Official Journal of TESMA
Regenerative Research
www.regres.tesma.org.my
E-ISSN 2232-0822
Tissue Engineering and Regenerative Medicine Society of Malaysia

Regenerative Research 4(2) 2016 15-24

EFFICACY AND SAFETY OF AUTOLOGOUS BONE MARROW CELL THERAPY IN TREATMENT OF ACUTE MYOCARDIAL INFARCTION

Lazwani Kolandaiveloo[1,2], Marjan Sadat Seghayat[1], Farahnaz Amini[1*]

[1]School of Healthy Aging, Medical Aesthetics and Regenerative Medicine, Faculty of Medicine and Health Science, UCSI University, Kuala Lumpur, Malaysia.
[2]Laurent Bleu Medical Clinic, Laurent Bleu Medical Centre, UCSI University KL Campus, North Wing

ARTICLE INFO

Published online: 8th March, 2016
*Corresponding Author: Assoc. Prof Dr. Farahnaz Amini
Email: farahnaz@ucsiuniversity.edu.my

KEYWORDS

Bone Marrow Cell; Myocardial Infarction; Safety

ABSTRACT

Acute myocardial infarction (aMI) is rising worldwide. The ischemia that occurs to the infarcted heart area leads to poor functional recovery of the left ventricle. The purpose of this study was to evaluate the efficacy and the safety of bone marrow cells (BMC) in treating acute myocardial infarction in both men and women. A structured literature review was done using different keywords. A total of 12 studies with 1027 participants met inclusion/exclusion criteria. There were 5 studies with 668 participants which aspirated the bone marrow cells from control group but either sham or placebo injection was done in this group. One study has not aspirate any bone marrow cells in control group but injected placebo in this group. Patients' characteristics including age, race, gender, diabetic condition, smoking, hypertension, duration of follow up, assessment methods, route of cell delivery, time point of BMC application and method of BMC preparation have varied between selected studies. In overall, out of 12 studies, 10 studies showed there were significant improvement in left ventricular performance as well as quality of life and reduce in mortality of patients after aMI with the use of autologous bone marrow cells (BMC). The outcome were measured using left ventricular ejection fraction, size of infarct, improvement in echocardiography and left ventricular end diastolic internal diameter. There were also some studies showed improvement in regional myocardial function after the administration of bone marrow cells. There were 2 studies that did not show any improvement in left ventricular ejection fraction after administration of BMCs. Different side effects with diverse prevalence were reported in these selected studies, generally, with lower prevalence in BMC group. In conclusion, bone marrow cells are usually safe and can improve the outcome of acute myocardial infarction.

1.0 Introduction

Cardiovascular disease is the leading cause of morbidity and mortality worldwide. Despite the advances in medical, catheter-based therapy and surgery interventions for acute myocardial infarction, the 1 year mortality remains as high as 13% and the 5 years prognosis for patients with heart failure remains as high as 50% (1).

Asian countries have their specific characteristic in regard with cardiovascular disease; there is a blended mortality demographic trend in Asia due to variety of educational level and economic situation in different countries (2). Besides, mortality rate of cardiovascular disease is comparatively higher

in Asian countries than western countries (294 versus 170 death per100 000 population) (3). According to WHO report, age adjusted mortality rate is 150.10 per 100 000 population in Malaysia, and previous studies which had been done in Singapore showed that mortality rate is higher among Malay and Indians compare to Chinese population (4).

Acute myocardial infarction (aMI), resulted from obstruction of coronary arteries, usually develops due to plaque rupture, fissuring and formation of superimposed thrombus (5). Despite all improvements in management of aMI, like fibrinolysis and rapid revascularization, still prognosis is poor due to lack of self-repaired to the damaged myocardium which can lead to complications such as heart failure (6-7).

Cell-based therapy is a promising novel adjuvant management, which has shown a great achievement in cardiac regeneration. Bone marrow is one of the rich sources of cells that play role in regeneration, growth and immune processes. Bone marrow contains different type of cells including mesenchymal, hematopoietic, endothelial progenitors, mononuclear and side population cells (8). Stem cells are undifferentiated and are able to proliferate, migrate and mature into specialized cells that can carry out specific functions (9). Besides bone marrow cells, other cells like progenitor, mononuclear cells are also used for repairing the damaged heart tissue as they can proliferate and differentiate into contractile as well as blood vessel cells (10-11).

