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Intramyocardial autologous CD34+ cell therapy for refractory angina: A meta-analysis of randomized controlled trials☆

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ABSTRACT

Background: Previous studies have demonstrated that intramyocardial human CD34+ cells may relieve symptoms and improve clinical outcomes in chronic refractory angina unresponsive to optimal medical therapy or not amenable to revascularization.
Methods: We performed a meta-analysis of randomized controlled trials (RCTs) to evaluate the impact of human CD34+ cells compared with placebo in chronic refractory angina. Primary efficacy outcomes in our analysis were angina frequency and exercise time. Primary safety outcomes included major adverse cardiovascular events such as myocardial infarction (MI), stroke and death.
Results: Three eligible randomized trials including 269 patients (placebo = 90, CD34+ = 179) were included. Dose of auto-CD34+ cells ranged from 5×10^4 to 5×10^5 cells/kg. Follow-up ranged from 6 to 24 months. In a pooled analysis, administration of CD34+ cells decreased the risk of all-cause mortality [OR 0.24, 95% CI (0.08–0.73), p = 0.01], reduced angina frequency [mean difference −2.91, 95% CI (−4.57 to −1.25), p = 0.0006] and improved exercise time [mean difference 58.62 s, 95% CI (21.19 to 96.06), p = 0.02] compared with control group. However, there was no significant difference in the risk of myocardial infarction (MI) and stroke between groups.
Conclusion: In a meta-analysis, intra-myocardial CD34+ cell therapy was superior to placebo in improving risk of all – cause mortality, angina frequency with an increase in exercise time, without a significant increase in adverse events. This analysis supports further trials of CD34+ cell therapy for ischemic heart disease.

1. Introduction

Over 850,000 patients in the US suffer from refractory angina [1, 2]. Currently, there are limited therapeutic options for these patients and their disabling symptoms have a significant impact on their quality of life [3]. Recently, the role of coronary microcirculation has been proposed as a critical pathophysiological pathway in refractory angina and novel strategies directed towards restoring myocardial microcirculatory function have evolved [4, 5]. Preclinical studies support cell-based therapy as a promising option for improving myocardial revascularization and cardiac regeneration [6]. Intramyocardial injection of human CD34+ cells is one method of delivery of cell-based therapy and this strategy has shown improved outcomes in "no-option" patients with chronic refractory angina not responsive to standard medical therapy or amenable to revascularization [7–10]. However, prior studies included a limited number of patients with wide variation in measured clinical end points. Recently, some meta-analyses of stem cell therapy for refractory angina have already been conducted [11, 12], one specifically evaluated the role of autologous CD34+ cells as a therapeutic option for refractory angina [13]. The objective of this study was to perform a systematic review and meta-analysis of studies to evaluate the effect of CD34+ cell therapy in patients with refractory angina.

2. Methods

2.1. Search strategy

We searched MEDLINE, EBSCO, Cochrane Register of Controlled Trials, Google Scholar, Web of Science and various scientific conference sessions for published material until April 1, 2017. We used the search

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terms – 'Refractory angina'; 'CD34+ cells'; 'Stem cells' and 'Angiogenesis' to identify all studies comparing autologous CD34+ cells vs. placebo for refractory angina. A manual search was performed in google and other major search databases such as heart.org, Medscape and Researchgate.com to identify relevant studies comparing CD34+ cells vs. placebo in refractory angina.

2.2. Study selection

Studies that met the following criteria were included: [1] enrolled patients ≥18 years of age with chronic refractory angina despite optimal medical management; [2] randomized controlled trials that compared autologous CD34+ cells vs placebo; and [3] had at least 1-month of follow-up. Our literature search was limited to English language studies published in peer-reviewed journals. We excluded studies that were performed in animal models and those that were published in foreign languages or non-peer-reviewed journals.

2.3. Data extraction and quality appraisal

Two investigators (P.V. and M.T.) independently searched for eligible studies. Any differences were reconciled by mutual consensus. The data was extracted in a standard format.

