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Evaluation of the effectiveness of infusion of bone marrow derived cell in patients with heart failure: A network meta-analysis of randomized clinical trials and cohort studies

Farhad Lotfi[1], Mojtaba Jafari[2], Mohsen Rezaei Hemami[3], Mahmood Salesi[4], Shekoufeh Nikfar[5], Hossein Behnam Morshedi[2], Javad Kojuri[6], Khosro Keshavarz*[1]

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Abstract

Background: The aim of this study was to investigate the effectiveness of bone marrow-derived cells (BMC) technology in patients with heart failure and compare it with alternative therapies, including drug therapy, cardiac resynchronization therapy pacemaker (CRT-P), cardiac resynchronization therapy defibrillator (CRT-D).

Methods: A systematic review study was conducted to identify all clinical studies published by 2017. Using keywords such as "Heart Failure, BMC, Drug Therapy, CRT-D, CRT-P" and combinations of the mentioned words, we searched electronic databases, including Scopus, Cochrane Library, and PubMed. The quality of the selected studies was assessed using the Cochrane Collaboration's tool and the Newcastle-Ottawa. The primary and secondary end-points were left ventricular ejection fraction (LVEF) (%), failure cases (Number), left ventricular end-systolic volume (LVES) (ml), and left ventricular end-diastolic volume (LVED) (ml). Random-effects network meta-analyses were used to conduct a systematic comparison. Statistical analysis was done using STATA.

Results: This network meta-analysis covered a total of 57 final studies and 6694 patients. The Comparative effectiveness of BMC versus CRT-D, Drug, and CRT-P methods indicated the statistically significant superiority of BMC over CRT-P (6.607, 95% CI: 2.92, 10.29) in LVEF index and overall CRT-P (-13.946, 95% CI: -18.59, -9.29) and drug therapy (-4.176, 95% CI: -8.02, -.33) in LVES index. In addition, in terms of LVED index, the BMC had statistically significant differences with CRT-P (-10.187, 95% CI: -18.85, -1.52). BMC was also dominant to all methods in failure cases as a final outcome and the difference was statistically significant i.e. BMC vs CRT-D: 0.529 (0.45, 0.62) and BMC vs Drug: 0.516 (0.44, 0.60).
In none of the outcomes, the other methods were statistically more efficacious than BMC. The BMC method was superior or similar to the other methods in all outcomes.

Conclusion: The results of this study showed that the BMC method, in general, and especially in terms of failure cases index, had a higher level of clinical effectiveness. However, due to the lack of data asymmetry, insufficient data and head-to-head studies, BMC in this meta-analysis might be considered as an alternative to existing treatments for heart failure.

Keywords: Bone marrow cell, CRT-D, Drug, CRT-P, Heart failure, Network meta-analysis

Conflicts of Interest: *None declared*
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Introduction

Heart failure is a chronic disease that is often referred to

Corresponding author: *Dr Khosro Keshavarz, khkeshavarz@sums.ac.ir*

1. Health Human Resources Research Center, School of Management and Medical Informatics, Shiraz University of Medical Sciences, Shiraz, Iran
2. Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran
3. Research Fellow South Cloisters, St Luke's Campus, University of Exeter, UK
4. Chemical Injuries Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran
5. Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy and Evidence-Based Medicine Group, Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran
6. Department of Cardiology, School of Medicine, Clinical Education Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

↑What is "already known" in this topic:
Some evidences have shown the effectiveness of bone marrow-derived stem cell therapy in patients with heart failure, and they have reported promising results. There are controversies about their effectiveness.

→What this article adds:
BMC method in general, and especially in terms of failure cases index, had a higher level of clinical effectiveness.

as congestive heart failure and is characterized by the inability of the heart to pump the blood needed for the tissues; moreover, the prevalence of this disease increases with age (1). The prevalence of cardiovascular diseases is increasing due to the increase in the incidence and prevalence of congestive heart failure, and the rise in the longevity of patients due to the use of new medical and surgical treatments (2). In addition, heart failure often occurs as an outcome of hypertension, cardiac ischemia, coronary artery disease, valvular heart disease, heart muscle disease, or cardiomyopathy, or several diseases occurring at the same time. Since the mentioned diseases increase the risk of irreversible heart failure, it is of great importance to identify and treat them (3).

Chronic heart failure and inadequate blood supply to the heart muscles (ischemic heart disease) are the most important causes of mortality in the world. The prevalence of this disease is 1% to 2% in the adult population, 6% in people over 65 years of age, and 10% in those over 75 years of age. Overall, it is estimated that around 15 million people worldwide have this disease (4). After the incidence of heart attack and chronic heart failure, the heart will not have the appropriate contractile power (5). Several methods of treatment are commonly used in the world for the treatment of this disease, among which we may note the followings: Drug Therapy, Cardiac Resynchronization Therapy Pacemaker (CRT-P), Cardiac Resynchronization Therapy Defibrillator (CRT-D), Left Ventricular Assist Device (LVAD), and RVAD (Right Ventricular Assist Device), artificial heart surgery, heart transplant, dietary regimen, and activity limitations. However, each mentioned method has its own limitations.

Nowadays, with the progress made in basic sciences and engineering, cell therapy has been introduced as a new and alternative method for the treatment of chronic diseases (6, 7). To justify cell therapy, it is said that different tissues of the body are made of cells, some of which have the ability to rebuild their own cells. For instance, the heart cells and some other cells have the ability to transform into other specialized cells (8).

