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Intracoronary infusion of autologous bone marrow cells and left ventricular function after acute myocardial infarction: a meta-analysis

M. Hristov [a], Nicole Heussen [b], A. Schober [c], C. Weber [a] *

[a] Institute for Molecular Cardiovascular Research (IMCAR) and Interdisciplinary Center for Clinical Research "BIOMAT", RWTH University Hospital Aachen, Aachen, Germany
[b] Institute for Medical Statistics, RWTH University Hospital Aachen, Aachen, Germany
[c] Department of Cardiology, Ludwig-Maximilians-University München, Germany

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Abstract

Recent clinical studies have demonstrated that intracoronary infusion of autologous bone marrow cells (BMC) in conjunction with standard treatment may improve left ventricular function after an acute myocardial infarction (AMI). However, the results of these studies remain controversial, as the studies were relatively small in size and partially differed in design. We reviewed primary controlled randomized clinical studies comparing intracoronary transfer of autologous non-mobilized BMC combined with standard therapy versus standard therapy alone in patients with AMI. We identified five randomized controlled clinical trials, three of which were also placebo- and bone marrow aspiration-controlled. Non-mobilized BMC were infused into the revascularized coronary target artery 6.6 ± 6.1 days after AMI. The mean follow-up period of 5.2 ± 1.1 months was completed by 482 patients, 241 of which received infusion of BMC. The effect of BMC on left ventricular ejection fraction (LVEF) as a major functional parameter was evaluated. Analyzing the overall effect on the change in LVEF between baseline and follow-up value revealed a significant improvement in the BMC-treated group as compared to the control group (P = 0.04). Thus, considering the increase in LVEF during follow-up, transplantation of BMC may be a safe and beneficial procedure to support treatment of AMI. However, the functional improvement observed with this form of therapy was altogether relatively moderate and the studies were heterogeneous in design. Hence, further efforts aiming at large-scale, double-blind, randomized and placebo-controlled multi-center trials in conjunction with better definition of patients, which benefit from BMC infusion, appear to be warranted.

Keywords: myocardial infarction • revascularization • bone marrow • follow-up studies • meta-analysis

Introduction

Acute myocardial infarction (AMI) is a major cause of cardiovascular mortality worldwide. Impaired myocardial contractility during AMI serves as a main predictor for ventricular dysfunction with subsequent development of chronic heart failure. Therefore, the timely and accurate re-canalization of acute coronary occlusion is of particular importance for improving survival, but also quality of life. Beyond the well documented and widely acknowledged advances in coronary revascularization including application of drug-eluting stents and

* Correspondence to: Prof. Christian WEBER
Institute for Molecular Cardiovascular Research, University Hospital Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany
Tel.: +49 241 80 88692
Fax: +49 241 80 82716
E-mail: cweber@ukaachen.de

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Table 1 Randomized controlled clinical trials employing intracoronary infusion of non-mobilized autologous BMC after AMI

Study (and design)	Control group	BMC-treated	Number of cells infused	Infusion time (days after AMI)	Follow-up (months)	Main endpoints
Chen *et al.* Am J Cardiol, 2004	n=35 (placebo)	n=34	$54.0 \times 10^9 \pm 8.5 \times 10^9$	18.0 ± 0.0	6	LVEF ↑, LVWM ↑ LVESV ↓, perfusion ↑
BOOST Lancet, 2004 (blinded)	n=30	n=30	$24.6 \times 10^8 \pm 9.4 \times 10^8$	4.8 ± 1.3	6	LVEF ↑, LVWM ↑
Janssens *et al.* Lancet, 2006 (double-blinded)	n=34 (placebo)	n=32	$30.4 \times 10^7 \pm 12.8 \times 10^7$	1.0 ± 0.0	4	LVEF‡, perfusion‡ infarct size ↓
ASTAMI	n=50	n=50	$87.1 \times 10^6 \pm 47.7 \times 10^6$	6.0 ± 1.6	6	LVEF‡, LVESV‡ infarct size‡
REPAIR-AMI (double-blinded)	n=92 (placebo)	n=95	$23.6 \times 10^7 \pm 17.4 \times 10^7$	4.0 ± 1.0	4	LVEF ↑, LVESV ↓

