STEM CELLS TRANSLATIONAL MEDICINE

HUMAN CLINICAL ARTICLE

Safety and Efficacy of Adult Stem Cell Therapy for Acute Myocardial Infarction and Ischemic Heart Failure (SafeCell Heart): A Systematic Review and Meta-Analysis

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ABSTRACT

Preclinical and clinical evidence suggests that mesenchymal stem cells (MSCs) may be beneficial in treating both acute myocardial infarction (AMI) and ischemic heart failure (IHF). However, the safety profile and efficacy of MSC therapy is not well-known. We conducted a systematic review of clinical trials that evaluated the safety or efficacy of MSCs for AMI or IHF. Embase, PubMed/Medline, and Cochrane Central Register of Controlled Trials were searched from inception to September 27, 2017. Studies that examined the use of MSCs administered to adults with AMI or IHF were eligible. The Cochrane risk of bias tool was used to assess bias of included studies. The primary outcome was safety assessed by adverse events and the secondary outcome was efficacy which was assessed by mortality and left ventricular ejection fraction (LVEF). A total of 668 citations were reviewed and 23 studies met eligibility criteria. Of these, 11 studies evaluated AMI and 12 studies evaluated IHF. There was no association between MSCs and acute adverse events. There was a significant improvement in overall LVEF in patients who received MSCs (SMD 0.73, 95% CI 0.24–1.21). No significant difference in mortality was noted (Peto OR 0.68, 95% CI 0.38–1.22). Results from our systematic review suggest that MSC therapy for ischemic heart disease appears to be safe. There is a need for a well-designed adequately powered randomized control trial (with rigorous adverse event reporting and evaluations of cardiac function) to further establish a clear risk-benefit profile of MSCs.

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SIGNIFICANCE STATEMENT

This study provides a comprehensive evaluation of the safety and efficacy of mesenchymal stem cell therapy for acute myocardial infarction and ischemic heart disease. Results from this systematic review suggest that this cellular therapy may be safe. A well-designed, adequately powered randomized controlled trial with rigorous adverse event reporting and comprehensive assessment of cardiac function is warranted. This will help establish a definitive risk-benefit profile of mesenchymal stromal cell therapy for ischemic heart disease.

INTRODUCTION

Despite major advances in the management of ischemic heart disease, it remains a leading cause of morbidity and mortality worldwide [1]. There has been interest in applying cellular therapy to restore cardiac function in ischemic heart disease. One cell type of interest is mesenchymal stem cells (MSCs, adult stem cells), which are a heterogenous population of pericytes that contribute to vascular homeostasis. When MSCs are expanded ex vivo and administered as a therapy, they act via a myriad of paracrine pathways to suppress inflammation and promote organ protection [2–4]. Moreover, MSCs can improve energetics by transferring mitochondria [5, 6]. MSCs are potent modulators of the immune system that suppress white blood cells and trigger anti-inflammatory responses; this may be especially effective in pro-inflammatory diseases [7, 8].

Previous highly cited clinical systematic reviews have suggested that cell therapy has no efficacy for ischemic heart disease [9, 10]. Of note, the results of these reviews have been driven predominantly by large clinical trials using

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autologous bone marrow mononuclear cells. Given that preclinical meta-analysis has suggested that MSCs may be more efficacious than other cell types in treating models of ischemic heart disease [11], a methodologically rigorous clinical systematic review focused on MSC therapy is needed. In addition, potential questions surrounding the safety of cellular therapy in this vulnerable population still remain (e.g., embolic phenomena) [12]. Therefore, the aim of this systematic review is to evaluate the safety and efficacy of MSC therapies in patients with ischemic heart disease, specifically acute myocardial infarction (AMI) and ischemic heart failure (IHF). This review will help inform future clinical trials of MSC therapy for ischemic heart disease.

Methods

The protocol for this review was prospectively registered with the PROSPERO database of systematic reviews (CRD420160 43540). The protocol was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol checklist, and the final report was prepared in accordance with the PRISMA checklist (Supporting Information Appendix 10) [13].

Search Strategy

Search strategies were developed in consultation with an information specialist (Supporting Information Appendix 1), and underwent a Peer Review of Electronic Search Strategy [14] (Supporting Information Appendix 2). Searches were performed in the following databases: Embase, PubMed/Medline, and Cochrane Central Register of Controlled Trials, from inception to September 27, 2017. ClinicalTrials.gov was searched for recently completed trials. We did not impose any language restrictions on our search. Reference lists of relevant reviews were searched for eligible articles.

Eligibility Criteria

We included interventional (controlled and noncontrolled, randomized and nonrandomized) and observational (cohort with contemporary or historical comparison group) studies that examined the safety and/or efficacy of MSCs administered to adults with AMI or IHF. Patients with cardiac diseases of nonischemic etiology were excluded, as well as nonadult participants and preclinical studies. MSCs were defined using the criteria outlined by the International Society for Cellular Therapy [15] as a general guide: (1) adherence to plastic, (2) specific antigen expression profile (i.e., CD105 (+), CD45 (−), HLA-DR (−), etc.), and (3) in vitro differentiation potential to osteoblasts, adipocytes, and chondroblasts. We excluded studies which treated patients with differentiated MSCs, other cell types or therapies, and MSCs engineered to alter the expression of particular genes (other than those used for imaging purposes). Depending on the study type, the patients receiving MSCs were compared to those receiving standard treatment for the management of AMI and IHF or placebo.

