitor cells, and bone marrow mononuclear cells have been reported to participate in therapy of damaged cardiomyocytes\(^9\). In addition, it was found that these cells can repair damaged myocardium through paracrine\(^10\).

Bone marrow mesenchymal stem cells (BM-MSCs) are the most widely studied MSC types. Many experimental studies have shown that BM-MSCs can improve heart function after AMI\(^11-13\). Although BM-MSCs are not abundant in bone marrow nucleated cells, accounting for only 0.01%, they can be expanded one billion times in vitro without losing stem cell activity\(^4\). It had been found that BM-MSCs not only differentiated into cardiomyocytes to promote cardiomyocyte regeneration when they were transplanted into the heart in vivo\(^15,16\), but also secrete growth factors, cytokines, chemokines, and microRNAs to improve tissue microenvironment, effectively reduce the adverse remodeling and inflammation of cardiomyocytes. Additionally, the secreted proteins of BM-MSCs have immunosuppressive properties by regulating T cells, B cells and monocytes\(^17-20\).

In clinic, Autologous bone marrow MSCs have been expanded in vitro and transplanted to treat myocardial infarction\(^7\). However, reviewing the clinical study of BM-MSCs on AMI from 2004 to 2017, it was found that compared with the control group, only two clinical research results showed that BM-MSCs can increase the left ventricular ejection fraction of patients\(^21\). Our research aims to conduct a randomized, single-blind, parallel-controlled multicenter clinical trial using BM-MSCs injection with independent intellectual property rights in China. It is hoped that this study will show whether BM-MSCs injection transplantation is effective and safe in patients with ST-segment elevation myocardial infarction (STEMI), and provide a reliable basis for clinical promotion.

1. Methods

1.1 Participants

- This study is a randomized single-blind, parallel-controlled multicenter clinical trial that started in March 2008 and ended in July 2010. A total of 43 patients came from 6 hospitals in Beijing (the
People's Liberation Army Navy General Hospital, Beijing Armed Police General Hospital, Chinese
People's Liberation Army General Hospital, Beijing Huaxin Hospital, Beijing Tongren Hospital, Beijing
Chaoyang Hospital West Hospital), including 39 males and 4 females. Their age ranged from 39 to
76 years, with an average age of (58.9 ± 11) years. Based on the agreement of the Center Clinical
Trial Ethics Committee and the Helsinki Declaration, we produced the research protocol as shown in
Fig. 1. Eligible STEMI patients who had an onset time of less than 1 month were older than 18 years,
was successful revascularization with infarct-related vascular blood flow returning to TIMI level 3,
and all patients enrolled in the study signed an informed consent form and promised to complete all
Follow-up plan. Exclusion criteria included the following eight items: 1. Patients with refractory
persistent ventricular tachycardia; 2. Patients with high heart block and not controlled by pacemaker;
3. Patients with pepatic or kidney dysfunction (ALT > 80U/L, Cr > 440 mmol/L); 4. Patients with
bleeding disorders or malignant tumors; 5. Patients with autoimmune disease or any serious fatal
disease; 6. Patients with contraindications for coronary intervention; 7. patients with the following
other heart diseases: congenital heart disease (ventricular defect, atrial defect, arterial duct
Congenital malformations such as patent); primary heart valve disease; active myocarditis;
pulmonary heart disease; hyperthyroid heart disease, mucoedema heart disease, etc. 8. Patients with
mental illness, no self-awareness, and no precise expression and cooperation.

1.2 Randomization and Study Treatment

Participants' random numbers were generated by the network, and technical services were provided by
the China Cardiovascular and Cerebrovascular Diseases Professional Network (CCVD), which was not
related to this clinical trial. The participant's information was entered into the computer. If the patient met
the inclusion criteria, the system would give a random number and grouping to determine the
randomization of the patient. The 43 patients were randomly divided into a cell transplantation group
(BM-MSCs injection via coronary artery perfusion, n = 21) and a control group (all other treatments except
cell transplantation were the same as the cell transplantation group, n = 22). Those who were
unsuccessful in revascularization withdrew from this study.

1.3 Preparation of BM-MSCs injection

The collection and separation of bone marrow are performed in a sterile room. Under lidocaine local
anesthesia, 80 ml of bone marrow was extracted from the patient's posterior superior iliac crest and
placed in heparinized saline. The BM-MSCs injection was prepared by the Stem Cell and Regenerative
Medicine Center of the Institute of Field Transfusion of the Academy of Military Medical Sciences
according to standard procedures.