LVEF, left ventricular ejection fraction; LVWM, left ventricular wall motion; LVESV, left ventricular end-systolic volume. Data on cell number and time of infusion are mean ± SD. ‡ indicates no changed

treatment with anti-platelet aggregation and statins, recent evidence suggests that transplantation of autologous bone marrow cells (BMC) may further improve therapeutic outcomes after AMI [1–4]. Adult bone marrow contains stem/progenitor cells, which can differentiate into distinct mature cell types, including hematopoietic cells but also cells of the vascular wall [1–6]. Notably however, an intravenous infusion of BMC after AMI in an animal model improved cardiac function by preventing cardiomyocyte apoptosis and reducing ventricular remodeling [7]. While recent evidence indicates that a true (trans)-differentiation of BMC into cardiomyocytes as well as their incorporation into the myocardial vasculature *in vivo* occurs at best rarely [8, 9] and thus remains controversial, these positive effects could be rather explained by secretion of cytokines and growth factors in terms of paracrine mechanisms of action [10, 11]. Accordingly, the paradigm has been introduced that purified and enriched BMC, particularly when delivered in the proximity of ischemic myocardial areas, may assist in the improvement of myocardial perfusion and contractility after an AMI. This intriguing approach of transplanting BMC into the target coronary artery has been pursued by several controlled clinical trials [12–18] over the past four years. While initial studies were primarily feasibility and safety phase I studies [12, 13], the prime underlying rationale has been to examine whether BMC therapy may recover left ventricular (LV) function, thus reducing the extent of persistent heart failure. However, these studies were small in size and partially inconsistent in design. Furthermore, recent results from randomized (placebo)-controlled studies in larger patient collectives challenge the major benefit proposed for BMC infusion [16, 17]. Therefore, we were prompted to perform a meta-analysis of published controlled randomized clinical trials employing intracoronary infusion of autologous, non-mobilized BMC for repair of damaged myocardium after AMI to assess the overall efficacy of this treatment option.

Materials and methods

Inclusion criteria

For inclusion in the meta-analysis, reports had to be of primary randomized and controlled studies published in peer-review journals or reported as abstracts at scientif-

ic meetings. They had to describe direct comparison between intracoronary infusion of autologous, non-mobilized BMC and standard medical treatment (with or without intracoronary infusion of placebo saline) in patients with AMI.

Search strategy

Medical Subject Heading terms for the Internet search included: *clinical trial*, *controlled, randomized, myocardial infarction, bone marrow, autologous, transplantation,* and *repair*. Five controlled, randomized and prospectively performed clinical studies on intracoronary infusion of BMC after AMI were identified and included in the systematic review. Altogether, these studies included 482 analyzable patients with AMI, 241 of which received intracoronary infusion of autologous BMC in addition to standard treatment. The studies were performed in Germany, Belgium, Norway and China, and the results were published between 2004 and 2006 as original contributions or were reported for the first time at the American Heart Association Scientific Sessions (Dallas, November, 2005). Clinical trials were summarized in Table 1.

Extraction of results

After identification of the eligible studies, the data were made available and two independent investigators extracted values of interest. The main analysis was restricted to the values of the LV ejection fraction (LVEF) at baseline and during follow-up.

Analysis

Analyses based on follow-up measurements of LVEF and on change in LVEF between baseline and follow-up values, respectively. Mean and standard deviation (SD) was reported for each study. Mean and SD of the change are unavailable from the reports by Chen *et al.*, Janssens *et al.*, ASTAMI and REPAIR-AMI [14, 16, 17, 18]. The mean change in each group can be obtained by subtracting the follow-up mean from the baseline mean. However, the information of baseline and follow-up measurement does not allow calculating the SD of the changes. The SD of the change from baseline, when baseline and follow-up SD are known, was estimated using

$$SD_{BMC,change} = \sqrt{SD^2_{BMC,baseline} + SD^2_{BMC,follow-up} - (2 \cdot R_{BMC} \cdot SD_{BMC,baseline} \cdot SD_{BMC,follow-up})}$$

for the BMC group and similarly for the control group.