Outcome Measures

The primary outcome of our study was safety, which was assessed based on the frequency of adverse events (AE). AEs were grouped according to the timing of the event (i.e., acute events occurring <24 hours and delayed events occurring >24 hours post treatment) and the organ system affected (i.e., cardiovascular, pulmonary, gastrointestinal, renal, and neurological). Our secondary outcomes focused on the efficacy of MSC therapy evaluated using mortality and changes in left ventricular ejection fraction (LVEF). LVEF at the latest outcome window reported was used for analysis. In several studies cardiac function was measured by more than one modality; however, we only included one modality per study for the analysis of the LVEF outcome. The modality was chosen a priori based on a hierarchy of LVEF modalities, established by expert opinion of cardiologists on our review team (PJD, DJS), from most to least accurate: magnetic resonance imaging (MRI), echocardiogram with contrast, regular echocardiogram and radionuclide angiography scan, sestamibi scan, and cardiac catheterization. A number of tertiary outcomes that were measured at the latest follow-up were assessed. These outcomes included health-related quality of life (QoL), performance status (i.e., New York Heart Association Functional Classification), and other indices of cardiac function, including wall motion score, end-systolic and diastolic volume, stroke volume index, myocardial perfusion, and major adverse cardiac events (MACE).

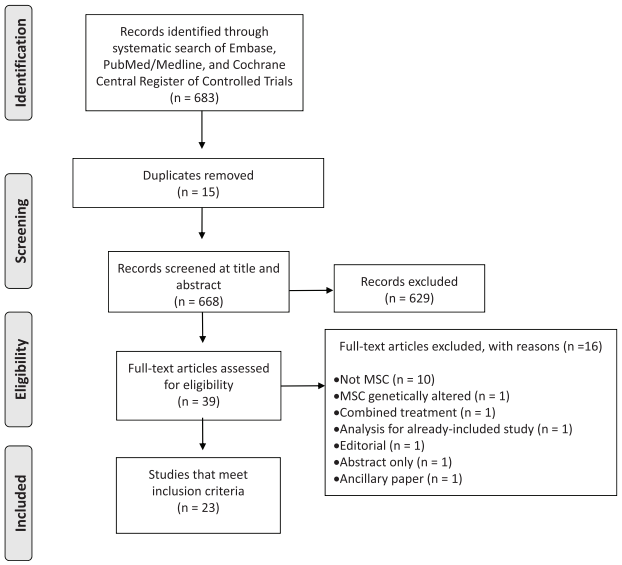

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process.

Study Selection Process

After collating citations identified by our literature search, all duplicate studies were removed. Titles and abstracts were screened for inclusion by four independent reviewers (J.Z., Y.D., S.M., and J.M.). Titles and abstracts deemed potentially relevant were recorded and the full text articles were obtained. Two independent reviewers screened the full articles to assess final eligibility, with disagreements settled by consultation with a senior team member (M.M.L.) to achieve consensus. The study selection process was documented and reported using a flow diagram as recommended by the PRISMA (Figure 1).

Data Collection

Data abstraction was performed by four independent reviewers (J.Z., Y.D., S.M., and J.M.) using standardized forms created in DistillerSR (Evidence Partners, Ottawa, ON). Reviewers discussed discrepancies and if consensus could not be reached, a senior team member (M.M.L.) made a final decision. Each reviewer independently documented publication characteristics (i.e., year of publication, journal, and

corresponding author), study populations (i.e., eligibility criteria, age, gender, and comorbidities), intervention details (i.e., type, route, condition, timing, dose, and volume), study designs (methods, setting, sample size, and number of centers), and clinical endpoints (i.e., AEs and efficacy outcomes). In the case of missing or unclear data for the primary or secondary outcome measures, an attempt was made to contact the primary study author for clarification.

Risk of Bias

All studies that met inclusion criteria were assessed for risk of bias according to the Cochrane Risk of Bias Tool for randomized control trials in duplicate by independent reviewers (J.Z., Y.D., S.M., and J.M.) [16, 17]. Publication bias was evaluated with funnel plots.

Statistical Analysis

Studies were pooled using Comprehensive Meta-Analysis (version 3; Biostat Inc., USA). For dichotomous safety and efficacy outcomes, fixed-effects Peto odds ratios were calculated and presented with accompanying 95% confidence intervals [18]. Peto odds ratios were used due to the expected rarity of events. This method allows for this inclusion of continuity corrections of 0.5 for all zero cells across outcomes, allowing us to estimate odds ratios for studies reporting no events in a treatment arm. For continuous outcomes, standardized mean differences were calculated using a random effects inverse-variance model and presented with accompanying 95% confidence intervals. Standardized mean differences were used due to the variety of measurement methods used for the outcomes of interest (i.e., LVEF, left ventricular end systolic volume [LVESV], left ventricular end diastolic volume [LVEDV]). A post hoc analysis was also done using a weighted mean difference. Results reported at the latest outcome window were used for analysis. Studies which did not provide data in a format suitable for inclusion in a meta-analysis (i.e., no control group) were analyzed descriptively.