1.4 Injection of BM-MSCs via coronary artery

- The preoperative preparation of BM-MSCs undergoing coronary artery transplantation is the same as
PCI. 10 to 14 days after PCI, firstly, the patient was inserted with an ultra-long guide wire, and inserted
into the guide wire balloon catheter (OTW balloon) along the extra long guide wire to the distal end of
the stent. The guidewire was then withdrawn and the balloon pressure was filled until there was no forward blood flow. Finally, in the case of complete closure of the target vessel, BM-MSCs injection was injected into the infarct-related arterial hypertension through the central lumen of the guidewire balloon catheter. During the operation, each balloon pressure was filled for 2 minutes to block the blood flow, and then the perfusion was restored for 2 minutes. The above process was repeated 6–8 times, and the patient did not undergo angiography again after the cell implantation. Patients were monitored for chest pain, changes in ECG and intracavitary pressure changes during surgical procedures.

1.5 Echocardiography

The subjects underwent echocardiography before and 12 months after surgery, and the left ventricular ejection fraction was measured by Simpson method. The color heart ultrasound system (GE, USA) uses VIVID7, the probe is S4, and the frequency is 2 ~ 4 MHz. we would collect four standard two-dimensional images (the parasternal long axis and short axis, apical two-chamber and four-chamber view).

1.6 Myocardial metabolic imaging examination

The purpose of cardiac metabolic imaging was to evaluate the changes in left ventricular myocardial metabolic defects before and after BM-MSCs transplantation. The SPECT image was divided into 20 segments, and the score was determined according to the degree of attenuation of myocardial nuclide uptake in each segment (0 points = adequate intake, 1 minute = slight decrease in intake, 2 points = moderate reduction in intake, 3 points = reduced ingestion, 4 points = intake defect). The sum of the scores of each segment was obtained to quantify the myocardial metabolic defect, that is, the higher the value, the larger the range of myocardial metabolic defects. Cardiac metabolic imaging was read by a professional nuclear medicine physician.

Patients with hyperlipidemia were treated with oral hypolipidemic drugs (inositol niacinate 0.2 g or reserpine) 2 hours before the examination. If the patient had diabetes, eating a small amount of food 1 h before the examination. we used the automatic blood glucose meter to measure the blood sugar. According to the patient's blood sugar situation, oral glucose or subcutaneous injection of insulin was considered for blood glucose regulation, and finally the patients' blood glucose was controlled in the range of 7.8 to 8.8 mmol/L. The participants were intravenously injected with the imaging agent 18F-FDG 810Mci (296–370 MBq) after 30 minutes of blood glucose regulation. Myocardial metabolism was observed after 45 min-60 min of injection. The 18F-FDG (18F-deoxyglucose) was provided by Atomic High Tech of China Institute of Atomic Energy. The imaging instrument used GE's Millennium VG Hawkeye SPECT (single photon emission computed tomography) with 511Kev high-energy collimator and dual probes in L mode. The acquired images were processed by the ECToobox heart software, and the horizontal long axis, vertical long axis, short axis images and bullseye image were reconstructed.

1.7 Observation
Primary endpoint: the change of myocardial metabolic activity (SPET detection) 6 months after autologous BM-MSCs transplantation. Changes in left ventricular ejection fraction (LVEF) at 12 months after transplantation of autologous BM-MSCs.

Secondary endpoint: incidence of cardiovascular events, overall mortality, and adverse events at 12 months after transplantation of autologous BM-MSCs.

1.8 Follow-up criteria

- The increase in 18-FDG intake of BM-MSCs in the 6 months after transplantation constitutes a statistical difference with that before transplantation. The increase in 18-FDG intake at 6 months after BM-MSCs transplantation constitutes a statistical difference with the control group. Those with the above two comparison differences was determined to be effective for myocardial reconstruction of BM-MSCs.
- The increase in LVEF at 1 year after BM-MSCs transplantation constitutes a statistical difference with that before transplantation. The increase in LVEF at 1 year after BM-MSCs transplantation constitutes a statistical difference with the control group. Those with the above two comparison differences were determined to improve the cardiac function effective of BM-MSCs.
- Safety evaluation was based on coronary angiography, laboratory abnormalities, and incidence of adverse events.