Stem cells have two general sources: 1) embryonic stem cells (ESCs) and 2) adult stem cells derived from blood and bone marrow and can repair a tissue when it is damaged. These cells are more specialized than embryonic stem cells (9). Stem cells have many uses in the treatment of various diseases such as spinal cord injury, hormonal impairment, various types of syndrome, infertility, chronic hepatitis, pancreatitis, diabetes mellitus, and ischemic heart diseases such as congestive heart failure, etc. (10). Different types of therapies for heart failure are subject to some limitations; for example, in many studies, inappropriate drug therapy is reported as the most common cause of exacerbating heart failure (11).

The repair of the heart muscle cells is the latest therapeutic method. In this method, stem cells are transferred into the heart muscle, and a proper condition is created to generate new cells in the damaged area. Often, bone marrow cells are used for cell transplantation in the heart muscle (12-14), and these cells are studied in the majority of clinical trials. When applying this method, there is no need to culture the cells before injecting them to patients, and it is the most important advantage of using these cells (15). These cells are able to replace or repair the damaged cardiac arteries and tissues. Because of the positive and promising results found in a number of clinical trials around the world, this method has received much attention (16, 17). In 2005, the US Food and Drug Administration confirmed the effectiveness of cell therapy in cardiac patients (18).

Many clinical trials have been conducted in the world to evaluate the effectiveness of bone marrow-derived stem cell therapy in patients with heart failure, and they have reported promising results (19-27). In addition, a number of studies have also reported that the use of this new technology for the treatment of heart failure is safe; however, as they stated, it is necessary to carry out clinical trials in higher phases with larger sample sizes (16, 28-31).

Despite the availability of the studies mentioned above, the use of this new technology in the health system of the country requires a comprehensive investigation in order to provide a clear picture of the effectiveness of this technology, as compared with other new therapies. In view of that, this study aimed to evaluate the clinical effectiveness of intracoronary/intra-myocardial infusion of bone marrow-derived cells (BMC) in patients with heart failure, as compared with alternative therapies including drug therapy, CRT-P, and CRT-D.

Methods

Data Resources and Search Strategy

In order to investigate the effectiveness of BMC technology in comparison with the other common therapies used for patients with heart failure, we conducted a systematic review of the studies that published from inception up until December 30, 2017, in electronic databases, including PubMed, Scopus, and Cochrane Library. We used several keywords, including (Myocardial infarction OR Chronic ischemic heart disease OR ischemic cardiomyopathy OR heart failure OR congestive heart failure), (Bone marrow cells OR bone marrow-derived cells OR stem cell OR bone marrow mononuclear cell OR MNC OR BMC OR BMNC), (Pharmacotherapy OR Drug Therapy OR Medication Therapy), (Cardiac Resynchronization Therapy Defibrillator OR CRT-D), Cardiac Resynchronization Therapy Pacemaker (CRT-P), and combinations of the mentioned keywords.

Study selection and data extraction

To select the studies for the systematic review, we set the inclusion criteria and only included articles reporting randomized controlled clinical trials and cohort studies published in English that investigated the clinical effectiveness of BMC technology and compared it with alternative therapies, including Drug Therapy (Include angiotensin-converting-enzyme (ACE) inhibitor, Beta Blockers such as Enalapril, Candesartan, Carvedilol, Metoprolol, and Nebivolol), CRT-P, and CRT-D in patients with chronic heart failure, ischemic heart disease, acute myocardial infarction, ischemic cardiomyopathy, and congestive heart failure.

Moreover, in order to include the studies in the meta-

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analysis, we only selected the studies with the following PICO:

Population: Patients with heart failure

Intervention: BMC

Comparators: Drug Therapy, CRT-P, and CRT-D

Outcomes: The expected outcomes were as follows: "left ventricular ejection fraction (LVEF) (%), failure cases (Number), left ventricular end-systolic volume (LVES) (ml), and left ventricular end-diastolic volume (LVED) (ml)". Based on the exclusion criteria, we excluded animal studies, studies without a control group, Case-Report, Case- Series, Cross-Sectional, Case-Control, review studies, and economic evaluation studies.

After the initial search, duplicated articles were removed, and the titles and abstracts of the remaining articles were evaluated by two people separately to identify and eliminate unrelated items and articles that did not meet the inclusion criteria. The results obtained by these two people were rechecked once and the controversial cases were resolved by referring to the articles. In the next step, the full texts of the articles, which were selected in the previous stage, were studied and articles that met the aforementioned inclusion criteria were selected. The PRISMA guideline was used for the systematic review of the articles (32). Using the predefined form, the necessary information was extracted from the text of selected articles based on inclusion and exclusion criteria. The outcome measures included left ventricular ejection fraction (LVEF) (%), left ventricular end-systolic volume (LVES) (ml), and left ventricular end-diastolic volume (LVED) (ml) and failure cases (Number) (Composite of all-cause mortality, stroke, rehospitalization for items that were left out of treatment.)

