Canadian Journal of Cardiology 30 (2014) 1370–1377

Systematic Review/Meta-analysis

Autologous Transplantation of Bone Marrow/Blood-Derived Cells for Chronic Ischemic Heart Disease: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Studies focused on cell therapy for chronic ischemic heart disease (CIHD) have been published with conflicting results. In this meta-analysis, we aimed to assess the effectiveness and safety of autologous bone marrow/blood-derived cell transplantation in patients with CIHD.

Methods: Randomized controlled trials (RCTs) were identified in PubMed, OVID, EMBASE, and Cochrane Library reviews and reference lists of relevant articles. Weighted mean difference was calculated for changes in left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV), and left ventricular end-diastolic volume (LVEDV) using a random-effects model.

Results: Nineteen trials with a total of 886 patients were included. Compared with controls, patients who received transplantation of bone marrow/blood-derived cells had significantly improved LVEF (3.54%; 95% confidence interval [CI], 1.92%-5.17%; $P < 0.001$) and LVESV (−8.96 mL; 95% CI, −13.64 to −4.28 mL; $P < 0.001$). No significant improvement in LVEDV (−0.75 mL; 95% CI, −9.80-8.30 mL; $P = 0.22$)

RÉSUMÉ

Introduction : Les études portant sur le traitement cellulaire de la cardiopathie ischémique chronique (CIC) ont publié des résultats contradictoires. Dans cette méta-analyse, nous avions pour but d'évaluer l'efficacité et l'innocuité de la transplantation autologue de cellules dérivées du sang et de la moelle osseuse chez les patients ayant une CIC.

Méthodes : Les essais cliniques aléatoires (ECA) étaient relevés des revues de PubMed, OVID, EMBASE et de la Bibliothèque Cochrane, et des listes bibliographiques d'articles pertinents. La différence moyenne pondérée des changements dans la fraction d'éjection ventriculaire gauche (FEVG), du volume télésystolique du ventricule gauche (VTSVG) et du volume télédiastolique du ventricule gauche (VTDVTG) était calculée en utilisant un modèle à effets aléatoires.

Résultats : Dix-neuf (19) essais regroupant 886 patients étaient inclus. Comparativement aux témoins, les patients qui subissaient la transplantation de cellules dérivées du sang et de la moelle osseuse montraient une amélioration significative de la FEVG (3,54 %; intervalle

Ischemic heart disease (IHD) remains a major cause of morbidity and mortality in the developed and, more recently, the developing world.[1] Despite the most advanced medical therapy and coronary artery revascularization techniques, such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), which have improved prognosis and survival, chronic ischemic heart disease (CIHD) is a leading cause of congestive heart failure and angina refractory to conventional therapies.[2] In light of an enlarging patient population with CIHD, investigation of alternative treatments, such as limiting or stopping the progression of the ischemic damage by regenerative therapies, are needed. Stem/progenitor cells are characterized by their ability to self-renew as well as differentiate into specialized cells, which highlights their therapeutic potential in regenerative medicine. Therefore, in recent years, autologous bone marrow– or peripheral blood-derived cell transplantation has emerged as a promising therapeutic modality for the treatment of CIHD on the basis of its possible ability to induce neovascularization and tissue regeneration.[3-5]

In general, current evidence has documented the safety and feasibility of cell transplantation in patients with IHD.[4-6] Also, it is reported to improve left ventricular (LV) function and exercise capacity in patients with acute myocardial infarction.[5,7] However, many studies that focused on cell therapy as a specific prophylactic measure for CIHD have had conflicting results. In this meta-analysis of randomized controlled trials (RCTs), we aimed to assess the safety, effectiveness, and potential benefits of autologous transplantation of bone marrow/blood–derived cells for the therapy of CIHD.

Received for publication November 21, 2013. Accepted January 21, 2014.

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See page 1376 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2014.01.013

was detected. Subgroup analysis revealed that significant improvement in LVEDV was observed in patients with lower baseline LVEF. Moreover, there were trends in favor of a benefit for LV function and remodelling when intramyocardial cells were injected during coronary bypass surgery and the bone marrow mononuclear cell number was $\leq 1 \times 10^8$. Furthermore, cell therapy was associated with a significant decrease in all-cause death (relative risk: 0.49; 95% CI, 0.29-0.84; $P = 0.01$).