2.4. Outcomes

The primary efficacy outcome was change in angina frequency and exercise time. The primary safety outcome included major adverse cardiovascular events such as MI, stroke and death.

2.5. Statistical analysis

The results of each outcome were expressed as summary estimates of odds ratio (OR) and 95% confidence intervals (CIs). The odds ratio (OR) estimate of each study was calculated by the random-effects model using the DerSimonian and Laird method [14]. Heterogeneity of effects among studies was estimated by Higgins I – squared (I^2) test [15]. Study heterogeneity of $I^2 > 50\%$ was considered significant. $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using Cochrane RevMan version 5.3.

3. Results

3.1. Search Results

A total of 2754 references were identified. After a detailed evaluation of the title, abstract and application of inclusion and exclusion criteria,

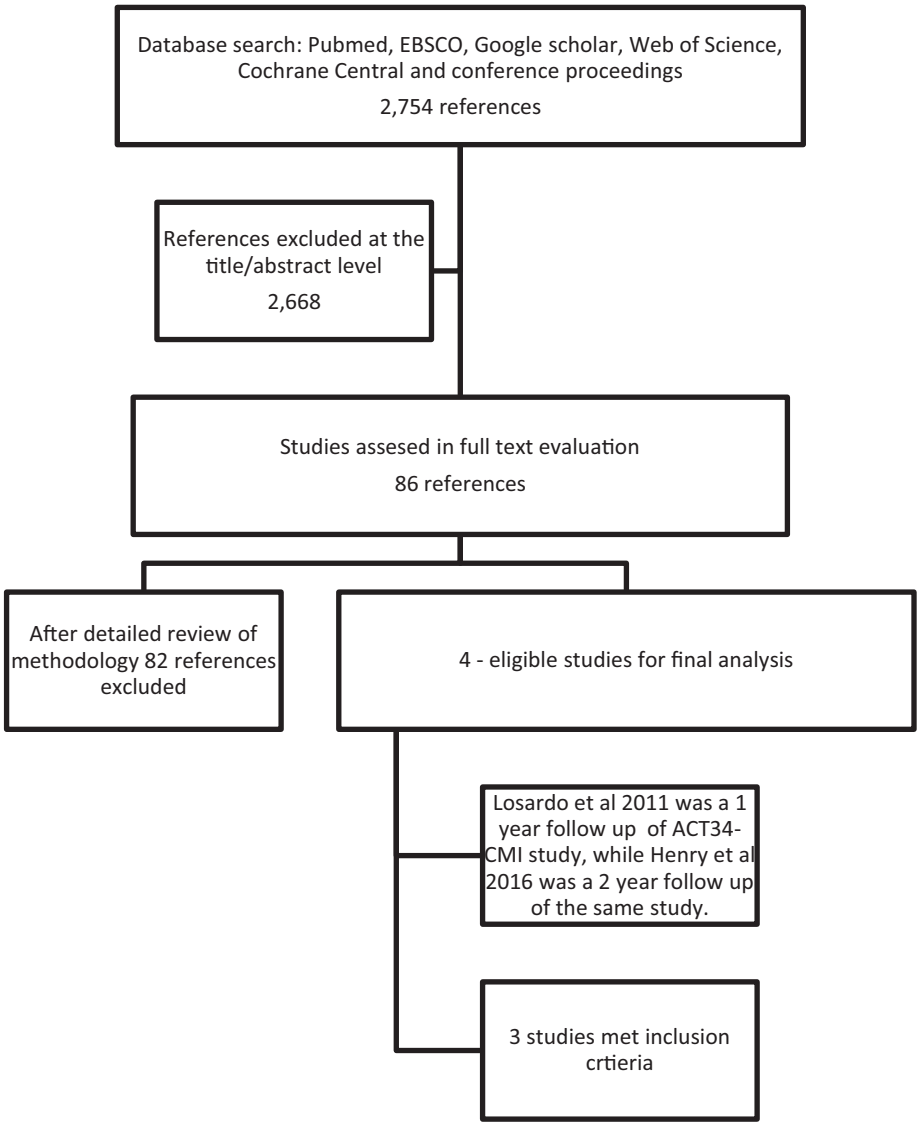

Fig. 1. Flow diagram for the included studies.