1.9 Statistical analyses

Statistical analysis was performed using SPSS10.0 statistical software. The measurement data were expressed as mean ± standard difference (± SD), and the comparison of means between the two groups was analyzed by analysis of variance; P < 0.05 was considered as significant difference.

2. Result

2.1 Research protocol

2.2 Patient characteristics

The data of the tested patient is shown in Fig. 2. In the BM-MSCs transplantation group, 19 patients completed a 6-month follow-up and 18 patients completed a 1-year follow-up. In the direct PCI group, 21 patients completed a 6-month follow-up, and 19 patients completed a 1-year follow-up. One case in each group was lost to follow-up due to the patients' emigration. One patient died in the BM-MSCs transplantation group. There were no significant differences in the baseline clinical characteristics of the two groups of subjects (Table 1).
Table 1
Baseline clinical data of the enrolled patients

|                          | BM-MSCs (n = 21) | Control (n = 22) | P     |
|--------------------------|------------------|-----------------|-------|
| Age (years)              | 59.3 ± 9         | 58.6 ± 11       | NS    |
| Sex (male/female)        | 20/1             | 19/3            | NS    |
| Body mass index (kg/m²)  | 28.3 ± 3.3       | 28.5 ± 3.7      | NS    |
| Dyslipidemia (case)      | 6                | 7               | NS    |
| Diabetes mellitus (case) | 8                | 5               | NS    |
| Hypertension (case)      | 13               | 11              | NS    |
| Current smoker (case)    | 8                | 6               | NS    |
| Family history of coronary artery disease (case) | 9 | 9 | NS |
| Previous myocardial infarction (case) | 0 | 0 | NS |
| Previous percutaneous coronary intervention (case) | 0 | 0 | NS |
| Infarct related artery:  |                  |                 |       |
| Left anterior descending (case) | 13 | 11 | NS |
| Left circumflex artery (case) | 7 | 9 | NS |
| Right coronary artery (case) |        |                 |       |
| NYHA                     |                  |                 |       |
| Class I (case)           | 7                | 5               | NS    |
| Class II (case)          | 10               | 13              | NS    |
| Class III (case)         | 3                | 4               | NS    |
| Class IV (case)          | 1                | 0               | NS    |
| LVEF (%)                 | 57.2 ± 10.2      | 53.7 ± 6.4      | 0.18  |
| Pre-PCI TIMI blood flow  |                  |                 |       |
| Class 0 or I             | 19               | 21              | NS    |
| Class II                 | 2                | 1               | NS    |
| Class III                | 0                | 0               | NS    |
| After PCI TIMI blood flow|                  |                 |       |
| Class IV                 | 0                | 1               | NS    |
| Class V                  | 21               | 21              | NS    |
| Class VI                 |                  |                 |       |
### BM-MSCs (n = 21) Control (n = 22) P

|                          | BM-MSCs | Control | P     |
|--------------------------|---------|---------|-------|
| Plasma CK peak (U/L)     | 2516 ± 1007 | 2638 ± 1598 | NS    |
| Plasma CK-MB peak (U/L)  | 97 ± 33  | 105 ± 41 | NS    |
| Plasma cTnI peak (ng/ml) | 10.9 ± 9.7 | 11.1 ± 10.5 | NS    |
| Systolic pressure at admission | 141 ± 23 | 139 ± 21 | NS    |
| Diastolic pressure at admission | 83 ± 16 | 81 ± 14 | NS    |
| Pre-PCI thrombolysis     | 0       | 1       | NS    |
| Pre-PCI GPIIb/IIIa blocker | 15    | 18      | NS    |
| Drugs                    |         |         |       |
| Aspirin                  | 21      | 22      | NS    |
| Clopidogrel              | 17      | 19      | NS    |
| Beta blocker             | 21      | 22      | NS    |
| Nitrate                  | 17      | 17      | NS    |
| ACEI                     | 3       | 5       | NS    |
| ARB                      | 21      | 22      | NS    |
| Statins                  |         |         |       |