The value R for the correlation coefficient is imputed from the BOOST study [15] using

$$R_{BMC} = \frac{SD^2_{BMC,baseline} + SD^2_{BMC,follow-up} - SD^2_{BMC,change}}{2 \cdot SD_{BMC,baseline} \cdot SD_{BMC,follow-up}}$$

for the BMC group and similarly for the control group.

A random effect model was chosen to combine results due to heterogeneity between study specific results [19]. Analysis was performed with Review Manager 4.2.3 (©2003 The Cochrane Collaboration).

Results

Five clinical studies [14–18] eligible for meta-analysis were identified by an Internet search. Study design was restricted only to randomized controlled clinical trials employing non-mobilized BMC. Table 1 shows the distribution of these studies according to study design, transplantation procedure and main endpoints at follow-up. These studies included 482 patients at follow-up and were performed in University Hospitals and established referral clinics. The results were published or reported between 2004 and 2006. Bone marrow was aspirated from the iliac crest under local or general anesthesia yielding a mean volume of 72 ± 39 ml. Nucleated, non-mobilized BMC were separated and purified according to current recommendations for good manufacturing practice. In two of the studies BMC were cultured overnight or for 10 days [14, 15]. BMC were primarily infused into the revascularized target coronary artery using over-the-wire balloon catheter technique in 248 patients 6.6 ± 6.1 days after AMI. Cell viability prior to infusion was more than 90%. The mean follow-up period of 5.2 ± 1.1 months was completed by 241 patients in the control group and by 241 patients in the BMC group. Trials employing peripheral blood progenitor cells mobilized by granulocyte colony-stimulating factor for infusion were not included, due to problems related to study design and patient selection, *i.e.* one study was stopped because of increased restenosis rates [20] and one study did not see spontaneous improvement of LVEF in the control group [21].

Among the five randomized controlled trials included in our meta-analysis, three studies [15, 16, 18] were additionally (double)-blinded in design.

Table 2 Change in global LVEF during follow-up across the clinical studies included

Study	Patient group	Sample size	Baseline mean ± SD	Follow-up mean ± SD	Change mean ± estimated SD	*R*
Chen *et al.*	Control	35	48.0 ± 10.0%	54.0 ± 5.0%	6.0 ± 7.0%	
	BMC	34	49.0 ± 9.0%	67.0 ± 3.7%	18.0 ± 6.6%	
BOOST	Control	30	51.3 ± 9.3%	52.0 ± 12.4%	0.7 ± 8.1%	0.757
	BMC	30	50.0 ± 10.0%	56.7 ± 12.5%	6.7 ± 6.5%	0.856
Janssens *et al.*	Control	34	46.9 ± 8.2%	49.1 ± 10.7%	2.2 ± 7.0%	
	BMC	32	48.5 ± 7.2%	51.8 ± 8.8%	3.3 ± 4.6%	
ASTAMI	Control	50	47.7 ± 5.5%	52.1 ± 5.2%	4.4 ± 3.7%	
	BMC	50	47.3 ± 6.9%	51.4 ± 4.1%	4.1 ± 4.0%	
REPAIR-AMI	Control	92	47.0 ± 10.6%	50.0 ± 14.4%	3.0 ± 9.4%	
	BMC	95	48.0 ± 8.8%	54.0 ± 10.7%	6.0 ± 5.5%	

Only in three of the trials [14, 16, 18], the control group (n = 161) received placebo medium infused in a similar manner as the BMC-suspension. It has been claimed that this control medium was indistinguishable from the BMC suspension in order to preserve a placebo effect at least in some of the studies. It is of note that the same three trials [14, 16, 18] were the first studies to also perform aspiration of bone marrow in the control group. In addition, the recent REPAIR-AMI trial was conceived as a multi-centre study [18]. Thus, although all of the studies were controlled and randomized, they show differences in design.

Our meta-analysis unveiled robust evidence for a significant heterogeneity between the studies, in particularly with regards to the change in LVEF from baseline to follow-up ($P < 0.00001$, Table 3). As a major parameter characterizing myocardial function, the effects of BMC on LVEF were thus evaluated using the random effect model (Tables 2 and 3). Analyzing the overall effect on the change in LVEF between baseline and follow-up value revealed a significant improvement in the BMC-treated group as compared to the control group ($P = 0.04$, Table 3). In contrast, comparing the overall effect on follow-up LVEF did not reveal a significant difference between both groups ($P = 0.16$, Table 3).