Quality Assessment

The quality of all RCT studies was assessed by the Cochrane Collaboration's tool (33), and the quality of cohort studies was evaluated by the Newcastle-Ottawa Quality Assessment Scale: Cohort Studies. In the Cochrane Collaboration's tool, each study is assessed based on six domains of bias: "selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias"; and all domain, assessments are included of these items: "Random sequence generation, Allocation concealment, Blinding of participants and personnel, Blinding of outcome assessment, Incomplete outcome data, Selective reporting and Anything else, ideally prespecified"; each item is assessed based on three options (high, low, or unclear). Accordingly, the mean of each option is calculated for all studies in the systematic review. To assess the cohort studies, the questions listed in the Newcastle-Ottawa Evaluation Scoreboard (34) were answered; in the four-choice questions, the two options a and b were given a star, while in questions with three or few choices, only option a was given a star. Finally, calculating the total number of answers receiving stars, i.e., Selection (4*), Comparability (2*), and Outcome (3*), the study was given stars and the quality of the study was evaluated. The maximum number of stars that a study could receive was nine stars. The studies with at least five stars or more were considered acceptable in terms of quality. Hence, in the end, the studies that met the selected criteria and indices had an acceptable level of quality based on the Cochrane Collaboration's tool or Newcastle-Ottawa and had similar methodologies were enrolled in the network meta-analysis.

Data Analysis

The search and review of the databases mentioned above did not result in finding any study that had directly compared BMC technology with other available therapeutic methods. Hence, there was an attempt to find clinical trials and cohort studies conducted on BMC; in addition, we extracted data on the effectiveness of other different technologies that had been separately reported by various studies and then compared them with the effectiveness of BMC technology. Therefore, in order to integrate the results of the reviewed studies, we applied network meta-analysis carried out using Excel and STATA software.

Therefore, as mentioned above, in this study we first adopted a systematic review approach and extracted data on the effectiveness of BMC technology and other treatment alternatives. Then, using network meta-analysis, we compared the effectiveness of the studied methods with each other and analyzed and reported the results.

In this network meta-analysis, the data analysis was performed using indirect command and random effect method. In this type of meta-analyses, first, the available comparisons are meta-analyzed and then their results are combined to carry out an indirect meta-analysis.

For various outcomes, the pooled odds ratios from randomized trials and cohort studies in the systematic review of BMC compared with PLB and Other Alternatives with PLB were computed using meta-analysis. Cochran's Q test and I2 index were used with P-value<0.1 were applied to assess heterogeneity among the RCTs and cohort studies included in the meta-analysis. Because of heterogeneous data random-effects model was used. To assess heterogeneity and for calculation of direct & indirect effects, "mean" and "indirect" commands in STATA 11.2 were used.

Bucher et al. method was used to calculate the indirect effects (19). In this method, the effects of BMC in comparison with common treatment methods can be estimated indirectly via using the direct estimators for the effects of BMC relative to PLB (effect $_{\text{BMC, PLB}}$) and PLB relative to CRT (effect $_{\text{CRT-D, PLB}}$):

$\text{Effect}_{\text{BMC, CRT-D}} = \text{effect}_{\text{BMC, PLB}} - \text{effect}_{\text{PLB, CRT-D}}$

The indirect estimator variance of Effect $_{\text{BMC, CRT}}$ is the sum of the direct estimators' variances:

$\text{Variance}_{\text{BMC, CRT-D}} = \text{variance}_{\text{BMC, PLB}} + \text{variance}_{\text{PLB, CRT-D}}$

To assess the indirect effects of BMC vs. PLB with Drug or CRT-P vs. PLB, we used the same formula.

The consistency and transitivity assumptions network meta-analysis were assessed. We could not investigate the consistency, because we did not have direct compassion between BMC, CRT-P, CRT-D, and Drug. For the transitivity assumption, proper inclusion and exclusion were implemented to get similarity between arms. The only potential modifier was the follow-up time. The mean duration of follow-up in the four groups was similar (p=0.343).

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In this study, for each outcome, a table with nine comparisons was provided. We first conducted five direct comparisons and then combined their results, and performed four indirect comparisons; as a result, the four existing therapies were compared with BMC. For the first three outcomes, the difference in mean values after the intervention was compared between the two groups. For the outcome of failure cases, the odds ratios were compared with each other. When collecting the data, it was not possible to obtain data on standard deviations from the baseline in each treatment group; as a result, we only extracted data on standard deviations before and after the intervention separately. Therefore, by estimating the correlation between the parameters before and after the study in each group (using the data extracted from all the studies), the standard deviation from the baseline in each group was estimated with an approximate level of accuracy.

Results

Study Screening, Characteristics, and Quality of Included Studies

A total of 21985 articles were found after conducting searches in the electronic databases and checking the references. After conducting several reviews, we conducted a meta-analysis of the studies that met the inclusion criteria and had an acceptable level of quality on the basis of the desired criteria (Fig. 1). A total of 57 studies that had been

