Original article

Intramyocardial Autologous Cell Engraftment in Patients with Ischaemic Heart Failure: A Meta-Analysis of Randomised Controlled Trials

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Background: **Intramyocardial cellular delivery provides a promising therapeutic strategy for ischaemic cardiac dysfunction. However, individual studies have reported controversial results.**

Methods: **Relevant trials were identified by systematic search of MEDLINE, EMBASE, the Cochrane database, and CINAH database. Studies, which applied randomised design and compared intramyocardial cell injection with placebo or optimal medical therapy in patients with chronic ischaemic heart failure, were eligible.**

Results: **A total of 210 participants in five randomised controlled trials were included. The pooled analyses showed that cell therapy did not significantly improve left ventricular ejection fraction compared with the control (95% CI −0.35 to 0.31, $p = 0.91$). Nevertheless, cell therapy provided a benefit in increasing 6-min walk distance (95% CI 21.09 m–142.62 m, $p = 0.008$), improving MLHF score (95% CI −25.21 to −3.55, $p = 0.009$), and lowering the incidence of NYHA functional class deterioration (95% CI 0.05–0.76, $p = 0.02$). However, the novel procedure did not result in a significant reduction in all-cause mortality. Conversely, cell therapy did not significantly increase the risk of ventricular tachycardia or acute heart failure, however we were underpowered to evaluate these endpoints.**

Conclusions: **Intramyocardial cell therapy was feasible in treating patients with ischaemic heart failure.**

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Keywords. Myoblast; Bone marrow mononuclear cell; Ischaemic; Heart failure; Meta-analysis

Introduction

Despite advances in the treatment of coronary artery disease, ischaemic heart failure develops in a considerable number of patients after their first acute myocardial infarction [1]. An estimated five million patients in the US suffer from clinically manifested heart failure and account for the approximately one million hospital admissions per year [2]. Although there are multiple drugs and implantable devices that can treat the symptoms of heart failure, clinical prognosis in the growing number of patients with chronic heart failure remains poor. There exists an increasing need to find new therapeutic strategies to reduce the high mortality or morbidity in this population.

Intramyocardial cell injection is evolving as a new therapeutic strategy to improve clinical symptoms or prognosis of patients with chronic left ventricular dysfunction of an ischaemic origin. Among these stem-like cell populations used widely in clinical practice, skeletal myoblasts are an easily accessible source of autologous precursor cells committed to a myogenic, functionally contractile phenotype. Myoblasts are resistant to ischaemia, inflammatory conditions and oxidative stress, and are able to form new myotubes in damaged myocardium [3]. Moreover, the cell population releases trophic growth factors that exert an anti-fibrotic effect and enhance cardiac performance and myocardial perfusion through the stimulation of local angiogenesis [4,5]. Preclinical animal research with myoblasts have shown graft survival after transplantation to ischaemic areas of the heart and formation of new contractile tissue that demonstrably improves multiple measures of cardiac function [6–8]. Recently, several clinical studies have documented a positive safety profile and signs of clinical benefit as well [9,10]. In addition, autologous bone marrow mononuclear cells (BMMNCs) are also commonly used for ischaemic heart disease and ischaemic heart failure [11,12]. A recent study suggested that the

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method of cell isolation may affect both the function and recovery of BMMNCs from aspirates [13]. Furthermore, patients with ischaemic heart disease have shown reduced function of BMMNCs as demonstrated in an in vitro hindlimb ischaemia study [14], suggesting the possibility of limited clinical benefits from autologous cell therapy in patients with chronic disease. Nevertheless, BMMNCs therapy might be associated with moderate but significant improvement in global cardiac systolic function in patients with ischaemic heart failure [12]. However, up-to-date clinical utility and the value of intramyocardial skeletal myoblast and BMMNCs therapy for ischaemic heart failure has hitherto not been definitively established. Here, we systematically investigated the feasibility and safety of the novel procedure in patients with ischaemic heart failure by a meta-analysis of randomised controlled trials (RCTs).