Statistical heterogeneity was assessed using the I^2 statistic, or the Cochrane Q test, depending on the analysis method. An I^2 value of >50% was judged as representing important heterogeneity requiring further exploration. For the Cochrane Q test, a p value of <.10 was deemed to indicate substantial heterogeneity. Publication bias was assessed via funnel plots. We also conducted exploratory subgroup analyses to determine whether the efficacy of the MSCs varied by disease type (AMI vs. IHF), study design (randomized control trial [RCT] vs. non-RCT), MSC source (bone marrow or umbilical cord), MSC route of administration, immunocompatability of MSCs (allogeneic vs. autologous origin), and timing of MSC administration.

RESULTS

The literature search identified 668 unique citations. Abstract and full-text screening identified 23 studies (1,148 patients) to be included for data extraction (Figure 1). Reasons for full-text study exclusion are presented in Figure 1.

Study Characteristics

Of the 23 included studies, 11 evaluated AMI (n = 509 patients) [19–29] and 12 evaluated IHF (n = 639 patients) [12, 30–40] (Table 1). Of these studies, eight were RCTs that evaluated AMI (n = 429 patients) [19–21, 23, 24, 27, 29] and five were RCTs that evaluated IHF (n = 472 patients) [30, 34, 36, 37, 39, 40]. The number of evaluated patients who received MSCs ranged from 9 to 58 patients for the AMI studies and from 6 to 107 patients for the IHF studies. Follow-up duration ranged from 6 to 60 months. Of the studies evaluating AMI, seven studies specified safety [20, 22, 23, 25, 26, 28, 29] and four studies specified efficacy [19, 21, 24, 27] as their primary outcome. Secondary outcomes assessed included safety [21, 24] or efficacy [20, 22–24, 26]. Of the IHF studies, four studies evaluated safety [31, 34, 35], four studies evaluated efficacy [30, 34, 37, 40], and four studies evaluated both [12, 36, 38, 39] as the primary outcome. Secondary outcomes assessed included efficacy [31, 32, 34, 35] or both efficacy and safety [37].

Intervention Characteristics

Of the 11 studies evaluating AMI, 7 studies used autologous MSCs [19, 21, 24, 26–29] and 4 studies used allogeneic MSCs [20, 22, 23, 25] (Table 2). Of the 12 studies evaluating IHF, 9 studies used autologous MSCs [12, 30, 31, 34, 36–39] and 3 studies used allogeneic MSCs [32, 35, 40]. The majority of studies (18/23) used bone-marrow derived MSCs [12, 19–21, 23, 24, 26–28, 30–32, 34, 36–39, 41] and the remaining used either MSCs that were umbilical cord-derived (4/23) [22, 25, 35, 40] or adipose tissue-derived (1/23) [29]. Comparisons consisted of standard treatment (5/23) [12, 21, 24, 38, 40], saline (4/23) [19, 27, 37, 39], heparinized saline (1/23) [22], historical control (1/23) [26], vehicle placebo (3/23) [23, 29, 34], sham procedure (1/23) [30], plasmalyte A (1/23) [20], or the study did not include a comparison group (5/23) (Table 2) [25, 28, 31, 35, 36]. One study compared allogeneic MSCs to autologous MSCs and did not use a control group [32]. The number of allogeneic donors were reported in four studies [20, 22, 23, 32], while three studies [25, 35, 40] did not report this information.

The routes of MSC administration were intracoronary (12/23) [12, 19, 21, 22, 24, 25, 27–29, 35, 39, 40], intravenous (3/23) [20, 23, 31], and intramyocardial (4/23) [26, 30, 36, 37]. Studies evaluating IHF also included endocardial (2/23) [32, 33] and epicardial (2/23) [34, 38] routes of administration. Timing of MSCs administration for studies evaluating treatment for AMI ranged from 24 hours to 27 days after percutaneous coronary intervention (PCI) for AMI studies or during/after coronary artery bypass grafting (CABG) in IHF studies [34, 38]. MSC doses ranged from 1 dose of 2×10^6 cells/kg to 10×10^9 cells/kg and 3×10^6 cell/kg to 2×10^8 cells/kg for AMI and IHF studies, respectively. Details on cell manufacturing and characterization are reported in Supporting Information Appendix 3.

Primary Outcome—Safety

Acute Adverse Events (<24 hours)

In AMI and IHF studies, acute cardiac AEs were not significantly different between MSC (7/292) and comparison (0/128) groups (Peto OR 3.20, 95% CI 0.70–14.61) (Table 3). Specific acute AEs that occurred in the MSC group included arrhythmias (n = 3 events), MI (n = 2 events), vessel obstruction during procedure (n = 1 event), and pericardial effusion (n = 1 event). Treatment attributable acute AEs (i.e., events deemed by study investigators to be caused by MSC therapy) were