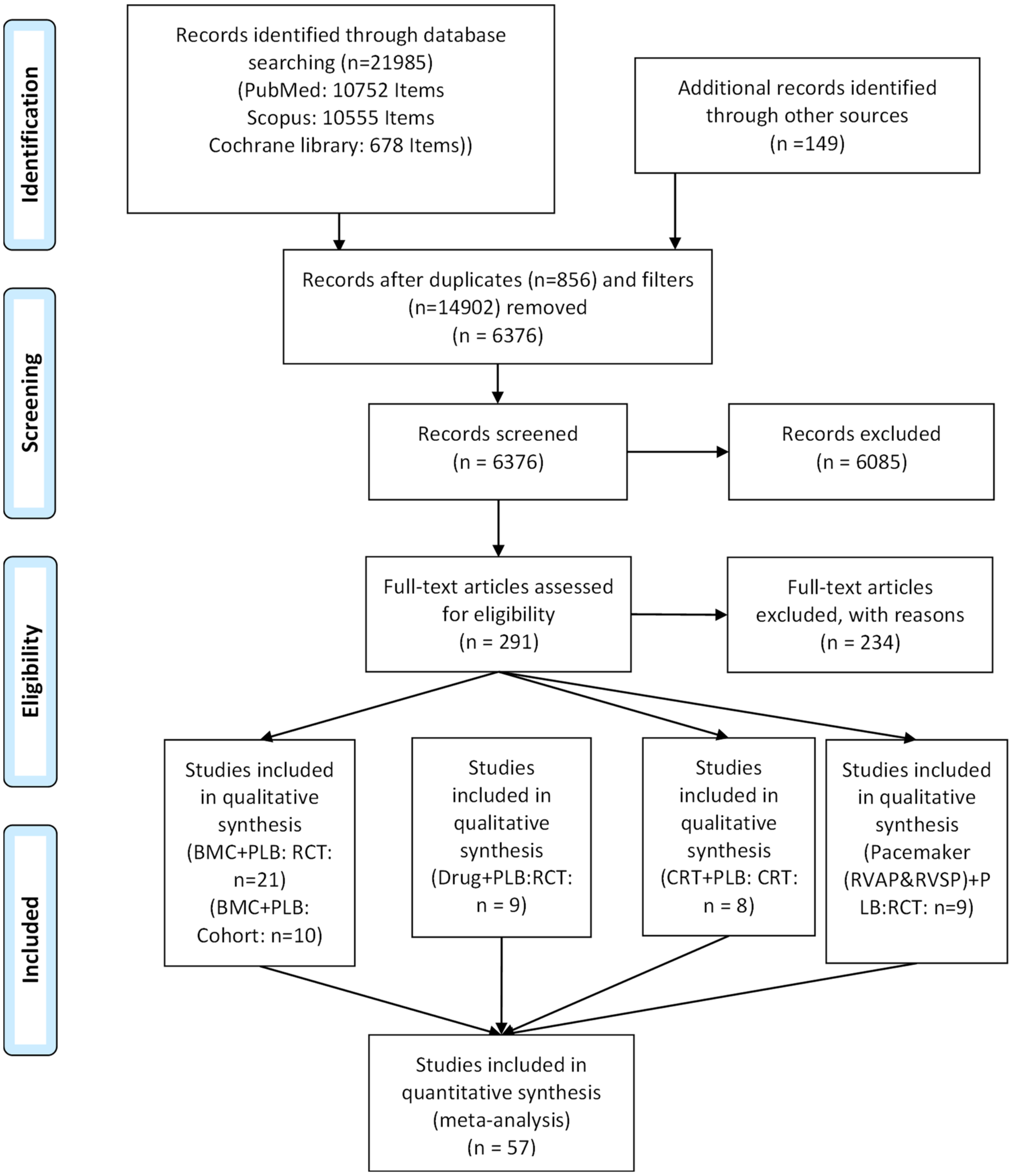

Fig. 1. Diagram of the process of selecting clinical trials and cohort studies which investigated the alternatives under the study

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conducted on a total of 6694 patients were finally analyzed. Table 1 presents the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials. In addition, as the results of the studies indicated, the Cochrane Collaboration's tool obtained an average for all the studies in the systematic review was 70% low risk of bias, 14% Bias unclear and 16% High risk of bias. Total ten studies described all domain of the Cochrane Collaboration's tool and using Randomized Control Trial design; others all described over three domains, so we had not an article with high risk in all