From first ever clinical application of bone marrow cell in treating acute myocardial infarction in March 2001 till now, there are mixed data regarding outcome of cell therapy in cardiovascular disease and acute myocardial infarction precisely (12). There are lots of ongoing studies in this area. The present review is aimed to appraised and summarize them in order to assess the safety and efficacy of this therapy for aMI.

2.0 Materials and methods

A literature search was performed in the PubMed, Google Scholar and Cochrane Database of Systematic Reviews (2002 – 2015). Literature search was done based on the free keywords and MESH terms including bone marrow cells, stem cells, mesenchymal cells, progenitor cells, mononuclear cells, acute myocardial infarction, cardiac ischemia, cardiovascular disease, coronary heart disease, ischemic heart disease, and angina. Only English literatures were included based on the PICO framework (Table 1).

Table 1 Summary of PICO

P-Patients	Patient who has had recent acute myocardial infarction
I- Intervention	Use of patients' own bone marrow cells.
C-Comparison	Patients with acute myocardial infarction who did not receive bone marrow cells.
O-Outcome	Improvement in myocardial function in acute myocardial infarction
Studies	Randomized control trials, Case studies, Retrospective studies

3.0 Results

A total of 12 articles with 1027 patients were chosen based on their relevant to the research objective. Out of these articles, 11 were randomized control studies and 1 was a case control study. All of these studies were done on patients who had acute myocardial infarction from different European countries and China. Intracoronary transplantation or injections were given using autologous bone marrow cells that include stem cells, mononuclear cells and progenitor cells. The efficacy of autologous bone marrow cells on the infarcted heart were assessed by degree of improvement in left ventricular ejection fraction, left ventricular end diastolic diameter and peak systolic velocities using various means like echocardiography, 24 hour Holter, Doppler tissue, electrocardiogram and single photon emission computed tomography (SPECT). Table 2 shows data analysis and results of the selected articles.

Details of outcome, side effects, intervention including route of deliver, amount of bone marrow aspiration, cell type, cell preparation method, injected cells number, and point time intervention are summarized in table 3 and 4. There were 5 studies with 668 participants which aspirated the bone marrow cells from control group but either sham or placebo injection was done in this group. One study has not aspirated any bone marrow cells in control group but injected placebo in this group.

4.0 Discussion

Cell based therapy for tissue regeneration is a promising strategy to repair damaged tissues especially for organs with slow self-regeneration such as heart. This review provides cumulative evidence from several clinical trials regarding therapeutic strategies using autologous bone marrow cells (BMC) for patients with myocardial infarction. Despite of

Table 2 Characteristics of selected articles

Author	Title	Journal/ Year	Study Design	Sample size	Patients characteristics
Jerome et al. (13)	Intracoronary autologous mononucleated bone marrow cell infusion for acute myocardial infarction: results of the randomized multicenter BONAMI trial	European Heart Journal /2011	Randomized control clinical trial	101	ST-segment elevation myocardial infarction (STEMI).
Jaroslav et al. (14)	Autologous transplantation of mononuclear bone marrow cells in patients with acute myocardial infarction: The effect of the dose of transplanted cells on myocardial function	American Heart Journal/ 2006	Randomized control clinical trial	66	Patients with a first acute ST-elevation MI treated by coronary angioplasty with stent implantation.
Kai et al. (15)	Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial	Lancet /2004	Randomized control clinical trial	60	Patients within 5 days of the onset of symptoms of a first ST-segment elevation myocardial infarction, had undergone successful PCI with stent implantation in the infarct- related artery, and had hypokinesia or akinesia involving more than two thirds of the left-ventricular
Bodo et al. (16)	Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans	Circulation/ 2002	Case control study	20	Patients had suffered transmural infarction
Shao-Liang et al. (17)	Effect on Left Ventricular Function of Intracoronary Transplantation of Autologous Bone Marrow Mesenchymal Stem Cell in Patients With Acute Myocardial Infarction	American Journal of Cardiology /2004	Randomized control clinical trial	69	Patients with AMI and angiography or angioplasty within 12 hours of onset of chest pain
Volker et al. (19)	Intracoronary Bone Marrow Derived Progenitor Cells in Acute Myocardial Infarction	New England Journal /2006	Double-blind, placebo-controlled, randomized multicenter trial	204	Patients with acute ST-elevation myocardial infarction and had been successfully reperfused by means of stent implantation