Table 1
Characteristics of the various studies included in the meta-analysis.

Study	N	Study design	Previous CABG (%)	Previous PCI (%)	Study groups CD34+ vs. placebo	Follow-up	Age mean ± SD (years)
Losordo 2007 [8]	24	Prospective double blind RCT	87.5	87.5	5×10^4 cells/kg vs. placebo 1×10^5 cells/kg vs. placebo 5×10^5 cells/kg vs. placebo	6 months	62.4 (range, 48 to 84)
Losordo 2011 (1 year follow up of ACT34-CMI study) [7]	167	Prospective double blind RCT	93	83	1×10^5 cells/kg vs. placebo 5×10^5 cells/kg vs. placebo	12 months	61 ± 8.9
Renew 2016 [10]	78	Prospective double blind RCT	87	91	1×10^5 cell/kg up to 1×10^7 cells/kg vs. placebo	24 months	64 ± 8
Henry 2016 (2 year follow up of ACT34-CMI study) [9]	167	Prospective double blind RCT	93.9	83.8	1×10^5 cell/kg and 5×10^5 cells/kg vs. placebo	24 months	60.9 (range, 41 to 91)

we included a total of 3 studies comparing intramyocardial delivery of CD34+ cells versus placebo for refractory angina (Fig. 1). The years of publication ranged from 2007 to 2016 (Table 1). The manuscript by Losardo et al. 2011 reported a 1 year analysis of ACT34-CMI study while Henry et al. reported a 2 year follow up of the same number of patients. We used the reported data from Henry et al. 2016 for our clinical outcomes and from Losardo et al. 2011 for outcomes not reported in the 2 year follow up. We made sure that data did not overlap between these two studies in our analysis.

3.2. Study characteristics

Table 1 summarizes the characteristics of included studies. Baseline characteristics, procedural details and patient follow up were similar between groups. A total of 269 patients (placebo = 90, CD34+ cells = 179) were included. The dose of autologous-CD34+ cells ranged from 5×10^4 to 5×10^5 cells/kg.

3.3. Outcomes

In patients with refractory angina, administration of CD34+ cells was associated with a significantly lower frequency of angina (Mean Difference (MD) −2.91; 95% CI: −4.57 to −1.25, p = 0.0006) (Fig. 2) and higher exercise time compared with placebo (Fig. 3). Table 2 reports the major adverse cardiovascular events including death, MI, stroke and cardiac hospitalization. The risk of MI (OR 0.77, 95% CI: 0.36–1.63, p = 0.49) or stroke (OR 0.50, 95% CI 0.08–3.06, p = 0.45) did not differ between the CD34+ cell and placebo groups (Figs. 4, 5). All-cause mortality was significantly lower in patients treated with CD34+ cells compared with placebo (OR 0.24, 95% CI: 0.08–0.73, p = 0.01) (Fig. 6).

3.4. Test of heterogeneity and publication bias

There was no significant heterogeneity for all – cause mortality (*P*-heterogeneity = 0.62, I^2 = 0%), exercise time (*P*-heterogeneity = 0.6, I^2 = 0%) or MI (*P*-heterogeneity = 0.78, I^2 = 0%). In contrast, a high degree of heterogeneity was seen for angina frequency (*P*-heterogeneity < 0.0001, I^2 = 94%).

4. Discussion

The main findings of our meta-analysis of RCTs comparing intramyocardial autologous CD34+ cells vs placebo for refractory angina are that [1] there was significant difference between patients treated with CD34+ cells versus placebo with respect to mortality, angina frequency and exercise time; [2] Intramyocardial delivery of autologous CD34+ cells is a safe strategy in selected patients with refractory angina with no evidence of an increased risk of adverse events such as MI or stroke. These results provide strong evidence supporting a beneficial effect of intramyocardial delivery of autologous CD34+ cell-based therapy in refractory angina and a rationale for larger, definitive RCTs.