Table 1. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials

Bias domain	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
Source of bias	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Anything else, ideally prespecified
Author/Year							
Traverse and Colleagues (2011) USA (47)	+	+	+	+	+	+	+
Abraham and Colleagues (2004) USA (67)	+	+	+	+	+	+	+
St John Sutton and Colleagues (2003)USA (69)	+	+	+	+	+	+	+
Young and Colleagues (2003) USA (70)	+	+	+	+	+	+	+
Thibault and Colleagues (2013) Canada (71)	+	+	+	+	+	+	+
Linde and Colleagues (2008) Sweden (74)	+	+	+	+	+	+	+
Kitzman and Colleagues (2010) USA (75)	+	+	+	+	+	+	+
Van Veldhuisen and Colleagues (2009) Netherlands (76)	+	+	+	+	+	+	+
Matsumori and Colleagues (2003) Japan (78)	+	+	+	+	+	+	+
Imrie and Cirillo and Levy and Ascoli and Moccetti Colleagues (2000) Canada and Brazil and USA and italy and Switzerland (82)	+	+	+	+	+	+	+
Wohrle and Colleagues (2010) Germany (45)	+	+	+	+	+	?	+
Menardi and Colleagues (2008) Italy (73)	+	+	?	?	+	+	?
Piepoli and Colleagues (2010) Italy (52)	+	+	?	?	+	+	?
Cicoira and Colleagues (2002) Italy(80)	+	+	-	+	+	+	?
Pokushalov and Colleagues (2010) Russia (39)	+	+	+	-	+	+	?
Turan and Colleagues (2012) Germany (46)	+	+	+	+	-	+	?
Bristow and Colleagues (2004) USA (68)	+	+	-	+	+	+	?
Muto and Colleagues (2013) Italy (72)	+	+	-	+	+	+	?
Ang and Colleagues(2008) UK (37)	?	?	+	+	+	+	-
Perin and Colleagues (2011) USA (42)	+	+	-	+	+	?	?
Palazzuoli and Colleagues (2002) Italy (79)	+	+	+	+	-	?	?
Assmus and Colleagues (2006) Germany (38)	+	-	+	+	+	?	?
Silva and Colleagues (2009) Brazil (50)	+	+	?	?	+	-	+
Suarez and Colleagues (2007) Spain (49)	+	+	?	?	+	-	?
Cao and Colleagues (2009) USA (53)	+	+	?	?	+	+	-
Herbots and Colleagues (2009) Belgium (56)	+	+	-	+	+	?	?
Tsutamoto and Colleagues (2001) Japan (81)	+	+	?	?	+	-	?
Hendrikx and Colleagues (2006)USA (41)	+	+	-	+	+	-	+
Yao and Colleagues (2009) China (44)	+	+	-	+	+	-	+
Quyyumi and Colleagues (2011) USA (51)	+	+	-	+	+	-	+
Muto and Colleagues (2009) Italy (85)	+	+	-	-	+	+	+
Cho and Colleagues (2011) Korea (87)	+	-	-	+	+	+	+
Chen and Colleagues (2004) China (54)	-	-	+	+	+	+	?
Grajek and Colleagues (2010) Poland (55)	+	+	-	-	+	?	+
Cano and Colleagues (2010) Spain (84)	+	+	-	+	+	-	?
Occhetta and Colleagues (2015) Italy (88)	+	+	-	-	+	+	?
Traverse and Colleagues (2010) USA (48)	+	+	-	-	+	?	?
Yao and Colleagues (2008) China (43)	-	+	-	+	+	-	+
Cohen Solal and Colleagues (2004) France (77)	+	+	+	+	-	-	-
Hamer and Colleagues (1989) Australia (83)	+	+	+	+	-	-	-
Patel and Colleagues (2005) USA (40)	+	+	-	-	+	-	?
Flevari and Colleagues (2009) Greece (86)	+	+	-	-	+	-	?

Key: + Low risk of bias, ? Unclear risk of bias, - High risk of bias

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domains. In addition, we evaluated the quality of cohort studies using the Newcastle-Ottawa Quality Assessment Scale, and the results showed that all the selected studies had a high-quality score of 7; thus, they had an acceptable level of quality (minimum score of five). Table 2 presents a summary of the characteristics of the selected studies, including the comparison arm, the duration of the study, and the number of patients.

Outcomes

Figure 2 shows the schematic of the various comparisons. Tables 3 to 6 present the number of studies that reported the outcomes of LVEF, LVES, LVED, and failure cases for BMC, CRT-D, Drug, CRT-P, and placebo group. The LVEF outcome was the most frequently studied outcome that was reported in 56 studies, and the failure cases were the least frequently studied outcome that was reported in 31 studies.

Table 2. The characteristics of the selected studies in the network meta-analysis