Methods

Inclusion Criteria

The clinical trials were eligible for inclusion if (1) study design involved patient's randomisation and matching control; (2) participants were diagnosed with chronic systolic heart failure of an ischaemic origin with the mean left ventricular ejection fraction (LVEF) of less than 40%; (3) types of interventions involved additional autologous precursor cell therapy versus complementary evidence-based therapy for ischaemic heart failure or placebo; (4) cells were transferred intramyocardially as an adjunct to revascularisation surgery or by percutaneous endomyocardial injection. Trials would be excluded if the delivery route was intracoronary transfer, or if cardiac dysfunction resulted from non-ischaemic aetiology.

Search Strategy

Eligible studies were identified from systemic searches of MEDLINE, EMBASE, Cochrane Central Register of Controlled trials, and CINAH databases (until July 2012). Complex search strategies were formulated using the following MESH terms and text words: ischaemia, coronary heart disease, myocardial infarction, heart failure, cardiac dysfunction, cardiac insufficiency, intramyocardial, endomyocardial, epimyocardial, cell-based cardiac repair, cell therapy, cell transplantation, cell implantation, cell injection, cell transfer, cell engraft, and randomised. In addition, we also conducted an extensive search of the citation database (ISI Web of Science) using cross-references from the eligible articles to ensure that no clinical trials were missed. The search was restricted to English-language literature.

Study Enrollment and Data Collection

To identify the eligible studies, two investigators (C.K., W.F.) reviewed all citations in duplicate and independently. The data, such as characteristics of the study, participant characteristics, treatment strategies, and follow-up duration from each study, were extracted. LVEF, 6-min walk distance, Minnesota Living with Heart Failure (MLHF) score, and the occurrence of major adverse clinical events (MACEs) (e.g. all-cause mortality, New York Heart Association (NYHA) class deterioration, incidence of acute heart failure, and ventricular tachycardia) were also recorded. Any differences or disagreements were resolved through consensus. A numerical score between 0 and 5 was assigned as a measure of study design based on the validated scale put forward by Jadad and colleagues [15].

Data Analysis

Treatment effect of dichotomous data was expressed as risk ratio (RR) with 95% confidence intervals (CI) and that of continuous data as weighted mean difference (WMD) with standard deviation (SD), which were calculated using random-effects models. Alternatively, when outcomes according to continuous data were measured using different scales, the data would be combined and analysed using standardised mean difference (SMD). For studies with no event of interest in a treatment group, 1.0 was added to all cells for continuity correction [16]. Statistical heterogeneity across the enrolled trials was quantified using the I^2 statistic on a scale of 0–100% (75% represented very large between-study inconsistency). Data stratified according to cell type injected, injection method (endomyocardial or epimyocardial), follow-up duration, baseline LVEF level, and design of the control were analysed by subgroup analyses. Sensitivity analyses were conducted to examine the robustness of the effect by alternatively using fixed-effect model, and by omitting each trial at a time from analysis when the analysed trials were no less than three and thereafter computing meta-analysis estimates for the remaining studies. The potential publication bias among enrolled trials was qualitatively assessed using funnel plot method. Results were considered statistically significant at $p < 0.05$. The pooling analyses were performed using Review Manager 5.1 software (Cochrane Collaboration, Copenhagen, Denmark).

Results

Selected Studies and Characteristics

The flow of the selection process for potentially eligible trials and reasons for exclusion are illustrated in Fig. 1. Briefly, from the initial literature search we identified 562 items in electronic databases. After elaborative screening five studies were eligible for inclusion in analysis [10,17–20] and no additional relevant study was identified from the references and citations of eligible articles.

Baseline characteristics for each of the eligible trials are shown in Table 1. In the five enrolled trials, a total of 210 patients with ischaemic heart failure, with the follow-up duration ranging from six months [10,18–20] to 12 months [17], were included for analysis. Among them 135 were randomly allocated to cell treatment group (115 receiving skeletal myoblasts in four trials [10,17,18,20] and 20 receiving BMMNCs in one trial [19]) and 75 to the control group (35 for standard medical therapy and 40 for placebo). The mean age of participants ranged from 59 years to 70 years. The majority of participants was male and