Our meta-analysis showed significantly lower angina frequency and improved exercise time with intramyocardial autologous CD34+ cell therapy compared to placebo in refractory angina. These results are

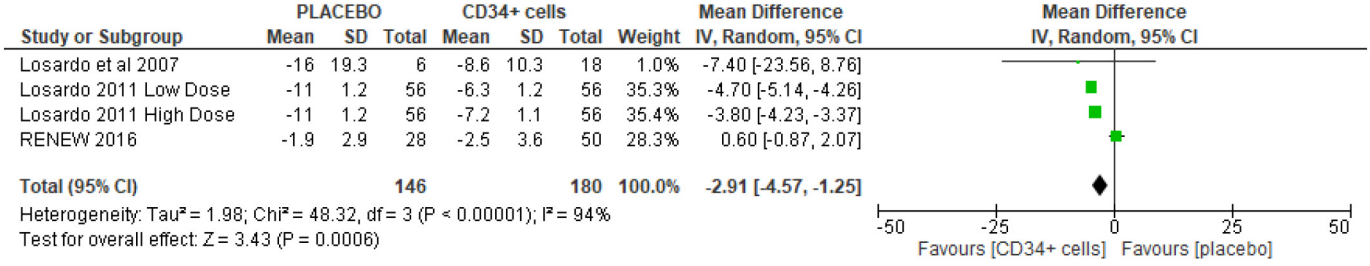

Fig. 2. Forest plot showing odds ratio (OR) of angina frequency with autologous CD34+ cells versus placebo for patients with refractory angina at follow-up. M-H: Mantel-Haenszel.

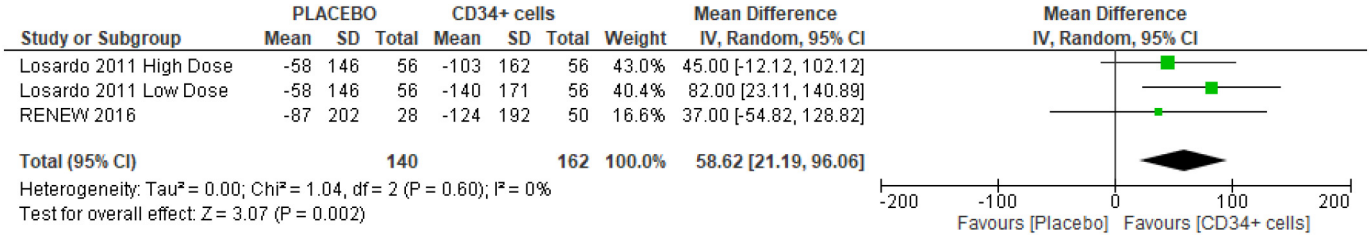

Fig. 3. Forest plot showing odds ratio (OR) of exercise time with autologous CD34+ cells versus placebo for patients with refractory angina. M-H: Mantel-Haenszel.

Table 2
Major complications reported in all the studies included in the meta-analysis.

Study ID	CD34+	Control
Losordo 2007 [8]	- Death – 0 - MI – 0 - Stroke – 1 (5×10^5 cells/kg)	- Death – 0 - MI – 0 - Stroke – 0
Losordo 2011 (1 year follow up of ACT34-CMI study) [7]	- Death – 0 - MI – 6 (3 in low dose; 3 in high dose) - Stroke – 2 (high dose) - Cardiac hospitalization/ER visits – 34 (16 in low dose, 18 in high dose)	- Death – 3 - MI – 7 - Stroke – 1
Henry 2016 (2 year follow up of ACT34-CMI study) [9]	- Death – 3 (1 in low dose, 2 in high dose) - MI – 15 (9 in low dose, 6 in high dose) - Stroke – 5 (2 in low dose, 3 in high dose)	- Death – 7 - MI – 10 - Stroke – 1
Renew 2016 [10]	- Death – 2 - MI – 2 - Stroke – 0 - Cardiac hospitalization – 21	- Death – 3 - MI – 3 - Stroke – 0 - Cardiac hospitalization – 9