Study	Trial design	No. of patients		treatment duration (Mean follow-up)	
		Therapy group	Control group	Therapy group (month)	Control group (month)
BMC vs Placebo (RCT studies)					
Ang and Colleagues(2008) UK (37)	RCT	21	20	6	6
Ang and Colleagues(2008) UK (37)	RCT	21	20	6	6
Assmus and Colleagues (2006) Germany (38)	RCT	35	23	3	3
Pokushalov and Colleagues (2010) Russia (39)	RCT	55	54	12	12
Patel and Colleagues (2005) USA (40)	RCT	10	10	6	6
Hendrikx and Colleagues (2006)USA (41)	RCT	10	10	4	4
Perin and Colleagues (2011) USA (42)	RCT	20	10	6	6
Yao and Colleagues (2008) China (43)	RCT	24	23	6	6
Yao and Colleagues (2009) China (44)	RCT	12	12	12	12
Wohrle and Colleagues (2010) Germany (45)	RCT	29	13	6	6
Turan and Colleagues (2012) Germany (46)	RCT	42	20	12	12
Traverse and Colleagues (2011) USA (47)	RCT	58	29	6	6
Traverse and Colleagues (2010) USA (48)	RCT	30	10	6	6
Suarez and Colleagues (2007) Spain (49)	RCT	10	10	3	3
Silva and Colleagues (2009) Brazil (50)	RCT	10	6	6	6
Quyyumi and Colleagues (2011) USA (51)	RCT	16	15	6	6
Piepoli and Colleagues (2010) Italy (52)	RCT	19	19	12	12
Cao and Colleagues (2009) USA (53)	RCT	41	45	48	48
Chen and Colleagues (2004) China (54)	RCT	34	35	3	3
Grajek and Colleagues (2010) Poland (55)	RCT	31	14	12	12
Herbots and Colleagues (2009) Belgium (56)	RCT	33	34	4	4
BMC vs Placebo (Cohort studies)					
Akar and Colleagues (2009) Turkey (57)	Cohort	25	25	18	18
Yerebakan and Colleagues (2011) Germany (58)	Cohort	35	20	18	18
Perin and Colleagues (2004) Brazil (59)	Cohort	11	9	12	12
Manginas and Colleagues (2006) Greece (60)	Cohort	12	12	11	11
Mocini and Colleagues (2006) Italy (61)	Cohort	18	18	3	3
Stamm and Colleagues (2007) Germany (62)	Cohort	20	20	6	6
Turan and Colleagues (2010) Germany (63)	Cohort	17	15	6	6
Bartunek and Colleagues (2005) Belgium (64)	Cohort	19	16	4	4
Yousef and Colleagues (2009) Germany (65)	Cohort	62	62	60	60
Katritsis and Colleagues (2005) Greece (66)	Cohort	11	11	4	4
CRT-D vs Placebo					
Abraham and Colleagues (2004) USA (67)	RCT	85	101	6	6
Bristow and Colleagues (2004) USA (68)	RCT	599	308	6	6
St John Sutton and Colleagues (2003)USA (69)	RCT	172	151	6	6
Young and Colleagues (2003) USA (70)	RCT	187	182	6	6
Thibault and Colleagues (2013) Canada (71)	RCT	44	41	12	12
Muto and Colleagues (2013) Italy (72)	RCT	60	113	12	12
Menardi and Colleagues (2008) Italy (73)	RCT	100	20	12	12
Linde and Colleagues (2008) Sweden (74)	RCT	419	191	12	12
Drug vs Placebo					
Kitzman and Colleagues (2010) USA (75)	RCT	35	36	12	12
Van Veldhuisen and Colleagues (2009) Netherlands (76)	RCT	380	372	12	12
Cohen Solal and Colleagues (2004) France (77)	RCT	28	22	6	6
Matsumori and Colleagues (2003) Japan (78)	RCT	148	144	6	6
Palazzuoli and Colleagues (2002) Italy (79)	RCT	24	24	12	12
Cicoira and Colleagues (2002) Italy (80)	RCT	54	52	12	12
Tsutamoto and Colleagues (2001) Japan (81)	RCT	20	17	4	4
Imrie and Cirillo and Levy and Ascoli and Moccetti Colleagues (2000) Canada and Brazil and USA and italy and Switzerland (82)	RCT	214	212	4	4
Hamer and Colleagues (1989) Australia (83)	RCT	16	14	6	6
CRT-P vs Placebo					
Cano and Colleagues (2010) Spain (84)	RCT	28	21	12	12
Cano and Colleagues (2010) Spain (84)	RCT	32	21	12	12
Muto and Colleagues (2009) Italy (85)	RCT	40	75	54	54
Flevari and Colleagues (2009) Greece (86)	RCT	9	6	12	12
Flevari and Colleagues (2009) Greece (86)	RCT	10	6	12	12
Cho and Colleagues (2011) Korea (87)	RCT	45	15	>7 day	>7 day
Cho and Colleagues (2011) Korea (87)	RCT	34	15	>7 day	>7 day
Occhetta and Colleagues (2015) Italy (88)	RCT	33	22	19	19
Occhetta and Colleagues (2015) Italy (88)	RCT	244	22	19	19

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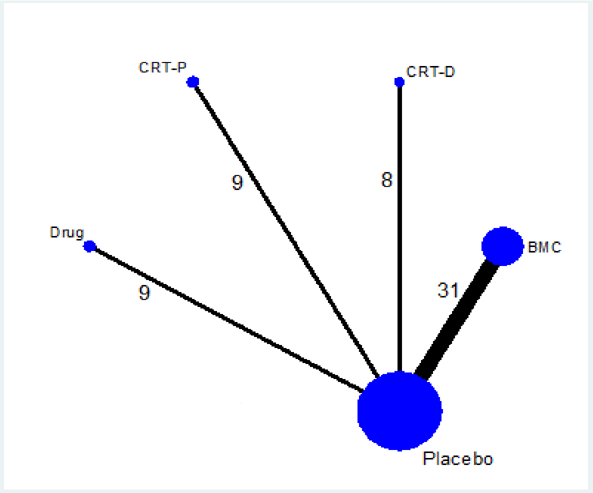

Fig. 2. Network plot between the groups (efficacy outcome)
Number of studies VS Placebo in meta-analysis (31 (BMC), 8 (CRT-D), 9 (Drug) and 9 (CRT-P)).
Nodes are weighted according to the number of studies including the respective interventions. Edges are weighted according to the mean control group risk for comparisons between placebo and active treatment.

LVEF change from baseline

Based on the results of meta-analysis, as presented in Table 3, the level of LVEF in BMC, CRT-D, and Drug groups show a significant difference as compared with the placebo group. The mentioned methods, as compared with the placebo, resulted in a more significant increase in LVEF (Comparisons 1-3). However, we did not observe a significant difference between the CRT-P group, as compared with the placebo group, in terms of LVEF (Comparison 4).

Afterward, we combined the results of the meta-analysis for indirect comparisons, and it was observed that CRT-D and Drug methods did not have a significant difference with the BMC method in terms of changes in LVEF (Comparison 5 and 6). However, there was a significant difference between the BMC method and the CRT-P method; in other words, the BMC method, as compared with the CRT-P method, resulting in a more significant increase in LVEF (Comparison 7).