Ge et al. (20)	Efficacy of emergent transcatheter transplantation of stem cells for treatment of acute myocardial infarction (TCT-STAMI)	Heart /2006	Double blind Randomized control clinical trial	20	patients who were admitted within 24 h after the onset of symptoms of a first ST segment elevation myocardial infarction and had successfully undergone PCI with stent implantation in the infarct-related artery
Muhammad et al. (21)	The BALANCE Study Clinical Benefit and Long-Term Outcome After Intracoronary Autologous Bone Marrow Cell Transplantation in Patients With Acute Myocardial Infarction	Journal of the American College of Cardiology /2009	Case control study	62	Patients with urgent angiography post AMI
Ketil et al. (22)	Intracoronary Injection of Mononuclear Bone Marrow Cells in Acute Myocardial Infarction	New England Journal/2006	Randomized control clinical trial	50	The presence of ST-elevation myocardial infarction of the anterior wall and treatment with PCI 2 to 12 hours after the onset of symptoms, successful PCI with stent implantation performed on the culprit lesion in the left anterior
Huang et al. (23)	Timing for intracoronary administration of bone marrow mononuclear cells after acute ST-elevation myocardial infarction: a pilot study	Stem Cell Research & Therapy/2015	Randomized control clinical trial	104	A history of first acute ST-elevation myocardial infarction and treatment with PCI 2 to 12 hours after symptom onset; successful PCI with stent implantation in the culprit lesion of the infarct-related artery
Assmus et al. (24)	Long-term clinical outcome after intracoronary application of bone marrow-derived mononuclear cells for acute myocardial infarction: migratory capacity of administered cells determines event-free survival	European Heart Journal/2014	Double-blind, placebo-controlled, randomized trial, performed in 17 centres	204	Patients who had an acute ST elevation myocardial infarction successfully reperfused with stent implantation with a residual significant LV regional wall motion abnormality.

inconsistencies between these studies in terms of types of BMCs being used, route of administration and number or cells, outcome of majority of these studies established safety and efficacy of therapy. Apparently, time between aMI and administration of BMCs and method of delivery are not critical factors that can influence efficacy of autologous bone marrow cells since there was wide range of time point between aMI and cell therapy in these studies. Variety of the clinical parameters such as contraction velocities, myocardial viability and left ventricular end diastolic internal diameter had been evaluated, however measuring LVEF was the standard parameter for assessment of out come in all studies.

In addition, demographic and medical history of participants such as age, BMI, alcohol consumption, smoking, history of CHD, income and educational level might be an important factor on efficacy as well as safety of this therapy. Among selected articles, 2 articles have 204 participants each. "Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (PREMIER-AMI) trial" which had been well designed, had reported promising result. Also, multi centres study by Assmus *et al*. (24) with long term follow up reported that all individual major adverse clinical endpoints tended to occur less frequently in the BMC group.

Table 3 Details of outcome and side effect of BMC therapy in patients of selected studies