Table 1. Study characteristics

Author (year)	Study type	Patients included (*n* analyzed)	Patients evaluated (*n* [% male])		Follow-up duration (months)
			T	C	
Acute myocardial infarction					
Chen (2004) (China)	RCT	69	34 (94)	35 (97)	6
Chullikana (2015) (India)	RCT	20 (safety) 19 (efficacy)	10 (100)	10 (80)	24
Gao (2013) (China)	RCT	43	21 (100)	22 (86)	24
Gao (2015) (China)	RCT	115	58 (95)	58 (88)	18
Hare (2009) (USA)	RCT	53	34 (82)	19 (79)	6
Houtgraaf (2012) (Netherlands)	RCT	13	9 (69)	4 (31)	6
Lee (2014) (South Korea)	RCT	58	30 (90)	28 (89)	6
Musialek (2015) (Poland)	Single-arm	10	10 (50)		12
Rodrigo (2013) (Netherlands)	Historical control	54	9 (78)	45 (78)	60
Wang (2014) (China)	RCT	58	28 (68)	30 (53)	6
Yang (2010) (China)	Single-arm	16	16 (NR)		6
Ischemic heart failure					
Bartunek (2017) (Belgium)	RCT	271	107 (89)	136 (90)	10
Chen (2006) (China)	NRCT	45	22 (88)	23 (92)	12
Guijarro (2016) (France)	Single-arm	10	10 (90)		12
Hare (2012) (USA)	Non-controlled	30	15 (87)	15 (87)	13
Heldman (2014) (USA)	RCT	59	19 (95)	11 (91)	12
Karantalis (2014) (USA)	Single-arm	6	6 (100)		18
Li (2015) (China)	Single-arm	15	15 (60)		24
Mathiasen (2013) (Denmark)	Single-arm	31	31 (84)		36
Mathiasen (2015) (Denmark)	RCT	59	40 (90)	20 (70)	6
Viswanathan (2010) (India)	NRCT	30	15 (100)	15 (93)	6
Wang (2006) (China)	RCT	24	12 (75)	12 (67)	10
Zhao (2015) (China)	RCT	59	30 (80)	29 (66)	6

Abbreviations: C, control group; NR, not reported; NRCT, non-randomized controlled trial; RCT, randomized controlled trial; T, treatment group.

rarely reported and are outlined in Supporting Information Appendix 5, Table 5a.

Delayed Adverse Events (≥24 hours)

All-cause delayed AEs included fever, respiratory, cardiac, hematological, gastrointestinal, renal, infections (only one study specified type of infection [respiratory [22]]), malignancy/cancer, and other events (Table 3). Other delayed AEs reported included events associated with administration site reaction, metabolic, musculoskeletal, skin, vascular, eye, surgical procedures, and the immune system (Table 3). There was a statistically significant difference in neurological events between MSC (17/303) and comparison (4/259) groups (Peto OR 3.79, 95% CI 1.26–11.41). Details on the type and severity of neurological AEs were not reported. Treatment attributable delayed AEs occurred infrequently and are outlined in Supporting Information Appendix 5, Table 5b.

Secondary Outcomes—Efficacy

Mortality

A total of four AMI studies (36%, *n* = 236 patients) [20–22, 27] and six IHF studies (50%, *n* = 498 patients) [12, 30, 34, 37, 39, 40] reported on mortality. There was no overall significant difference in the risk of mortality between MSC and control groups (Peto OR 0.68, 95% CI 0.38–1.22). In our subgroup analysis by disease type, there was no significant difference in the AMI studies (Peto OR 0.53, 95% CI 0.10–2.64) or the IHF studies (Peto OR 0.71, 95% CI 0.38–1.32) (Figure 2).

Left Ventricular Ejection Fraction

A total of 10 AMI studies (*n* = 473 patients) [19–24, 26–29] and 5 IHF studies (*n* = 216 patients) [12, 34, 37, 39, 40] reported data on LVEF that could be included in the meta-analysis. Patients treated with MSCs had a significantly increased LVEF compared to control (SMD 0.72, 95% CI 0.24–1.21, I^2 = 88%) (Figure 3). Measurement methods of LVEF are included in Supporting Information Appendix 4. In a post hoc analysis using weighted mean difference, patients treated with MSCs had a 4% increase in ejection fraction compared to control (WMD 4.25, 95% CI 1.37–7.13, I^2 = 90%) (Supporting Information Appendix 6, Figure 6f).

LVEF Subgroup Analyses

In our planned exploratory subgroup analysis by disease type, there was a significant increase in LVEF in patients treated with MSCs for AMI compared to control (SMD 0.65; 95% CI 0.02–1.27, I^2 = 88%), but no difference for IHF patients (SMD 0.81, 95% CI −0.14 to 1.77, I^2 = 90%) (Figure 3). The positive significant increase associated with MSC therapy remained after extreme values from one study were removed [19] (SMD 0.40, 95% CI 0.03–0.77, I^2 = 67%).

LVEF increased significantly for allogeneic MSCs (SMD 0.98, 95% CI 0.18–1.79, I^2 = 86%); however, no significant difference in LVEF was observed in patients who had been administered