LVES change from baseline

Based on the results of a meta-analysis presented in Table 4, it can be observed that BMC, CRT-D, and Drug groups had a significant difference with the placebo group in terms of LVES since the mentioned methods resulted in a more significant decrease in LVES, as compared with the placebo (Comparisons 1-3). However, the CRT-P group did not show significant differences compared to the placebo group in terms of LVES (Comparison 4).

Afterward, we combined the results of the meta-analysis for indirect comparisons, and it was observed that the CRT-D method did not have a significant difference with the BMC method in terms of the changes in LVES (Comparison 5). However, the difference between the BMC method and Drug and CRT-P methods was significant. In other words, LVES reduced more significantly in the BMC method, as compared with CRT-P and Drug methods (Comparisons 6 and 7).

LVED change from baseline

Based on the results of meta-analysis, as presented in Table 5, BMC and Drug groups had a significant difference compared to the placebo group, in terms of LVED. In other

Table 3. Network meta-analysis for comparison of LVEF after intervention between the two groups

Comparison		Treatment		Meta-analysis (Random effect)		Indirect comparison	
id	Number of studies	Treatment 1	Treatment 2	Mean difference (CI 95%)	p	Mean difference (CI 95%)	p
1	31	BMC	placebo	4.420 (2.779, 6.060)	<0.001		
2	7	CRT-D	placebo	5.679 (2.458, 8.901)	0.001		
3	9	Drug	placebo	3.199(2.268, 4.131)	<0.001		
4	9	CRT-P	placebo	-2.178 (-5.479, 1.122)	0.196		
5		BMC	CRT-D			-1.259 (-4.87, 2.35)	0.495
6		BMC	Drug			1.221 (-0.66, 3.11)	0.204
7		BMC	CRT-P			6.607 (2.92, 10.29)	<0.001

Table 4. Network meta-analysis for comparison of LVES after the intervention between the two groups

Comparison		Treatment		Meta-analysis (Random effect)		Indirect comparison	
id	Number of studies	Treatment 1	Treatment 2	Mean difference (CI 95%)	p	Mean difference (CI 95%)	p
1	24	BMC	placebo	-11.201 (-14.198, -8.204)	<0.001		
2	6	CRT-D	placebo	-11 (-20.427, -1.574)	0.022		
3	6	Drug	placebo	-7.025 (-9.440, -4.610)	<0.001		
4	9	CRT-P	placebo	2.746 (-0.811, 6.302)	0.13		
5		BMC	CRT-D			-.201 (-10.09, 9.69)	0.969
6		BMC	Drug			-4.176 (-8.02, -.33)	0.033
7		BMC	CRT-P			-13.946 (-18.59, -9.29)	<0.0001

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Table 5. Network meta-analysis for comparison of LVED after the intervention between the two groups

Comparison		Treatment		Meta-analysis (Random effect)		Indirect comparison	
id	Number of studies	Treatment 1	Treatment 2	Mean difference (CI95%)	p	Mean difference (CI 95%)	p
1	25	BMC	Placebo	-6.769 (-9.579, -3.959)	<0.001		
2	6	CRT-D	Placebo	-8.305 (-31.224, 14.614)	0.478		
3	7	Drug	Placebo	-9.109 (-13.739, -4.478)	<0.001		
4	9	CRT-P	Placebo	3.418 (-4.782, 11.619)	0.414		
5		BMC	CRT-D			1.536 (-21.55, 24.63)	0.895
6		BMC	Drug			2.34 (-3.08, 7.75)	0.397
7		BMC	CRT-P			-10.187 (-18.85, -1.52)	0.021

words, the mentioned methods resulted in a more significant reduction in LVED, as compared with the placebo (Comparisons 1 and 3). However, LVED reduced more significantly in CRT-D and CRT-P groups, as compared with the placebo group. (Comparisons 2 and 4).

Then, we combined the results of the meta-analysis for indirect comparisons and it was observed that CRT-D and Drug methods did not have a significant difference compared to the BMC method in terms of the level of changes in LVED (Comparisons 5 and 6). However, the BMC method had a significant difference with the CRT-P method, as the BMC method resulted in a more significant reduction in LVED, as compared with the CRT-P method (Comparisons 7).

Failure cases after the intervention

Based on the results of meta-analysis, as presented in Table 6, BMC, CRT-D, and Drug groups had a significant difference compared to the placebo group in terms of failure cases, as the mentioned methods resulted in a more significant reduction in failure cases, as compared with the placebo (Comparisons 1-3). It should also be noted that we did not find proper data about this outcome in the pacemaker method; hence, we did not report this outcome for the pacemaker method.

We also combined the results of the meta-analysis for indirect comparisons and it was observed that CRT-D and Drug methods had a significant difference with the BMC method in terms of failure cases. In other words, the failure cases in the BMC method was significantly lower than that in the CRT-D, and Drug methods (Comparisons 5 and 6).

Discussion

The present study was the first network meta-analysis study that indirectly evaluated the effectiveness of intracoronary / intra-myocardial infusion of bone marrow-derived cells (BMC) in patients with heart failure and compared it with common therapies in Iran including Drug Therapy, CRT-P, and CRT-D. In order to evaluate the effectiveness, first, we conducted a systematic review of the evidence on the clinical effectiveness of the methods. The available studies were selected using a set of inclusion criteria and evaluated in terms of some specific outcomes including LVEF (%), failure cases (N), LVES (ml), and LVED (ml). Finally, the studies that were eligible for meta-analysis underwent a network meta-analysis. As stated, we used the network meta-analysis method because of the absence of studies that have directly assessed and compared the mentioned methods.