Author	Outcome	Side effect
Jerome et al. (13)	Myocardial viability improved in 34% patients in the intervention group compared with 16% in the control group (P = 0.06). Intracoronary autologous BMC administration to patients with decreased LVEF after AMI was associated with improvement of myocardial viability in multivariate but not in univariate analysis	- One patient in the intervention group died from sudden death 1 month after STEMI. - An implantable cardioverter defibrillator was inserted for primary prevention within the 3-month follow-up in one patient in the control group and four in the BMC group
Jaroslav et al. (14)	Mononuclear bone marrow cell transplantation improves regional myocardial function of the infarcted wall in a dose-dependent manner	- Cell implantation did not cause any damage to the heart muscle, and no patient with uncomplicated cell implantation exhibited any increase in cardiac enzyme Levels. - There were 3 cell therapy–related complications. One patient developed an intimal dissection during repeat balloon inflations at the time of the cell implantation
Kai et al. (15)	Intracoronary transfer of autologous bone-marrow-cells promotes improvement of left-ventricular systolic function in patients after acute myocardial infarction.	- No patient died or was lost to follow-up. There were no additional ischaemic damage to the myocardium due to intervention. - In 6 months of follow-up, three controls and one patient from the BMC group needed at least one hospital admission for worsening heart failure. One person from the BMC group developed a non ST-segment elevation MI in the left circumflex territory 4 months after transfer of BMC into the left anterior descending coronary artery.
Bodo et al. (16)	The results demonstrate that transplanted autologous BMCs may lead to repair of infarcted tissue when applied during the immediate postinfarction period.	- No side effects were observed at any point of time.
Shao-Liang et al. (17)	Result showed that bone marrow mesenchymal stem cells significantly improved left ventricular function. Perfusion defects detected by positron emission tomography decreased significantly in the BMSC group after 3 months compared with those in the control group. Left ventricular end-diastolic volume and end-systolic volume decreased significantly. Serial cardiac echocardiographic monitoring demonstrated improvement of cardiac function 1 to 3 months after implantation of BMSCs, and improvement maintained nearly 6 months after the procedure.	- Not specified
Stefan et al. (18)	Intracoronary transfer of autologous bone marrow cells within 24 h of optimum reperfusion therapy does not augment recovery of global LV function after myocardial infarction, but could favourably affect infarct remodeling	- One control patient developed an acute in-stent thrombosis after 2 months and was successfully treated with a drug-eluting stent. One control and two BMSC patients developed recurrent angina, requiring dilatation of an in-stent stenosis. - During follow-up, one control patient was diagnosed with lung adenocarcinoma and one BMSC patient with squamous larynx carcinoma. Both were heavy smokers.

Volker S et al. (19)	Intracoronary administration of BMC is associated with improved recovery of left ventricular contractile function in patients with acute myocardial infarction	- In one-year follow up, death, was observed in 6 of control and 2 of BMC group. Myocardial infarction and re-hospitalization for heart failure was only observed in control group.
Ge et al. (20)	Emergent intracoronary transplantation of bone marrow mononuclear cells after AMI is practicable, and it improved cardiac function, prevented myocardial remodeling and increased myocardial perfusion at six months' follow up.	- No patients had a bleeding complication at the bone marrow puncture site. No angina aggravation, malignant diseases and substantial arrhythmias were found after PCI and intracoronary BMT or bone marrow supernatant transfer either in hospital or during follow up. All study patients are alive now.
Muhammad et al. (21)	BMC therapy leads to significant and longstanding improvements of LV performance as well as quality of life and mortality of patients after AMI. After BMC therapy, no side effects were observed, showing that BMC therapy is safe.	- Average mortality rates of 0.35% per year in the BMC group and of 2.35% per year in the control group
Ketil et al. (22)	No effects of intracoronary injection of autologous mononuclear BMC on global left ventricular function	- Contamination of the cell suspension with coagulase-negative staphylococci was discovered after treatment in one patient - 2 patients in BMC group had stent thrombosis in the acute phase, one has confirmed re-infarction - One patient in each group was re-hospitalized with progressive heart failure.
Huang et al. (23)	In AMI patients, intracoronary BMC infusion within 24 hours after the primary PCI is as effective as BMC infusion 3 to 7 days after primary PCI with respect to left ventricular contractile function recovery and remodeling.	- Angina pectoris attack was observed in 3 of control and 5 cases of BMC group - In 12 months follow up, combined events (death, recurrence of myocardial infarction and re-hospitalization for heart failure) was observed in 5 of control and 6 of BMC group
Assmus et al. (24)	Although the study was not powered to definitively show an effect of BMC administration on clinical outcome, the present 5-year clinical follow-up analysis demonstrated that all individual major adverse clinical endpoints tended to occur less frequently in the BMC group, with some of the combined endpoints even approaching statistical significance. An association between the migratory capacity of the administered BMC, and long-term clinical outcome was found.	- Individual predictors of adverse cardiovascular outcome and the potential interaction with BMC administration, combined cardiac and cardiovascular death, death of unknown origin and re-hospitalization for heart failure, was identified. A total of 28 patients suffered from these events, 18 in the placebo group and 10 in the BMC group.