Discussion

The results of the current systematic review revealed that transplantation of BMC after AMI represents a moderately effective treatment option when analyzing the change in LVEF between baseline and follow-up. However, comparing the follow-up values of LVEF *per se* between control and BMC-treated groups did not reveal statistically significant differences.

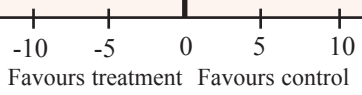
Published controlled clinical trials about infusion of non-mobilized BMC as a supportive treatment for AMI appear to be safe and feasible. This is largely based on the notion, that no apparent side effects or complications (*e.g.* arrhythmia, increased ischemia with subsequent micro-infarcts) have been reported. However, the studies remain controversial with respect to their effectiveness to improve heart function. While in two of the studies (Table 1) the BMC infusion did not improve myocardial function [16, 17], the majority of trials found better myocardial perfusion, increased LVEF and improved regional LV wall motion and systolic function [14, 15, 18]. Nevertheless, the beneficial effects of BMC infusion remain relatively modest in magnitude. In addition, recent data indicate that the BOOST trial did not provide long-term benefit of BMC infusion on LV systolic function after AMI compared with a randomized control group, but the study suggests an acceleration of LVEF recovery after BMC therapy at 18 months follow-up [15, 22]. These discrepancies may be explained by the variable range in the quantity of cells infused, but may also be attributable to differences in the time point of infusion (1 to 18 days after AMI) or the duration of the follow-up (3 to 6 months after AMI). Furthermore, a general limitation of these trials

Table 3 Estimation of the overall-effect of intracoronary BMC transplantation on LVEF after AMI

Review: BMC transfer after myocardial infarction
Comparison: 04 BMC *vs.* Control (change)
Outcome: 01 change in EF%

Study or sub-category	N	BMC Mean (SD)	N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
BOOST	30	6.70 (6.50)	30	0.70 (8.10)		18.58	6.00 [2.28, 9.72]
Janssens *et al.*	32	3.30 (4.60)	34	2.20 (7.00)		19.90	1.10 [-1.74, 3.94]
ASTAMI	50	4.10 (4.00)	50	4.40 (3.70)		21.44	-0.30 [-1.81, 1.21]
REPAIR-AMI	95	6.00 (5.50)	92	3.00 (9.40)		20.71	3.00 [0.78, 5.22]
Chen *et al.*	34	18.00 (6.60)	35	6.00 (7.00)		19.37	12.00 [8.79, 15.21]
Total (95% CI)	241		241			100.00	4.21 [0.21, 8.22]

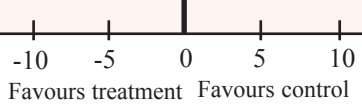
Test for heterogeneity: $Chi^2 = 51.34$, df = 4 ($P < 0.00001$), $I^2 = 92.2\%$
Test for overall effect: $Z = 2.06$ ($P = 0.04$)



Review: BMC transfer after myocardial infarction
Comparison: 04 BMC *vs.* Control
Outcome: 02 EF% at follow up

Study or sub-category	N	BMC Mean (SD)	N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
BOOST	30	56.70 (12.50)	30	52.00 (12.40)		18.08	4.70 [-1.60, 11.00]
Janssens *et al.*	32	51.80 (8.80)	34	49.10 (10.70)		19.44	2.70 [-2.02, 7.42]
ASTAMI	50	51.40 (4.10)	50	52.10 (5.20)		21.15	-0.70 [-2.54, 1.14]
REPAIR-AMI	95	54.00 (10.70)	92	50.00 (14.40)		20.21	4.00 [0.35, 7.65]
Chen *et al.*	34	67.00 (3.00)	35	54.00 (5.00)		21.11	13.00 [11.06, 14.94]
Total (95% CI)	241		241			100.00	4.78 [-1.94, 11.50]

Test for heterogeneity: $Chi^2 = 103.30$, df = 4 ($P < 0.00001$), $I^2 = 96.1\%$
Test for overall effect: $Z = 1.39$ ($P = 0.16$)



Total (95% CI): results over all studies. Test for heterogeneity: Chi² statistic with its degrees of freedom (df) and P-value; the statistic I^2 measuring the extent of inconsistency among results. Test for overall effect: Z statistic with P-value.