Table 2. Intervention characteristics

Author (year)	Source of MSCs	Comparison	MSCs Route, condition	Timing	Dosage and volume
Acute myocardial infarction					
Chen (2004)	Autologous	Saline	IC, Fresh	18 ± 0.5 days post-PCI	8–10 × 10^9,1 dose – NR
Chullikana (2015)	Allogeneic	Plasmalyte A	IV, Fresh from cryopreserved	2 days post-PCI	2 million cells/kg, 1 dose – 0.5 mL/kg
Gao (2013)	Autologous	Standard treatment	IC, Fresh	Post-PCI Mean 17 ± 1 days	3 ± 0.5 × $10^6$1 dose – 10 mL
Gao (2015)	Allogeneic	Heparanized saline	IC, Fresh	Within 5–7 days of PCI	6 × 10^6, 1 dose – 10 mL
Hare (2009)	Allogeneic	Placebo	IV, NR	Patients randomized 1–10 days post AMI	0.5, 1.6, 5 × 10^6 3 dose escalation cohorts - NR
Houtgraaf (2012)	Autologous	Placebo	IC, Fresh	24 hours post-PCI	17.4 ± 4.1 × 10^6 1 dose - NR
Lee (2014)	Autologous	Standard treatment	IC, Fresh	BM aspiration done 4 ± 2 days post-admission; culture took 25.0 ± 2 days	7 ± 1 × 10^7 1 dose - NR
Musialek (2015)	Allogeneic	No comparison	IC, Fresh from cyropreserved	Within 5–7 days of PCI	30 × 10^6 1 dose – 30 mL
Rodrigo (2013)	Autologous	Historical control	IM, Fresh	21 ± 3 days post-MI/PCI	31 ± 2 × 10^6 1 dose – 5 mL
Wang (2014)	Autologous	Saline	IC, Fresh	14 days post-PCI	2 × 10^8 1 dose – 2 mL
Yang (2010)	Autologous	No comparison	IC, Fresh	NR	1 ± 2 × 10^7 1 dose - NR
Ischemic heart failure					
Bartunek (2017)	Autologous	Sham procedure	IM, Frozen	NR	NR 1 dose – 0.5 mL
Chen (2006)	Autologous	Standard treatment	IC, Fresh	BM aspiration done 8 days post-PCI; culture for 7 days	5 × 10^6, 1 dose – NR
Guijarro (2016)	Autologous	No comparison	IV, Fresh	NR	40 × 10^6 1 dose – 2-3 mL
Hare (2012)	Allogeneic	Autologous	EC, NR	NR	0.2, 1, 2 × 10^8 3 dose cohorts – 5.0 mL each
Heldman (2014)	Autologous	Placebo	EC, Fresh from cyropreserved	During cardiac catheterization. Mean time since first MI is 10 ± 10 years.	2 × 10^8 1 dose – 5.0 mL
Karantalis (2014)	Autologous	Placebo	EP, Fresh from cyropreserved	Post-CABG; mean time between last MI and study enrollment was 675 days	2 × 10^7 or 2 × 10^8 1 dose – 5.0 mL
Li (2015)	Allogeneic	No comparison	IC, Fresh	NR	3, 4, or 5 × 10^6 1 dose – NR
Mathiasen (2013)	Autologous	No comparison	IM, unclear	NR	Mean 22 × 10^6 1 dose - NR
Mathiasen (2015)	Autologous	Saline	IM, Fresh	NR	Mean 78 ± 68 × 10^6 1 dose – 2–3 mL
Viswanathan (2010)	Autologous	Standard treatment	EP, Fresh from cryopreserved	During CABG; BM culture took 3–4 weeks	3 × 10^6 to 26 × 10^6 1 dose – 1 mL
Wang (2006)	Autologous	Saline	IC, Fresh	NR	NR 1 dose – 30 mL
Zhao (2015)	Allogeneic	Standard treatment	IC, unclear	NR	NR 1 dose – 20 mL

Dose is provided as reported by the study or the mean ± SD number of cells delivered to patients. Abbreviations: C, control groups; EC, endocardial; EP, epicardial; FBS, Fetal Bovine Serum; HSA, Human Serum Albumin; IC, intracoronary; IM, intramyocardial; IV, intravenous; MSCs, mesenchymal stromal cells; NR, not reported; NRCT, non-randomized controlled trial; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; T, treatment group.

autologous MSCs (SMD 0.60, 95% CI −0.02 to 1.22, I^2 = 89%) (Supporting Information Appendix 6, Figure 6a). MSCs from an umbilical cord source increased LVEF compared to control treatment (SMD 1.71, 95% CI 0.67–2.76, I^2 = 87%) (Supporting Information Appendix 6, Figure 6b). MSCs from either adipose tissue (SMD 1.03, 95% CI −0.21 to 2.27) or bone marrow (SMD 0.53, 95% CI 0.00–1.05, I^2 = 86%) did not increase LVEF compared to control.

With regard to administration route, MSCs increased LVEF when administered by intracoronary injection (SMD 0.81, 95% CI 0.14–1.47, I^2 = 91%) and intramyocardial injection (SMD 1.64, 95% CI 1.00–2.28). There was no statistically significant difference in LVEF when MSCs were given either epicardially (SMD 0.20, 95% CI −0.48 to 0.88) or intravenously (SMD 0.27, 95% CI −0.15 to 0.69, I^2 = 0%) (Supporting Information Appendix 6, Figure 6c). There