Conclusions: Current evidence showed that cell therapy moderately improved left ventricle function and significantly decreased all-cause death in patients with CIHD and supports further RCTs with larger sample size and longer follow-up.

de confiance [IC] à 95 %, 1,92 %-5,17 %; $P < 0,001$) et du VTSVG (−8,96 ml; IC à 95 %, −13,64 à −4,28 ml; $P < 0,001$). Aucune amélioration significative du VTDVG (−0,75 ml; IC à 95 %, −9,80-8,30 ml; $P = 0,22$) n'était détectée. L'analyse en sous-groupes révélait que l'amélioration significative du VTDVG était observée chez les patients ayant une plus faible FEVG au début. De plus, des tendances favorisant la fonction et le remodelage VG étaient observées lorsque l'injection intramyocardique des cellules était pratiquée au cours du pontage coronarien et que le nombre de cellules mononucléaires de la moelle osseuse était $\leq 1 \times 10^8$. En outre, la thérapie cellulaire était associée à une diminution significative de décès toutes causes confondues (risque relatif : 0,49; IC à 95 %, 0,29-0,84; $P = 0,01$).

Conclusions : Les données scientifiques actuelles montraient que la thérapie cellulaire améliorait modérément la fonction ventriculaire gauche et diminuait significativement les décès toutes causes confondues chez les patients atteints d'une CIC, et soutient davantage les ECA à plus vaste échantillon et au suivi à plus long terme.

Methods

Search strategy

The literature search was performed on PubMed, OVID, EMBASE, and the Cochrane Library through December 2013. Complex search strategies were formulated using the following Medical Subject Heading terms and text words: stem cell, stromal cell, bone marrow mononuclear cell, bone marrow cell, progenitor cell, ischemic cardiomyopathy, ischemic heart disease, ischemic heart failure, heart failure, myocardial ischemia, coronary artery disease, chronic myocardial infarction, old myocardial infarction, and chronic coronary total occlusion. Supplemental Appendix S1 shows the complete search strategy. To identify any studies missed by the literature searches, we hand searched reference lists of all eligible studies and relevant review articles.

Study selection

We included studies for which the following criteria were met: (1) they were RCTs, (2) there was follow-up of $\geq$3 months, (3) they were conducted in patients with CIHD, (4) the intervention consisted of any autologous bone marrow/blood−derived cells without restriction by cell number or administration route, (5) the patients in the comparator arm received standard therapy, and (6) measurements of mean value of left ventricular ejection fraction (LVEF) at baseline and follow-up were available. CHID was defined as the presence of stable angina, history of myocardial infarction for >3 months, and evidence of myocardial ischemia or previous revascularization (surgical or percutaneous). There was no restriction based on the publication year or language.

Data extraction

Two reviewers (PJ and XR) assessed the eligibility of studies using a standardized form developed for this purpose in duplicate and independently. Disagreements were adjudicated by a third reviewer. Data extraction was done by the same observers using a standardized data extraction form developed for this study. The following information was extracted from each study: study and patient characteristics, type and number of cells transplanted, route of delivery, primary intervention, the nature of the intervention and comparator, outcome of LV function and remodelling (eg, LVEF, left ventricular end-systolic volume [LVESV], or left ventricular end-diastolic volume [LVEDV]), and major adverse events. LV volumes were estimated from LV volume indexes when appropriate. When multiple imaging modalities, including echocardiography, magnetic resonance imaging, single-photon emission computed tomography and LV angiography, were used for cardiac function outcome assessment, magnetic resonance imaging and single-photon emission computed tomography data were preferentially included when available.

Quality assessment

According to standard criteria established by Juni et al.,[8] 2 independent reviewers (PJ and XR) assessed aspects of the reported methodological quality of each included study pertaining to generation of randomized sequence, concealment of treatment allocation schedule, blinding of outcome assessment, and adequacy of follow-up.

Data analysis

Statistical analyses in this study were carried out using RevMan software, version 5.2 (Cochrane Collaboration). Results were summarized as weighted mean difference (WMD) with the associated 95% confidence intervals (CIs) using a random-effects model. The χ^2 test was used to estimate heterogeneity across the studies, with a value of 50% or more indicating a substantial level of inconsistency. For studies that did not report the actual change (from baseline to follow-up) as mean $\pm$ standard deviation, the change in standard deviation was calculated by a standardized formula that was previously validated[9] when baseline and follow-up standard deviation are known. In addition, the relative risk (RR) was calculated for major adverse events. Results were considered statistically significant at $P < 0.05$. Funnel plots were used to investigate possible publication bias using Revman 5.2. Planned subgroup analyses were conducted based on type and dosage of injected cells (bone marrow−derived cells vs blood-derived cells and $\leq 1 \times 10^8$ bone marrow mononuclear cells [BMMNCs] vs $> 1 \times 10^8$ BMMNCs), route of