### 2.3 Comparison of echocardiographic parameters before and after surgery in two groups

There was no significant difference in LVEF between the two groups at baseline (P = 0.13). After 12 months, the LVEF improved significantly in the BM-MSCs group was significantly improved compared with that before transplantation. The control group also showed the same results as the BM-MSCs group; but there was no significant difference in LVEF improvement in two groups (P = 0.30) (Table 2).
### Table 2
Comparison of cardiac function between BM-MSCs group and control group

| LVEF (%) | Baseline | 12 months later |
|----------|----------|-----------------|
|          | Control ($n = 22$) | BM-MSCs ($n = 21$) | Control ($n = 19$) | BM-MSCs ($n = 18$) |
|          | 53.7 ± 6.4 | 57.2 ± 10.2 | 59.5 ± 5.6* | 62.0 ± 6.8* |

Compared with baseline BM-MSCs group,* $P < 0.05$; Compared with the baseline control group,# $P < 0.05$

### 2.3 Comparison of myocardial metabolic activity between two groups

The myocardial metabolic defect index at baseline of the two groups of patients was similar ($P > 0.05$). There was no significant difference between the two groups before and after treatment ($P > 0.05$). Compared with the control group, the myocardial metabolic defect in the BM-MSCs transplantation group did not improve after 6 months ($P > 0.05$), suggesting that the infarcted myocardium was not effectively replaced or repaired. (Table 3).

### Table 3
Comparison of static myocardial perfusion-metabolic defect index before and after treatment in BM-MSCs transplantation group and control group

| Static myocardial perfusion-metabolic defect index | Baseline | 6 months later |
|--------------------------------------------------|----------|---------------|
| Control ($n = 22$) | BM-MSCs ($n = 21$) | Control ($n = 19$) | BM-MSCs ($n = 18$) |
| 21.0 ± 5.5 | 21.9 ± 6.1 | 18.4 ± 4.8 | 18.6 ± 5.6 |

### 2.4 Follow-up results and safety assessment

During the follow-up period, the types and numbers of arrhythmias detected by Holter were similar in the two groups (Table 4). In the BM-MSCs group, there was no significant difference in blood leukocyte (WBC), creatinine (Cr) and carcinoembryonic antigen before and after transplantation, and alanine transaminase (ALT) and C-reactive protein (CRP) were significantly decreased (Table 5).

There were no adverse reactions such as stent thrombosis, recurrence of myocardial infarction, malignant arrhythmia, tumor and myocardial fibrosis in the two groups of patients during the peri-treatment period. 1 case of sudden death in the BM-MSCs group and one patient occurred microvascular embolism (Table 6).
### Table 4
Comparison of Holter between BM-MSCs group and control group

|                          | Baseline       | 12months later          |
|--------------------------|----------------|-------------------------|
|                          | Control(n = 22) | BM-MSCs (n = 21)        |
|                          | Control(n = 19) | BM-MSCs (n = 18)        |
| Supraventricular         |                |                         |
| premature beat            | 316.9 ± 173.9  | 310.7 ± 155.5           |
|                          | 313.6 ± 168.5  | 315.7 ± 190.3           |
| Supraventricular         | 5.2 ± 3.8      | 5.3 ± 3.4               |
| tachycardia              | 5.1 ± 3.6      | 4.9 ± 3.9               |
| Ventricular premature     | 89.6 ± 66.7    | 101.4 ± 63.8            |
| beat                     | 111.6 ± 53.4   | 99.6 ± 70.9             |
| Non-sustained ventricular | 2.1 ± 0.9      | 2.3 ± 0.5               |
| tachycardia              | 2.0 ± 0.8      | 2.5 ± 0.8               |

### Table 5
Changes of laboratory indexes before and after transplantation in BM-MSCs group (n = 18)

|                  | Baseline       | 12months later          | P     |
|------------------|----------------|-------------------------|-------|
| WBC×10^9         | 8.3 ± 0.8      | 7.9 ± 0.9               | NS    |
| ALT(U/L)         | 49.7 ± 14.5    | 38.3 ± 11.8             | < 0.05|
| Cr(µmol/L)       | 78.8 ± 19.5    | 76.5 ± 21.6             | NS    |
| CRP(mg/L)        | 11.3 ± 5.7     | 5.1 ± 4.9               | < 0.05|
| CEA(ng/ml)       | 2.3 ± 1.7      | 2.2 ± 1.6               | NS    |
### Table 6
Cumulative clinical events during the 12-month follow-up period in both groups

| Event                                | BM-MSCs (n = 18) | Control (n = 19) | P   |
|--------------------------------------|------------------|------------------|-----|
| Death                                | 1                | 0                | NS  |
| Recurrent myocardial infarction      | 0                | 0                | NS  |
| Admitted to hospital due to heart failure | 3   | 4                | NS  |
| Revascularisation:                   | 0                | 0                | NS  |
| Target vessel reconstruction         | 0                | 0                | NS  |
| Non-target revascularization         | 5                | 7                | NS  |
| Stroke                               | 0                | 0                | NS  |
| Malignant arrhythmia/syncope         | 0                | 0                | NS  |
| Tumor                                | 0                | 0                | NS  |
| Myocardial fibrosis                  | 0                | 0                | NS  |
| Microvascular embolization           | 1                | 0                | NS  |
| NYHA at 1 year follow-up             | 1.7 ± 0.6        | 1.7 ± 0.7        | NS  |