Table 3. Acute (<24 hours) and delayed (≥24 hours) adverse events

	Treatment (MSC)		Control		Peto OR (95% CI)
	Events	Total	Events	Total	<1 favors MSC
Acute adverse event (*n*)					
Fever (3)	0	42	0	12	0.22 (0.00–23.09)
Respiratory (3)	3	66	0	33	2.67 (0.32–21.82)
Cardiac (11)	7	292	0	128	3.20 (0.70–14.61)
Neurological (2)	1	19	0	19	2.79 (0.17–46.26)
Hematological (5)	0	85	0	12	0.04 (0.00–13.08)
GI (1)	0	30	–	–	n/a
Renal	–	–	–	–	n/a
Infection (3)	2	30	0	10	1.68 (0.12–23.50)
Allergic reaction (4)	0	68	0	12	0.08 (0.00–16.55)
Local complication (5)	0	93	0	29	0.25 (0.00–23.80)
Other (4)	2	109	0	58	2.25 (0.21–24.55)
Delayed adverse event (*n*)					
Fever (5)	7	68	3	27	0.92 (0.22–3.85)
Respiratory (6)	10	96	11	61	0.53 (0.21–1.33)
Cardiac (18)	95	503	58	394	1.35 (0.94–1.93)
Arrhythmia	33	377	17	237	1.24 (0.68–2.28)
CHF	17	150	6	85	1.68 (0.64–4.45)
MI	5	278	2	245	2.23 (0.43–11.57)
Biomarker	0	15	–	–	-
Other	40	402	33	321	0.96 (0.59–1.57)
Neurological (9)	17	303	4	259	3.79 (1.26–11.41)*
Hematological (9)	5	116	2	79	1.73 (0.33–9.17)
GI (5)	21	99	9	50	1.22 (0.52–2.84)
Renal (4)	7	80	1	36	2.52 (0.54–11.80)
Infection (7)	23	203	11	118	1.24 (0.59–2.58)
Malignancy/cancer (8)	1	235	1	147	0.61 (0.04–10.68)
Other (12)	39	74	18	29	0.68 (0.28–1.64)
Administration site reaction (3)	18	74	14	29	0.57 (0.25–1.33)
Metabolic (2)	3	40	1	10	0.72 (0.06–9.00)
Muscoskeletal (2)	6	40	1	10	1.50 (0.21–10.85)
Skin (2)	1	40	1	10	0.15 (0.00–4.89)
Vascular (2)	4	40	1	10	1.00 (0.10–9.84)
Eye (1)	1	30	–	–	n/a
Surgical procedures (1)	1	30	–	–	n/a
Injury, poisoning (1)	3	30	–	–	n/a
Immune system (1)	2	34	0	19	2.42 (0.22–26.61)

*$p < .05$; –, not reported; (), number of studies.

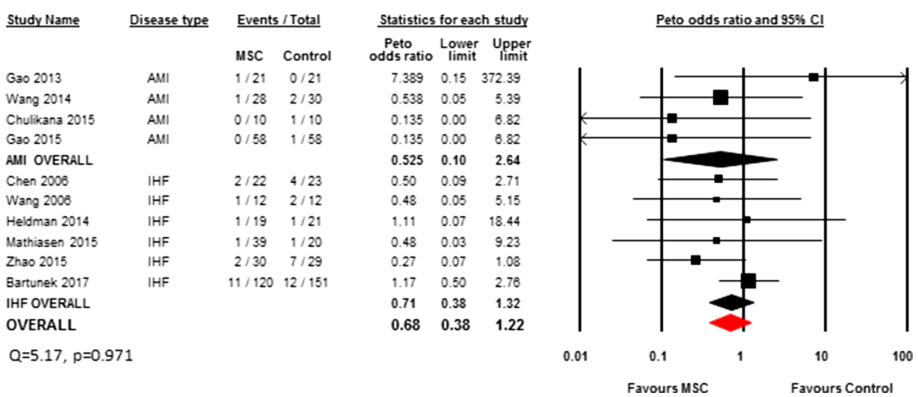

Figure 2. Peto odds ratio (95% CI) and pooled estimates for mortality.

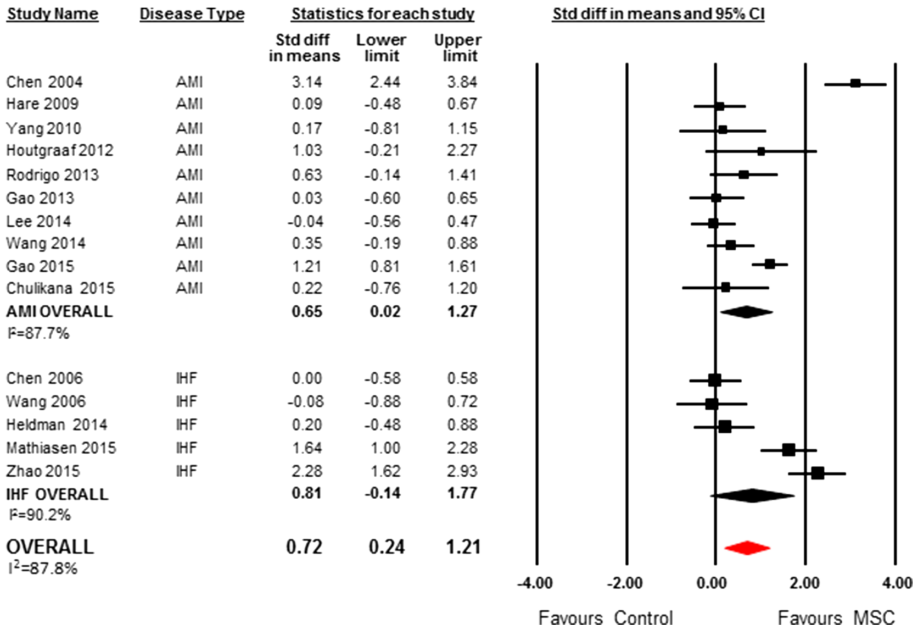

Figure 3. SMD (95% CI) and pooled estimates for left ventricular ejection fraction.

was a significant increase in LVEF reported in RCTs between MSC and control (SMD 0.84, 95% CI 0.26–1.41, I^2 = 89.6%), and no significant difference among non-RCTs (SMD 0.22, 95% CI −0.20 to 0.64, I^2 = 0%) (Supporting Information Appendix 6, Figure 6d).