Based on the results of network meta-analysis, comparison of the effectiveness of BMC with that of CRT-D, Drug, and CRT-P methods indicated a statistically significant superiority of BMC over CRT-P in LVEF index and, its superiority in LVES index over CRT-P and drug therapy. In addition, in terms of LVED index, the BMC had statistically significant differences than CRT-P. BMC was also dominant to Drug and CRT-D in failure cases as an effective index and the difference was statistically significant. Although, our findings of the effectiveness of the methods were not similar in all outcomes, according to failures cases which are considered as a final indicator and include patients' mortality, the BMC method was superior to the other methods and had a significant difference with them ($p<0.05$). In none of the outcomes, the other methods were statistically more efficacious than BMC. The BMC method was superior or similar to the other methods in all outcomes.

Comparing the BMC and CRT-D methods showed that the differences between the two methods in terms of LVEF,

Table 6. Network meta-analysis for comparison of failure after the intervention between the two groups

Comparison		Treatment		Meta-analysis (Fixed effect)		Indirect comparison	
id	Number of studies	Treatment 1	Treatment 2	OR (CI 95%)	p	OR (CI 95%)	p
1	20	BMC	Placebo	0.387 (0.25, 0.588)	<0.001		
2	4	CRT-D	Placebo	0.731 (0.56, 0.946)	0.017		
3	7	Drug	Placebo	0.750 (0.576, 0.977)	0.033		
4	0	CRT-P	Placebo	-	-		
5		BMC	CRT-D			0.529 (0.45, 0.62)	<.0.001
6		BMC	Drug			0.516 (0.44, 0.60)	<.0.001

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LVES, LVED, and failure cases were - 1.259 (p>0.05), -0.201 (p>0.05), 1.536 (p>0.05), and 0.529 (p<0.05), respectively. As it can be observed and taking into account the p-values, except for the outcome of failure cases, the other outcomes in the CRT method did not show significant differences with those in the BMC method. In other words, the BMC treatment method is superior to the CRT-D method only in terms of the mortality rate and failure cases; the two methods have a similar level of effectiveness in terms of other outcomes.

Comparison of the BMC and Drug methods revealed that the differences between the two methods in terms of LVEF, LVES, LVED, and failure cases were 1.221 (p>0.05), -4.176 (p=0.03), 2.34 (p>0.05), and 0.516 (p<0.05), respectively. As it can be observed and taking into account the p-values, the two outcomes of LVES and failure cases in the Drug method have significant differences compared to those in the BMC method. In other words, the BMC treatment method is superior to the Drug method in terms of LVES and failure cases; the two methods have a similar level of effectiveness in terms of other outcomes.

Comparing BMC and CRT-P methods showed that the differences between the two methods in terms of LVEF, LVES, and LVED were 6.607 (p<0.05), -13.946 (p<0.05), and -10.187 (p=0.02), respectively. There was not enough evidence about failure cases in the Pacemaker method. As it can be observed and taking into account the p-values, all the three outcomes in the Pacemaker method have, significant differences compared to those in the BMC method. In other words, the BMC treatment method is superior to the Pacemaker method in terms of LVEF, LVES, and LVED.

Therefore, with respect to the effectiveness of BMC method with that of CRT-D, Drug, and CRT-P methods in terms of the effective indices of LVEF, LVES, and LVED, we observed significant differences in some cases and non-significant differences in other cases; thus, our findings on the effectiveness of the methods were not similar. However, considering the effectiveness index of failure cases, which includes the patients' mortality and is considered as a final indicator, the BMC method was superior to the other methods and had a significant difference.

It should be noted that we did not find any meta-analysis study that had directly or indirectly compared the BMC treatment method with the other methods mentioned in this study; therefore, it was not possible to compare the results of this study with the results of other studies. However, there were many meta-analyses and systematic reviews that compared the effectiveness of BMC treatment method between a variety of patients with heart failure, either before and after treatment or between the cases and controls. The results of such studies indicate the superiority and effectiveness of BMC method, especially in the mortality index and LVEF index, when comparing patients before and after the treatment or when comparing the cases with the controls (21, 23, 35, 36). It is in line with the results of this study, which showed the medical effectiveness of BMC treatment method, as compared with the placebo.

The difference between basic treatments in patients before receiving each method is a limitation in this study. In addition, one of the limitations in this study is that the patients' selection may not be the same and the patients' characteristics may effect on the effectiveness of different methods.

Conclusion

The results of this study showed that the BMC method in general, and especially in terms of failure cases index, had a higher level of clinical effectiveness, as compared with the other studied treatment methods. Therefore, based on the aforementioned findings and the results of previous studies conducted on the treatment of heart failure, the use of BMC can be considered as an appropriate alternative to the existing therapies. However, due to the lack of data asymmetry, insufficient data and head-to-head studies, in this meta-analysis cannot be considered as a definitive alternative to existing treatments for heart failure. Of course, this conclusion is only in terms of clinical effectiveness. For making a better decision, when comparing this method with other methods, it is suggested that the two dimensions of cost and effectiveness should be assessed simultaneously.

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Conflict of Interests

The authors declare that they have no competing interests.

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