consistent with prior data from Phase II and Phase III clinical trials showing a significant improvement in symptoms and exercise capacity in patients with refractory angina not amenable to percutaneous coronary intervention [7–9]. Another recent met-analysis by the same authors demonstrated similar findings to ours [13]. Our pooled analysis supports the earlier findings and provides an independent assessment regarding the favourable effects of CD34+ cells in refractory angina. The mechanism for angina reduction remains unclear. Preclinical data suggest that CD34+ cells restore the microcirculation and improve myocardial tissue perfusion [16]. Additional evidence has suggested that CD34+ cells are involved in neovascularization of the myocardium via paracrine effects in the ischemic myocardium [17] although the exact mechanism of action cannot be determined from our study. There were also some differences between studies with respect to obtaining an accurate assessment of angina frequency. In addition, early termination of the RENEW trial could have some implications regarding active patient engagement and accurate capture of angina symptoms and exercise capacity [10].

There were no significant differences in safety outcomes of MI and stroke between the two groups. The major concerns with intramyocardial autologous CD34+ cell therapy were related to cell procurement and administration. Complications such as cardiac perforation during intramyocardial administration and MI during cell mobilization are possible. Based on our results there appears to be no increased risk of clinically determined MI or stroke in these patients. However, the application of imaging modalities such as myocardial perfusion imaging, cardiac positron emission tomography and cardiac magnetic resonance imaging in assessing myocardial damage from the administration of CD34+ cells remains investigational. Furthermore, technological advances and increasing operator experience will result in substantial reduction in procedure related complications from intramyocardial injection of autologous CD34+ cells. Our results on the beneficial effect of autologous CD34+ cells are in line with prior meta-analyses demonstrating a beneficial effect of other types of stem cells used for cell therapy in refractory angina [11, 12].

4.1. Test of heterogeneity

In our analysis, the test for heterogeneity was significant for angina frequency although we suspect that variation in the definition and data collection methods of angina frequency was the likely reason for the observed heterogeneity among the studies. It can be speculated that confounding factors such as underlying coronary anatomy, culprit vessel involved, reason the patient was deemed non-revascularizable

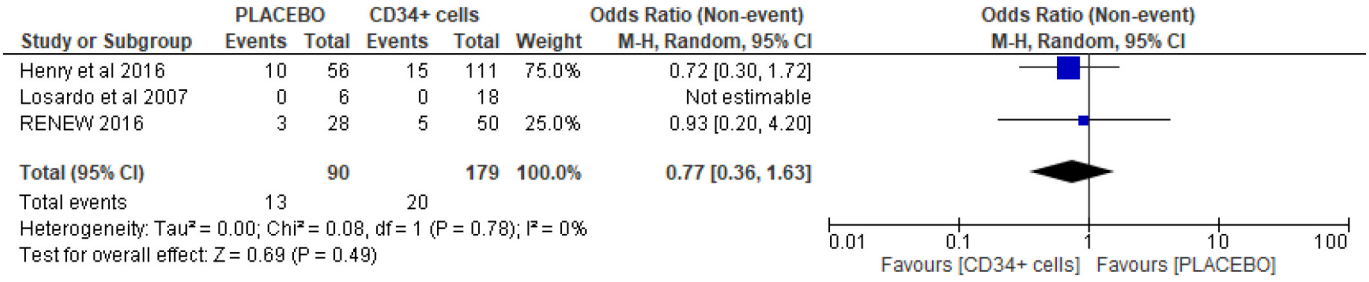

Fig. 4. Forest plot showing odds ratio (OR) of MI with autologous CD34+ cells versus placebo for patients with refractory angina. M-H: Mantel-Haenszel.