Table 4 Details of intervention in study and control group

Author	*Intervention (BMT group)*	*Intervention (Control)*
Jerome et al. (13)	Route of deliver: Intracoronary administration Amount of bone marrow aspiration: 50ml Cell type: autologous bone marrow cells Cell preparation: Flow cytometry: Yes Injected Cell number: 98.3 ± 8.7 × 106 Point time intervention: 9.3 ± 1.7 days after AMI	Neither bone marrow aspiration nor sham injection was performed in the control group
Jaroslav et al. (14)	Route of deliver: Intracoronary administration Amount of bone marrow aspiration: Cell type: autologous mononuclear bone marrow cells (CD45, CD3, CD16, CD19, CD33, and CD34) Cell preparation: After an overnight cultivation in serum-free medium Flow cytometry: Yes Injected Cell number: 1x 10^7 to 1 x 10^8 cells Point time intervention: 5-9 days after AMI	Neither bone marrow aspiration nor sham injection was performed in the control group
Kai et al. (15)	Route of deliver: Intracoronary administration Amount of bone marrow aspiration: Not mentioned Cell type: autologous bone-marrow cell (CD34+ cells) Cell preparation: 6–8 h after bone-marrow harvest, the final preparation of bone-marrow cells was Flow cytometry: Yes Injected Cell number: final suspension of 10 000 U/L Point time intervention: 1-5 days after AMI	Received optimum post-infarction medical treatment
Bodo et al. (16)	Route of deliver: Intracoronary administration Amount of bone marrow aspiration: 40ml Cell type: Cell preparation: 1x10^6 BMCs/mL were cultured and harvested next day Flow cytometry: Injected Cell number: to 3 mL cell suspension, each of which contained 1.5 to 4x10^6 mononuclear cells. 2.8x10^7; this consisted of 0.65±0.4% AC133-positive cells and 2.1±0.28% CD34-positive cells. Point time intervention: 7±2	Received standard therapy alone
Shao-Liang et al. (17)	Route of deliver: Intracoronary administration Amount of bone marrow aspiration: 60ml Cell type: autologous bone marrow Cell preparation: Cultured for 10 days Flow cytometry: No Injected Cell number: 6ml of the cultured BMSC suspension containing 8 to 10 x10^9 cells/ml was injected directly into the target coronary artery Point time intervention: 18± 0.5	60 ml of bone marrow was aspirated but 6 ml of standard saline rather than BMSC was injected through the coronary artery in the control group by using the same method described for the BMSC group.
Stefan et al. (18)	Route of deliver: Intracoronary administration Amount of bone marrow aspiration: 130 ml Cell type: $CD34^+$, $CD133^+$, $CD90^+$, $CD105^+$, $CD117^+$/c-kit, $CD73^+$ cells. Cell preparation: Centrifugation to reduce the volume to 10ml Flow cytometry: Yes Injected Cell number: 10 mL contained 304 x 106 (SD 128 x106) nucleated cells and 172 x 106 mononuclear cells Point time intervention: 24 hours after AMI	130 ml of bone marrow was aspirated but Placebo solution consisted of 0·9% sodium chloride, containing 5% autologous serum was injected. Optimum medical treatment and infusion of placebo.

