Research Article

Stem Cell Therapy for the Treatment of Chronic Ischemic Heart Disease

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Abstract

Chronic ischemic heart disease remains a major cause of morbidity and mortality worldwide. Several trials have been performed to evaluate benefit of stem cells transplantation to restore cardiac function in short- and long-term period after myocardial infarction. This concise review analyzes 15 clinical trials between 2005 and 2020 comprising 1372 patients (608 treated) and is aimed to: 1): assess percent increase in left ventricular ejection fraction (LVEF) and decrease in New York Heart Association (NYHA) class at 12 months after stem cells transplantation after acute myocardial infarction and 2) correlate LVEF percent increase with number of transfused stem cells.

Nine trials reported a significant percent LVEF increase and NYHA class decrease at 12 months after bone marrow and peripheral blood stem cells transplantation correlating with transplanted cells number. Caution should be exercised in the evaluation of these results due to the different stem cells utilized, transplant protocols and endpoints, and the small number of patients treated in some studies.

Keywords: Stem cells; Chronic ischemic heart disease; Transplantation; Clinical trials

1. Introduction

Chronic ischemic heart disease remains a major cause of morbidity and mortality worldwide and 50% of diagnosed cases dies within 5 years [1]. In this

context stem cells transplantation has been proposed as potential useful procedure and one of clinical options to reduce ischemic damage and restore cardiac function after acute myocardial infarction [2]. Different autologous or allogeneic stem cell types derived from bone marrow, peripheral blood, mesenchymal and cardiac cells have been utilized [2]. Notably, conflicting outcome results have been reported. Moreover, optimal stem cell type and dose as well as transplantation regimen have not been identified.

In addition, little is known about the potential benefits of stem cells transplantation in chronic ischemic heart disease. Aim of this concise review is to report the present knowledge about the potential benefit of stem cells therapy in chronic ischemic heart disease.

2. Methods

Clinical trials were selected applying as search terms "bone marrow cells", "stem cells", "mesenchymal cells", and "chronic ischemic heart disease" in www.pubmed.gov and Cochrane library from 2005 to 2020. Notably, studies were included if they were randomized blinded trials, randomized unblinded trials, non-randomized trials with a follow up ≥ 6 months.

Clinical trials including patients suffering from ischemic and non-ischemic heart failure, chronic heart failure, and acute and chronic angina were criteria of exclusion as well as clinical trials with incomplete outcome data (attrition bias).

Left ventricular ejection fraction (LVEF) increase and New York Heart Association (NYHA) class decrease were identified as the outcome parameters in long term follow up. LVEF was recorded before stem cells transplantation and then after 6 and 12 months in all studies, and over 12 months in selected studies, after stem cells transplantation. Statistical significance of percent LVEF increase at 12 months was recorded. NYHA class at baseline and 12 months after stem cells transplantation was also recorded.

2.1 End points

2.1.1 Primary: Assess percent increase in LVEF and decrease in NYHA class at 12 months after stem cells transplantation for acute myocardial infarction.

2.1.2 Secondary: Correlate LVEF percent increase and number of transfused stem cells.

3. Results

Selection data searched 15 clinical trials [3-17] evaluating the efficacy of stem cells transplantation in chronic ischemic heart disease from 2005 to 2020 and included: 5 randomized blinded trials, 6 randomized unblinded trials, and 4 non-randomized trials. A total of 1372 patients were enrolled of which 608 (551 males - median age 61 years) were treated. At baseline mean LVEF was 35.9% (range 26 – 46%). Bone marrow (BMC), peripheral blood (PBC), cardiac (CDC) or mesenchymal (MES) stem cells were utilized in 8, 3, 2 and 1 trials, respectively; both PBC and MES were utilized in 1 study. Total number of transplanted cells ranged from 5 x 10^6 to 1,500 x 10^6 (median 70 x 10^6) depending on cell type, cell population purification, and transplantation route.

Transplant procedure was intracoronary in 8 trials and intramyocardial in 6 trials; both procedures were utilized in one trial.

Nine trials reported a statistically significant percent LVEF increase between 4% to 19% (mean 9.6%) at 12 months after stem cells transplantation (*p* values ranging from 0.05 to 0.001) [3-11]. BMC and PBC stem cells were utilized for transplantation in all these studies (Table 2). A significant correlation was found between number of transplanted cells and percent LVEF increase (Pearson correlation coefficient 0.74, p=0.01) (Figure 1). Of interest, the highest LVEF percent increase was observed in patients transplanted with an elevated amount (400 x 10^6) of purified cells expressing CXCR4 molecule that regulates cardiac stem cells migration [11]. Transplant of either BMC and PBC unselected stem cells or CD133+ purified stem cells, that represent the most immature cell population which has shown to efficiently regenerate ischemic myocardium in pre-clinical models, attained analogous results (mean percent LVEF increase 7.8% and 8.2%, respectively). Similarly, no significative differences in percent LVEF increase were observed between patients who underwent intracoronary or intramyocardial transplantation (8.1% and 9.4%, respectively). NYHA class decrease from severe or moderate to mild was also detectable in all these trials at 12 months after stem cells transplantation (Table 1). By contrast, neither LVEF amelioration nor NYHA class decrease was reported in 6 studies [12-17] (Table 1). BMC, PBC, MES and CDC stem cells were transplanted in these trials (Table 2).