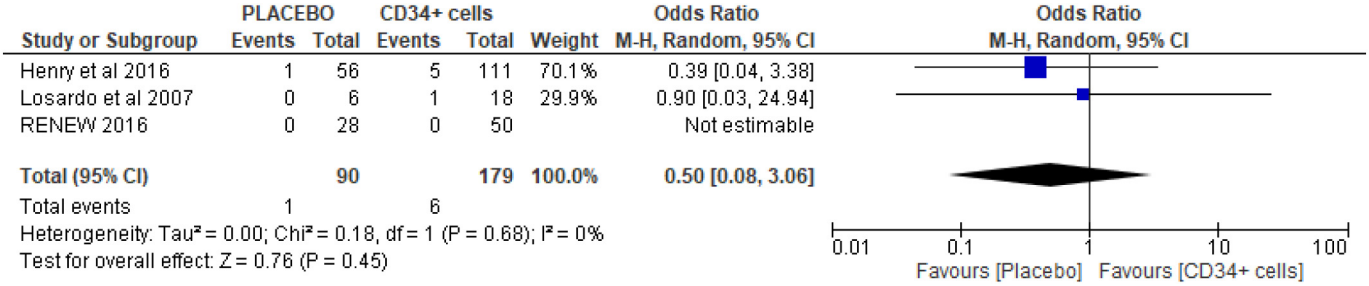

Fig. 5. Forest plot showing odds ratio (OR) of stroke with autologous CD34+ cells versus placebo for patients with refractory angina. M-H: Mantel-Haenszel.

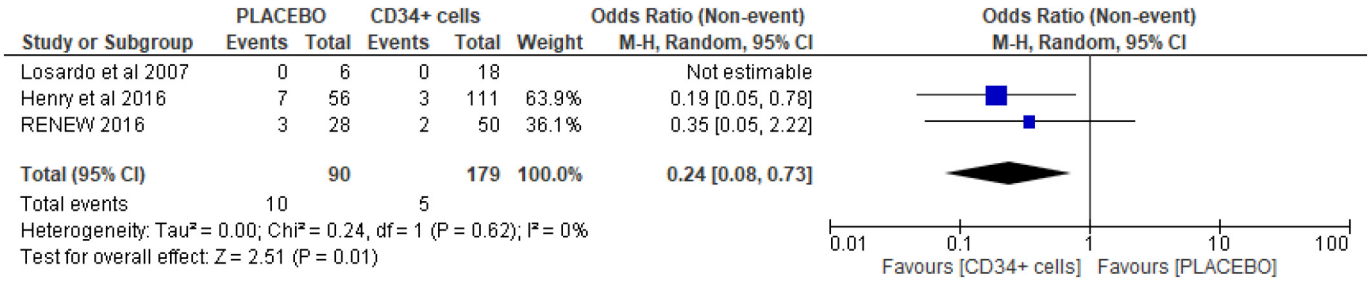

Fig. 6. Forest plot showing Odds Ratio (OR) of all cause mortality with autologous CD34+ cells or placebo for patients with refractory angina at follow-up. M-H: Mantel-Haenszel.

and extent of potential microcirculatory restoration or neovascularization may play a role.

4.2. Study limitations

The study has some potential limitations. First, our meta-analysis did not include individual patient-level data. Second, we cannot exclude the existence of potential unmeasured confounding factors due to multiple dosing regimens, cell isolation protocols, cell delivery methods, and definition of successful outcome. Third, the included studies had limited follow up and we cannot exclude the possibility that its effects may diminish over a longer follow-up period. Despite these limitations, our meta-analysis including randomized controlled trials provides valuable insight into the safety and efficacy of CD34+ autologous stem cells in refractory angina.

5. Conclusion

Overall, our meta-analysis clarifies that intramyocardial delivery of autologous CD34+ cells in patients with refractory angina is effective in reducing angina frequency and increasing exercise time. These benefits occur without an increased risk of adverse events such as all-cause mortality, stroke and MI. Further studies are required to evaluate the impact of this strategy on longer term safety and efficacy endpoints as well as cardiovascular hospitalization, quality of life, and health care costs.

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