Volker S et al. (19)	Route of deliver: Intracoronary administration Amount of bone marrow aspiration: 50ml Cell type: Bone marrow cells $CD34^+$, $CD133^+$, $CD45^+$ Cell preparation: BMCs were isolated with the use of Ficoll–Hypaque centrifugation and suspended in 10 ml of X VIVO 10 medium including 2 ml of the patient's own serum. Flow cytometry: No Injected Cell number: 236±174 $x10^6$ Point time intervention: 3-6 days after AMI	50 ml of bone marrow was aspirated but Placebo solution consisted of the 10 ml of X VIVO 10 medium, including 2 ml of the patient's own serum (without BMC) was injected
Ge et al. (20)	Route of deliver: Intracoronary administration Amount of bone marrow aspiration: 40ml Cell type: BM-MNCs with 4.7% positive for CD34 and 0.79% positive for CD133 Cell preparation: BM-MNCs were prepared by Ficoll-Hypaque gradient centrifugation. Flow cytometry: Yes Injected Cell number: 15 ml cell suspension containing about 4 x 10^7 Point time intervention: less than 24 hours of AMI	An equal volume of bone marrow supernatant mixed with heparinised saline was used
Muhammad et al. (21)	Route of deliver: Intracoronary administration Amount of bone marrow aspiration: 80 to 120 ml Cell type: $CD34^+$, CD133+, and $CD34^+$ cells Cell preparation: Cells were isolated by Ficoll density separation and washed 3 times with heparinized saline, before the residual erythrocytes were lysed with water. Flow cytometry: Yes Injected Cell number: 6.1 ± 3.9 x 10^7 cells Point time intervention: 7 ± 2 days	Neither bone marrow aspiration nor sham injection was performed in the control group. All the other procedures identical to the BMC group
Ketil et al. (22)	Route of deliver: Intracoronary administration Amount of bone marrow aspiration: 50ml Cell type: Heterogeneous mononuclear cells with $CD34^+$ cells was 0.7×10^6 Cell preparation: BM-MNCs on a Ficoll density gradient and washed and resuspended in heparin-treated plasma. Flow cytometry: No Injected Cell number: 68×10^6 Point time intervention: 4 to 8 days after AMI	No aspiration or sham injection was performed in the control group.
Huang et al. (23)	Route of deliver: Intracoronary administration Amount of bone marrow aspiration: (95 ± 16 ml) Cell type: CD34+ and CD133+ cells Cell preparation: BM-MNCs on a Ficoll density gradient and 3 washing steps were performed and cells were resuspended in heparinized saline Flow cytometry: Yes Injected Cell number: $(4.9 \pm 2.8) \times 10^8$ Point time intervention: 24 hours to 30 days after AMI	Saline infusion immediately after emergency PCI
Assmus et al. (24)	Route of deliver: Intracoronary administration Amount of bone marrow aspiration: Not mentioned Cell type: CD34+/CD45+, CD133+/CD45+, and CD45+/KDR+ cells Cell preparation: BM-MNCs on a Ficoll density gradient Flow cytometry: Yes Injected Cell number: Not clearly specified Point time intervention: 3-7days after AMI	Bone marrow was aspirated but Placebo (not specified) was injected

While most of the studies in this review support the improvement of LVEF and myocardial infarcted size with the use of autologous bone marrow cells; there were 2 papers, which did not support the evidence. Ketil *et al*. (22) noted that there was no improvement in global left ventricular function while Steffan *et al*. (18) mentioned that intracoronary transfer of autologous BMCs within 24 hours of reperfusion therapy does not augment recovery of global LV function after aMI. However, there was reduction in myocardial infarct size that postulates that BMCs could favorably affect the infarct remodeling. Although, these negative outcomes can be due to few loopholes in these studies. Possible acute side effects like

bleeding, intimal dissection, infection, death, aggravation of angina and substantial dysrhythmias and arrhythmias; and long lasting complication such as stent restenosis and malignancies evaluated in these studies, and majority of them showed minimum side effects or complications with the use of autologous BMC.

Short term follow-up of patients in some studies and discrepancies in various types of methods used to assess the improvement of myocardial functions are also part of limitations of the selected studies.

5.0 Conclusion

Though there were mixed outcomes of using autologous BMCs in aMI patients in these studies, majority of the papers do support the use of BMCs in improving aMI outcomes and has proven that it is also safe to use them. Negative outcome in the studies that could not support using autologous BMCs in aMI patients might be due to their design and lack of power owed to small sample size.

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