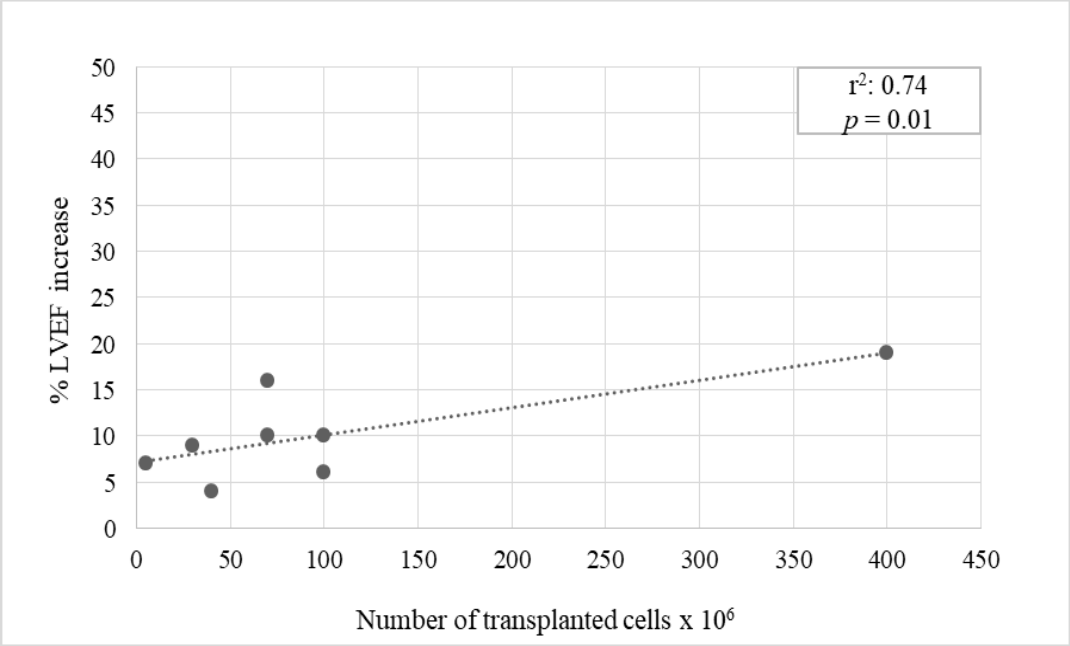

Figure 1: Correlation between percent LVEF increase and transplanted stem cells number in 9 clinical trials showing benefit at 12 months after myocardial infarction.

Authors [Ref. N.]	Patients				% LVEF follow up				P Value	NYHA class	
	Enrolled	Treated	Age (mean)	Male (treated)	Baseline	6 months	12 months	>12 months		Baseline	12 months
Erbs 2005 [3]	26	13	63	26	43 ± 2.0	58.9 ± 3.2	58.9 ± 3.2	58.9 ± 3.2	< 0.05	N/A	N/A
Stamm 2007 [4]	51	42	40	40	39 ± 8.7	50.2 ± 8.5	N/A	47.9 ± 6.0	= 0.01	III	II
Gyongyosi 2009 [5]	80	60	53	55	38.4 ± 5.8	42.9 ± 10.4	42.8 ± 9.7	-	=0.001	III	II
Pokushalov 2009 [6]	109	55	61	48	27.8 ± 3.4	32.8 ± 6.2	32.3 ± 4.1	-	= 0.02	III	II
Flores-Ramìrez 2010 [8]	7	7	56	6	28.0 ± 6.7	N/A	N/A	38.8 ± 10.3	<0.01	III	I
Turan 2011 [7]	56	38	62	20	46 ± 10	N/A	52 ± 8	-	= 0.01	III	I
Makkar 2012 [12]	436	25	52	25	39 ± 12	39 ± 12	-	-	n.s.	IV	IV
Hare 2012 [13]	96	30	63	26	27.1 ± 9.6	N/A	27.7 ± 9.3	-	n.s.	III	II
Honold 2013 [14]	154	133	60	133	40.3 ± 10.9	N/A	43.5	-	n.s.	II	II
Malliaras 2014 [15]	31	17	N/A	N/A	42.4 ± 8.9	N/A	48.2 ± 10.3	-	n.s.	I	I
Heldman 2014 [16]	65	33	61	33	35.8 ± 8.5 36.3 ±11.1	35.8 ± 8.5 36.3 ±11.1	35.8 ± 8.5 36.3 ±11.1	-	n.s.	II	II
Nassseri 2014 [9]	60	30	62	28	26.2 ± 5.6	33+8	-	-	< 0.05	IV	II
Trifunovic 2015 [10]	30	15	56	15	35.9 ± 4.7	N/A	45.4 ± 4.9	N/A	< 0.001	III	I
Aceves 2020 [11]	29	20	62	20	31 ± 2	49 ± 2	50 ± 1	-	< 0.001	III	I
Makkar 2020 [17]	142	90	55	76	39.9 ± 6	40.4 ± 7.07	-	-	n.s.	II	II

N/A: not available

Table 1: Clinical trials evaluating stem cells transplantation in chronic ischemic heart disease.