There was no significant difference in the increase in LVEF whether MSCs were administered 1–10 days (SMD 0.55, 95% CI −0.03 to 1.13, I^2 = 71%) or more than 10 days (SMD 0.67, 95% CI −0.22 to 1.56, I^2 = 92%) after an AMI (Supporting Information Appendix 6, Figure 6e).

LVEF in Studies Not Suitable for Meta-Analysis

There was one study evaluating AMI that did not provide data suitable for a meta-analysis [29]. This study reported a 4% improvement (52.1%–56.1%) in global LVEF in MSC-treated patients compared to the placebo group which is deteriorated by 1.7% (52.0%–50.3%) at 6 month follow-up [29]. There were five studies evaluating IHF that did not provide data suitable for meta-analysis. One RCT showed a significant improvement in LVEF [30] while another did not [32]. One non-RCT showed a significant improvement in LVEF [38]. Two single-arm studies reported a significant improvement in LVEF from baseline to follow-up [31, 34].

Tertiary Outcomes

Quality of Life

No studies evaluating AMI reported on QoL outcomes. Three RCTs evaluating IHF reported no significant differences in QoL between MSCs and comparator. One RCT with two treatment arms but no control group [32] did not report a significant difference between treatment groups (autologous vs. allogeneic), but did report a significant improvement post-treatment versus baseline. The mean reduction in Minnesota Living with Heart Failure Questionnaire scores among both groups at 12 months was 7.6 (p = .02) [32]. Two single arm studies reported a significant improvement post-treatment [35, 36], while one single arm study did not show a significant improvement in QoL [31].

Performance Status

New York Heart Association Functional Classification: Two studies evaluating IHF evaluated New York Heart Association Functional Classification (Supporting Information Appendix 7, Figure 7a) [12, 37]. There was no difference in performance status between the MSC group and control (SMD −1.01, 95% CI −2.46 to 0.45, I^2 = 91%). Eight studies were not included in the meta-analysis. Of these, three evaluated AMI patients, one single arm study showed a significant improvement in performance status [28], while one RCT and single-arm study [37] did not. Of five studies evaluating IHF, three studies showed a significant improvement in performance status [12, 31, 35], while two studies did not [32, 34].

Walk test: Five studies reported the 6-minute walk test (Supporting Information Appendix 7, Figure 7b) [23, 33, 37, 39, 40]. Overall, there was a significant improvement in the 6-minute walk test between the MSC group and control for both AMI and IHF (SMD 1.16, 95% CI 0.26–2.06, I^2 = 89%). There was no significant difference in the 6-minute walk test for AMI (SMD 0.25, 95% CI −0.31 to 0.81). For IHF studies, a significant difference was observed (SMD 1.41, 95% CI 0.31–2.52, I^2 = 90%). One single arm study [31] evaluating IHF reported a significant improvement in the 6-minute walk test and one RCT [32] did not.

Other tertiary outcomes of LVEDV, LVESV, wall motion, myocardial perfusion, and MACEs are presented in Supporting Information Appendix 8a–e. Measurement methods are included in Supporting Information Appendix 4.

Risk of Bias Assessment

No study fulfilled all seven criteria for low risk of bias (Figure 4). Four studies met six of seven risk of bias criteria [20, 30, 34, 37]. Nine studies described randomization procedures with a low risk of bias [20–23, 30, 32, 34, 37, 39]. Allocation concealment was performed in five studies with low risk of bias [20, 23, 32, 34, 37]. Double-blinding procedures were described in five studies with low risk of bias [20, 22, 30, 34, 37]. One study was at high risk for

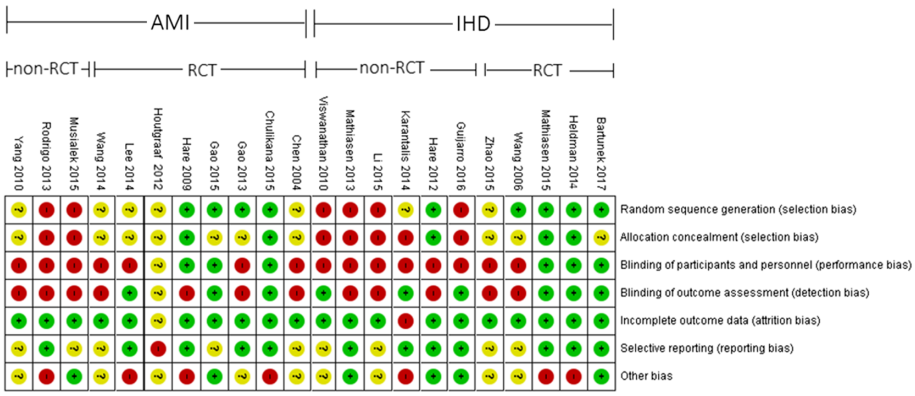

Figure 4. Risk of bias assessment.

incomplete outcome data reporting [34] and one study was at high risk for selective reporting [29]. Seven studies were deemed to be at a high risk of other biases [8, 20, 23, 24, 26, 33, 37]. Visually apparent asymmetry was present in the funnel plot of mortality (Supporting Information Appendix 9, Figure 9a) and LVEF (Supporting Information Appendix 9, Figure 9b) which might indicate that small studies produced bias in the random-effect model.