The graph is a forest plot where the confidence interval (CI) for each study is represented by a horizontal line and the point estimate is represented by a square. The size of the square corresponds to the weight of the study in the meta-analysis. The confidence intervals for totals are represented by a diamond shape. The individual study point estimate weighted mean difference (WMD) in a random effect model (using the DerSimonian and Laird method) - and confidence interval. The weight (%) represents the contribution of the studies to the overall result.

concerns the autologous nature of transplanted BMC, since recent clinical studies indicate that the number and/or quality of endothelial progenitor cells could be negatively affected during chronic coronary artery disease (CAD) [23, 24]. Although BMC are resistant to senescence and in general show rapid self-renewal and proliferation, impairment in their functional capacity during CAD could not be excluded. One possibility for functional recovery of BMC represents their short-term *ex vivo* cultivation prior infusion [14, 15]. Conversely, the inclusion of low-risk patients with initially well-preserved LV function may attenuate the extent of the effects observed [16, 25]. While Janssens *et al.* clearly found no effect by infusing BMC one day after optimal revascularization [16], more recent data indicated that patients with more severely impaired LV function or even delayed BMC infusion (> 4 days after AMI) showed a more pronounced benefit after cell therapy [18]. Finally, the methods for analyzing LV function differ considerably in quality and reproducibility, *e.g.* SPECT and MRI analysis in ASTAMI [17] *vs.* LV angiogram in REPAIR-AMI [18].

Although all studies included were controlled and randomized, their design was not entirely consistent. For example, some of the studies were placebo-controlled [14, 16, 18], and (double)-blind [15, 16, 18]. Notably, in the recent trial by Janssens and colleagues [16], which revealed limited effects on global LV function, control patients also underwent aspiration of bone marrow. In this study, BMC transplantation was performed one day after revascularization. Although in REPAIR-AMI and in a study by Chen *et al.* control patients also received aspiration of bone marrow, the BMC infusion was performed between days 4 and 18 after successful reperfusion and these studies reported a significant improvement in LV function [14, 18]. This implies that the BMC application in the study by Janssens and colleagues may have been too early and excludes the possibility that the complete procedure on bone marrow aspiration may exert a pronounced placebo effect or may contribute to the beneficial effects by causing a release of cytokines and growth factors involved in functional recovery [16]. Furthermore, the analyzed studies showed considerable heterogeneity and the size of the patient collectives varied at follow-up between 60 in BOOST and 187 in REPAIR-AMI [15, 18]. Hence, a standardization of the isolation and transplantation protocols, more comparable control procedures including bone marrow aspiration and placebo infusion and larger, multi-center patient collectives will be essential for a more meticulous evaluation of the overall effect.

Infusion of autologous BMC may represent a promising approach to support standard revascularization treatment of AMI when considering the significant increase in LVEF from baseline to follow-up, while comparing changes of the LVEF *per se* at follow-up without taking baseline values into account did not reveal improvement in LV function. Because the increase in LVEF from baseline to follow-up appears to be the convincing parameter from a clinical point of view, we may conclude that transplantation of BMC is beneficial for supporting classical treatment of AMI. However, the inconsistencies in study design appear as a limitation of our study. Thus, dissecting the differences in detailed sub-studies may further unveil that the patient selection, *e.g.* towards the severity of the initial functional impairment as well as the optimal time for BMC infusion (with or without previous *ex vivo* culture) requires more meticulous scrutiny.

Taken together, the present review summarizes state-of-the art regarding BMC transplantation after AMI and indicates the need to more precisely define criteria identifying those patients (*e.g.* at high risk for persistent deficits in LV function), for which a particular benefit from BMC therapy can be anticipated, even though positive effects observed across randomized and controlled trials were rather moderate. This notion highlights the need for large-scale, double-blind, randomized, placebo- and bone marrow aspiration-controlled, multi-centre trials with a standardized design, in order to validate and verify the effectiveness of BMC transfer as a reliable supportive therapy option after AMI.

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