### 3. Discussion

In the field of clinical research on stem cells, there are different reports on the types of transplanted cells, and there are also differences in the results of BM-MSCs cell transplantation on the improvement of cardiac function in clinical studies. In this study, autologous bone marrow BM-MSCs (prepared uniformly by the Stem Cell and Regenerative Medicine Center of the Field Transfusion Institute of the Academy of Military Medical Sciences) were selected and transplanted into the heart after infarction by intracoronary injection. The effect and safety of the transplantation were observed. The results showed: Compared with the control group, the 6-month metabolic imaging defect score of the BM-MSCs transplantation patients was not statistically significant, and the 12-month left ventricular ejection fraction did not constitute a statistically significant improvement. The reasons for the above results are as follows:

1. It is related to the insufficient number of the enrolled patients. The number of selected cases was determined on the basis that the difference between the different treatment groups when the primary endpoint is expected to be reached is 4–5%. If the difference between the different treatment groups was 4.5%, the bilateral test was carried out at a significant level of α = 0.05, and the test efficacy reached 80%. To draw a conclusion that the difference was statistically significant, then 34 patients were required in each group[^22]. During the implementation of this study, it was discovered that although the researchers explained in detail to the patients that the extraction of bone marrow had no adverse effects on the body, the patient had an instinctive fear of taking bone marrow, and they...
were very resistant. In this study, therefore, only 43 patients were eventually enrolled in 6 hospitals over the past two years, and the number of cases was seriously insufficient.

2. It is related to insufficient dose of transplanted cells. 80 ml bone marrow is extracted from the patient, extracted, cultured and expanded for 2 weeks to obtain $1 \sim 2 \times 10^6$ BM-MSCs $1 \sim 2 \times 10^6$ BM-MSCs. The number of cells may not reach the therapeutic dose. Perin [23] and colleagues compared the effects of three doses (25, 75 or $150 \times 10^6$ cells) of allogeneic BM-MSCs on adverse cardiac events and left ventricular remodeling. The results showed that the higher the dose of BM-MSCs, the fewer adverse cardiac events, the lesser the degree of left ventricular remodeling. In addition, the TRIDENT trial found that compared with the lower dose of BM-MSCs ($20 \times 10^6$), the higher dose group of BM-MSCs ($100 \times 10^6$) can improve LVEF and maintain the level of serum brain natriuretic peptide [24]. It is worth noting that the above-mentioned experiments showed that the number of cells with significantly improved cardiac function after BM-MSC transplantation was greater than $70 \times 10^6$. However, the number of cells transplanted into the patient in this experiment was $1 \sim 2 \times 10^6$, which was much smaller than $70 \times 10^6$. Therefore, compared with the control group, the experimental group was more likely to have a negative result.

3. The most appropriate time for cell transplantation may have been missed. The studies have shown that the appropriate time for stem cell transplantation should be after the inflammatory response and before scar extension [25]. Su Hyun Kim [26] and colleagues transplanted autologous BM-MSCs at $30 \pm 1.3$ days after PCI and found that compared with the control group, the BM-MSC group can significantly improve the left ventricular ejection fraction of patients. The cell transplantation time in this experiment was 10 to 14 days after PCI, which was not within the operating time range for obtaining positive experimental research results.

4. It may not be the optimal way for BM-MSCs transplantation in our experiments. Fukushima S [27] and others found that the transplantation methods of BM-MSC, such as intramyocardial injection, intracoronary injection or intravenous injection, are not satisfactory. There is still a need to develop new and more effective cell transplantation methods, such as the use of bioengineering technology for epicardial implantation [27–29]. In this study, BM-MSCs were transplanted into coronary arteries, and the number of cell survival was unknown [30], which affected the results of the experimental group.

