P-0347 Mesenchymal Stem Cell for Diabetes Mellitus Therapy: A Meta Analysis Study

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ABSTRACT

Background

There is general agreement to ensure promising result of mesenchymal stem cell therapy in diabetes, considering the risk and benefit based on evidence.

Aims

This meta analysis aimed to evaluate clinical effect of mesenchymal stem cell in diabetes mellitus in both type.

Methods

Screening of eligible publication was done independently by authors, in accordance to inclusion criterias such as: 1) written in English; 2) participants were being supervised for at least 1 month; 3) compared to standard treatment group; 4) study was published from 2008 and onwards; 5) the paper employed randomized controlled trials method, and; 6) any situation which altered endocrinologic status was excluded. All studies were reviewed using critical appraisal for clinical trials made by Centre for Evidence-Based Medicine Oxford University and risk of bias was determined using Cochrane Handbook for Systematic Reviews of Interventions. Selected papers was entered into Review Manager 5.3 and Graph Prism 8. Mean value of HbA1c was compared between before and after treatment, while $\geq 50\%$ decrease of insulin requirement was compared between a control group and the intervention group. Data was analyzed using mean and risk difference with fixed effects model to avoid heterogeneity. Heterogeneity was determined as significant at $P < 0.10$.

Results

Twenty two articles were included for analysis. The mean value were 36.5 ± 18 years of age; while the duration of DM were 11.4 ± 2.67 and 12.7 ± 5.65 years. ¹⁻⁶ MSC affected the decrease of HbA1C, C peptide, HOMA-IR and reduction of insulin requirement until 50%, thus were statistically significant ($p < 0.05$) compared with before intervention. Mean difference of HbA1c was 0.41 (0.25-0.57), while risk difference of $\geq 50\%$ insulin requirement decrease was 0.69 (0.52-0.86). Adverse effects were considered mild. Thus, the stem cell transplantation as a safe and effective treatment for selected patients with both types of DM.

Keyword: diabetes, stem cell, mesenchymal

INTRODUCTION

Mesenchymal stem cell (MSC) roles in diabetes type 1 and 2 therapy is explained in several pathways: 1) differentiate into IPC; 2) protection of endogen islet cell; 3) regeneration of islet, and; 4) reducing inflammatory process. Ability MSC transform to be IPC could release insulin in a glucose-dependent manner. There is general agreement to ensure promising result of mesenchymal stem cell therapy in diabetes, considering the risk and benefit based on evidence. Concerning the safety of MSC therapy, studies had shown MSC transplantation were safe and well tolerated. (Lee et al., 2006; Ho et al., 2012; Gabr et al., 2013; Hu et al., 2015; Xie et al., 2016)

METHOD

Selection of studies

Screening of eligible publication is independently by authors, which have inclusion criteria such as: 1) subjects were followed up for at least 1 month; 2) using control group; 3) use English language;; 4) study was published at least from 2008 and onwards and 5) clinical study phase 1-3. Exclusion criteria was studies that include any situation which altered endocrinologic status.

Search strategy

Literature search in this review was searched using key words: (Diabetes mellitus) AND (stem cell mesenchymal) in several database of Cochrane Central Register of Controlled trials (CENTRAL), Current Controlled Trials (ISRCTN), ClinicalTrials. gov, EMBASE, Elsevier, Nature and Google Scholar.

Data Extraction and Assessment

Obtained literatures were reviewed using critical appraisal tool for clinical trials by Centre for Evidence-Based Medicine Oxford University. Risk of bias of extracted data was determined by Cochrane Handbook for Systematic Reviews of Interventions (PRISMA).

Figure 1.0 Flow diagram shows record identification, screening and study inclusion process

Statistical Analysis

Extracted literatures were entered into Review Manager 5.3 and Graph Prism 8. Mean value of HbA1c before and after treatment along with remission prevalence between treated and untreated group were compared. Data was analyzed using mean difference with fixed effects model to avoid heterogeneity, according with the previously published guidelines for statistical reporting and the Cochrane Handbook for Systematic Reviews of Interventions. Heterogeneity was considered significant at $P < 0.10$.

Figure 2.0 a) Mean difference of HbA1c in experimental group and b) Forest plots shows risk difference of insulin requirement.

RESULT

Mean age of intervention participants and control group were 36.83 ± 18.08 years and 36.5 ± 18 years; while the duration of DM were 11.4 ± 2.67 and 12.7 ± 5.65 years. ¹⁻⁶ Diabetic status was monitored according to HbA1c level and followed for two years. Most studies applied single injection of allogenic mesenchymal stem cell from bone marrow, adipose and placenta. MSC affected the decrease of HbA1c, C peptide, HOMA-IR and reduction of insulin requirement until 50%, thus were statistically significant ($p < 0.05$) compared with before intervention.

DISCUSSION

Mesenchymal stem cell (MSC) able to differentiate into ICP and take part in beta cells regeneration by secreting cytokines and growth factors. Thus, MSC's ICP are able to prevent autoimmunity reaction against beta cells. In 2012 study, Si et al. showed that MSC infusion greatly increased endogenous beta cell regeneration in a diabetic rat, along with improved insulin sensitivity as shown by phosphorylated insulin receptor substrate 1 (IRS-1), protein kinase B (Akt), and GLUT4 elevation on target tissues. (Cho, Antuono, Glicksman, Wang, & Jonklaas, 2018). A meta analysis demonstrated by Gan, et al. (2018) stated that SC therapy was more efficient at reducing the glycated hemoglobin level compared with the control group in RCTs (SMD, 0.56; 95% CI; 0.06–1.06; and SMD, 1.63; 95% CI, 0.92–2.34, respectively).

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