Trials [Ref. N.]	Cells		Transplantation route	
	Source*	**Cells number**	**Intracoronary**	**Intramyocardial**
Erbs 2005 [3]	PBC(133+)	69 ± 14 x 10^6	+	
Stamm 2007 [4]	BMC(133+)	25 - 34 x 10^6		+
Gyongyosi 2009 [5]	BMC	1300 ± 1.64 x 10^6	+	
Gyongyosi 2009 [5]	BMC	200 x 10^6		+
Pokushalov 2009 [6]	BMC	41 ± 16 x 10^6		+
Flores-Ramìrez 2010 [8]	PBC(133+)	103 ± 164 x 10^6	+	
Turan 2011 [7]	BMC(133+)	99 ± 25 x 10^6	+	
Makkar 2012 [12]	CDC	12-17-25 x 10^6	+	
Hare 2012 [13]	MES	20-100-200 x 10^6		+
Honold 2013 [14]	PBC	183 ± 101 x 10^6	+	
Malliaras 2014 [15]	BMC	12.5- 25 x 10^6	+	
Heldman 2014 [16]	PBC	N/A		+
Heldman 2014 [16]	MES	N/A		+
Nassseri 2014 [9]	BMC(133+)	5 x 10^6	+	
Trifunovic 2015 [10]	BMC	70.7 ± 32.4 × 10^6		+
Aceves 2020 [11]	PBC(133+)	400 x 10^6		+
Makkar 2020 [17]	CDC	12-17-25 x 10^6	+	

*BMC (bone marrow cells), PBC (peripheral blood cells), CDC (cardiosphere-derived cells), MES (mesenchymal cells)

N/A: not available

Table 2: Stem cells source and transplantation route.

4. Discussion

Between 2000 and 2020 many clinical trials evaluating the efficacy of stem cells transplantation after acute myocardial infarction have been reported in the literature with conflicting results [10,18]. Jeevanantham et al. [19] published a systematic review and meta-analysis reporting 2,635 patients treated with BMC for ischemic heart disease. Authors concluded that BMC transplantation improved LVEF and that beneficial effects persisted for long-term with a median follow up of 6 months (range 3 months to 60 months) reducing mortality and recurrence of ischemic myocardial infarction. Cut-off number of transplanted BMC cells to obtain efficient response was 40 x 10^6cells.

Recently, we analytically reviewed 34 randomized trials in the period 2000 to 2020 that recruited 3142 patients (the largest number to date) evaluating the efficacy of stem cells transplantation on LVEF increase at 6 months after acute myocardial infarction. Despite the large number of patients

evaluated, results demonstrated uncertain efficacy of this therapeutic approach. In fact, 20 trials showed a significant LVEF increase while 14 trials did not show LVEF improvement [20]. These previous controversies have stimulated this concise review aimed to identify a possible benefit of stem cells transplantation at 12 or more months after myocardial infarction in patients affected by chronic ischemic heart disease. To this end we searched clinical trials on this topic and selected 15 trials published from 2005 to 2020.

Nine trials reported a statistically significant LVEF increase and NYHA class improvement at 12 months after stem cells transplantation whereas 6 studies did not report clinical benefit. Of interest, BMC and PBC stem cells were utilized for transplantation in all studies showing positive results and a statistically significant correlation was found between number of transplanted cells and percent LVEF increase. At variance with Jeevanantham et al. [19], positive results were observed in two trials in which less than 40 x 10^6 stem cells were transplanted. In agreement with literature data [2] myocardial function of transplanted patients was severely impaired with baseline ejection fraction between 26% and 46%. No significative differences were observed between patients who received either unselected BMC and PBC cells or 133+ BMC and PBC selected cells as well as between those that were transplanted either via intracoronary or intramyocardial route. In addition, MSC and CDC cells transplantation did not lead to ejection fraction improvement.

Results of current literature search seem to favor a moderate positive effect of stem cells transplantation on chronic ischemic heart disease at 12 or more months follow up. The positive effect was correlated with the number of transplanted cells. However, caution should be exercised in the evaluation of clinical trials due to the different stem cells utilized, transplant protocols and endpoints. Moreover, statistical significance of data analysis is limited by the small number of patients treated in some studies which affects the value of the results.

Therefore, large multicenter clinical trials aimed at the identification of optimal type and dose of cells as well as at the determination of the better transplantation protocol are needed to achieve a consistent response regarding the long-term effectiveness of stem cells therapy to improve cardiac function and quality of life of patients affected by chronic ischemic cardiomyopathy after acute myocardial infarction.

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