There was no significant difference between the incidence of the incidence of cardiovascular events, the total mortality, and incidence of adverse events in the BM-MSCs group and the control group. One patient in the BM-MSCs group had a small number of BM-MSCs, the culture time was extended to 19 days, and coronary microembolization occurred during coronary artery transplantation. The analysis may be due to the long culture time of BM-MSCs, which reduces the function and quality of cells, resulting in increased volume and enhanced adhesion, resulting in microthrombosis and microvascular spasm [31, 32]. One case of death occurred in the BM-MSCs group, and whether the cause was related to the heart is unknown.
The results of this study indicate that low-dose BM-MSCs (1 ~ 2 × 10^6) intracoronary transplantation is not inferior to traditional standard treatment after PCI for left ventricular function and myocardial remodeling after myocardial infarction. Under the condition that the BM-MSCs culture time length is appropriate, the incidence of cardiovascular events, total mortality and incidence of adverse events in patients with ST-segment elevation myocardial infarction will not be increased. At the same time, compared with pre-transplantation, BM-MSCs transplantation can improve left ventricular ejection fraction in patients with ST-segment elevation myocardial infarction, indicating that BM-MSCs transplantation is safe and effective.

Based on the existing reports and the results of this experiment, BM-MSCs is still an important donor for AMI cell transplantation therapy. However, if BM-MSCs are to achieve better therapeutic effects in the future, there is still necessary to improve the treatment regimen to enhance the therapeutic effect, such as the use of the optimal cell dose, optimal cell transplantation method, and the improvement of cell culture protocols to expand the BM-MSCs do not lose cell function, which requires further experimental and clinical studies to determine.

4. Conclusions

It is unreasonable to speculate that intracoronary transfer of autologous bone marrow MSCs could augment recovery of LV function and myocardial viability after acute myocardial infarction.

Abbreviations

BM-MSCs
Bone marrow mesenchymal stem cells
STEMI
ST-segment elevation myocardial infarction
NSTEMI
non-ST-segment elevation myocardial infarction
LV
Left-ventricular
SPECT
Single- photon emission tomography
SD
Standard difference
ALT
Alanine transaminase
CRP
C-reactive protein
AMI
Acute myocardial infarction
PCI
Percutaneous coronary intervention
CCVD
Cerebrovascular Diseases Professional Network
LVEF
left ventricular ejection fraction

Declarations

Ethics approval and consent to participate:

Provided in the Supplementary Files section

Consent for publication:

Not applicable.

Availability of data and material:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests:

At the time of this study, the all authors indicated no potential conflicts of interest.

Funding:

Scientific Research Projects of Sichuan Medical Planning Commission: Heart transplantation effect of stem cells–Study on Paracrine Mechanism(100306)

Contributions:

Zhang Runfeng, Zhang Ningkun, Chen Yu, Yang Yong were responsible for the preparation and characterisation of BM-MSCs for transplantation. Zhang Runfeng, Wang Jisheng were responsible for the conception of the study and organisation of the experimental design and coordination. Yu Jiang, Liu Zhenhong, Li Wensong were responsible for the writing of the manuscript. Zhang Runfeng, Zhang Ningkun, Cai Guocai, Chen Yu, Yang were responsible for the critical review of all experimental data and review and revision of the final manuscript. The authors read and approved the final manuscript.
Acknowledgement:

Thanks to the following 6 units of Cardiovascular and Cardiac Interventional Catheters for their support and assistance in this research: The Sixth Medical Center of PLA Genera Hospital, The Third Medical Center of Chinese PLA General Hospital, Chinese PLA General Hospital, The First Hospital of Tsinghua University, Beijing Tongren Hospital, Beijing West Hospital of Chaoyang Hospital.

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Figures
Standard Contrain:
Acute ST-segment elevation myocardial infarction
18-70 years old

The patient was selected within 24 hours:
Signing informed consent
Laboratory inspection
SPECT detection
Ultrasound heart function examination

Follow-up:
Laboratory inspection
SPECT detection

Figure 1
research protocol
46 patients enrolled in the trial

3 cases failed

43 random groups

21 cases of MSCs transplantation group

1 case died 3 days after surgery

19 patients completed 6 months of follow-up

18 cases completed 1 year follow-up

22 cases in the control group

1 case lost

21 patients completed 6 months of follow-up

19 cases completed 1 year follow-up

Figure 2
Test data