Discussion

Our systematic review evaluated the safety and efficacy of MSC therapy for IHF and AMI. Although the majority of studies reported AEs, the definitions and descriptions of these events were highly variable. Available evidence suggested that MSCs appeared to be largely safe in the studies that compared MSCs to a control group. The summary effect measures were marked by considerable heterogeneity; however, it appeared that MSCs improved LVEF but had no effect on mortality in the small number of studies conducted to date. Other outcomes of interest were rarely reported, limiting our conclusions.

We focused our review on carefully detailing AEs in this vulnerable population. Meta-analysis of the included studies with a control group did not detect a significant association between overall acute AEs and MSC administration. However, there was a significant increased risk for delayed neurological AEs with MSC therapy compared to control groups. The types of neurological AEs were not reported, limiting interpretation of this finding; however, it is possible that this could represent the consequences of microembolization within the cerebral microcirculation. Despite this effect, it should be noted that MSCs have demonstrated efficacy as therapy for serious neurological conditions, such as ischemic stroke [42]. The variable detail reported in AEs highlights the importance for future studies to completely document these elements (e.g., using recommended reporting guidelines such as the CONSORT harms extension) [43]. This will allow for a more precise profile of MSC related safety to be developed.

Patients receiving MSCs for AMI demonstrated an improvement in LVEF. Our sensitivity analyses demonstrated that even after the removal of the Chen et al. study [19], the effect of MSCs on LVEF remained. This improvement in LVEF for patients receiving MSCs is consistent with previous analyses of MSC therapy after PCIs [44, 45] and in stark contrast to previous highly cited systematic reviews of cell therapy for ischemic heart disease which demonstrated no effect [9, 10]. These latter reviews focused only on autologous cells and the results were driven by large trials of bone marrow mononuclear cells. Our review suggests that further optimization and evaluation of MSC therapy may be warranted in ischemic heart disease. Our review provides some suggestions for future trials, including the potentially increased efficacy of umbilical cord derived MSCs versus other sources, as well as potential increased efficacy of intracoronary or intramyocardial routes of administration versus other routes.

Also of potential relevance when considering future trials is the putative mechanism whereby MSCs are thought to act, which largely involves anti-inflammatory effects. This is reflected by its efficacy in acute graft-versus-host-disease [46], currently the only approved indication for MSC therapy. Thus, it is perhaps not surprising that MSCs had little effect in a chronic condition such as IHF which has a much lower level of inflammatory burden. Further supporting this anti-inflammatory indication is the single trial which administered MSCs immediately after AMI and demonstrated significant improvements in LVEF [29], as well as preclinical studies of MSCs that have demonstrated efficacy in very acute, largely perioperative and inflammatory settings [11].

Our study was able to identify several knowledge gaps. QoL and performance status were inconsistently reported and often lacked control data which limited our conclusions. The other tertiary outcomes (LVEDV, LVESV, wall motion, myocardial perfusion, and MACEs) were also infrequently reported. Future studies should include reporting of validated QoL assessments as well as detailed cardiac function reporting. Our systematic review also identified several issues with the MSC administration and cell product used in the included studies. For example, the criteria by Dominici et al. that defines MSCs were inconsistently reported. In addition, no study described assessments of cell potency prior to administration. We recommend that future studies enhance reporting and characterization of cell products used.

Our systematic review has limitations. First, there were a limited number of clinical MSC studies included, each with small sample size. Second, the majority of RCTs included in our analyses were deemed to be at a high risk of bias for several domains. Despite these limitations, we provide a comprehensive summary of MSC therapy for IHF and AMI, based on all available contemporary evidence.

Conclusion

Our study provides a comprehensive evaluation of the safety and efficacy of MSCs therapy for AMI and IHF. We did not identify any significant safety signals except delayed neurological events, which were poorly defined. Results from our systematic review suggest

that MSC therapy may be safe. A well-designed adequately powered RCT with rigorous AE reporting and comprehensive assessment of cardiac function is warranted. This will help establish a definitive risk-benefit profile of MSC therapy for ischemic heart disease.

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Author Contributions

M.L.: concept and design, data analysis and interpretation, manuscript writing, final approval of manuscript; S.M.: collection and assembly of data, data analysis and interpretation, manuscript writing; J.Z.: collection and assembly of data; R.(Y.Y.)D.: collection and assembly of data; J.M.: collection and assembly of data, data analysis and interpretation, manuscript writing; L.M.: concept and design, manuscript writing; P.J.D.: concept and design, manuscript writing; D.J.S.: concept and design, manuscript writing, final approval of manuscript; D.M.: concept and design, manuscript writing; D.I.M.: concept and design, manuscript writing. D.A.F.: Concept and design, data analysis and interpretation, manuscript writing, final approval of manuscript.

Disclosure of Potential Conflicts of Interest

P.J.D. reported advisory role for Boehringer Ingelheim and research funding from Abbott Diagnostics, Boehringer Ingelheim, Philips Healthcare, Roche Diagnostics, and Stryker. All other authors indicated no potential conflicts of interest.

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