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Featured Article

Stereotactic brain injection of human umbilical cord blood mesenchymal stem cells in patients with Alzheimer's disease dementia: A phase 1 clinical trial

Hee Jin Kim[a,b], Sang Won Seo[a,b,c], Jong Wook Chang[d,e], Jung Il Lee[b,f], Chi Hun Kim[g], Juhee Chin[a,b], Soo Jin Choi[e], Hunki Kwon[h], Hyuk Jin Yun[h], Jong Min Lee[h], Sung Tae Kim[i], Yearn Seong Choe[j], Kyung-Han Lee[j], Duk L. Na[a,b,k,*]

[a]*Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, 06351, Korea*
[b]*Neuroscience Center, Samsung Medical Center, Seoul, Korea*
[c]*Department of Clinical Research Design & Evaluation, SAIHST, Sungkyunkwan University, Seoul, Korea*
[d]*Stem Cell & Regenerative Medicine Center, Research Institute for Future Medicine, Samsung Medical Center, Seoul, Korea*
[e]*Biomedical Research Institute, MEDIPOST Co., Ltd, Seoul, Korea*
[f]*Department of Neurosurgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*
[g]*Department of Psychology, Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK*
[h]*Department of Biomedical Engineering, Hanyang University, Seoul, Korea*
[i]*Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*
[j]*Department of Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*
[k]*Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, Seoul, Korea*

Abstract

Introduction: We conducted a phase 1 clinical trial in nine patients with mild-to-moderate Alzheimer's disease to evaluate the safety and dose-limiting toxicity of stereotactic brain injection of human umbilical cord blood–derived mesenchymal stem cells (hUCB-MSCs).
Methods: The low- (n = 3) and high-dose (n = 6) groups received a total of 3.0×10^6 cells/60 μL and 6.0×10^6 cells/60 μL, respectively, into the bilateral hippocampi and right precuneus.
Results: No patient showed serious adverse events including fever during the 24-month follow-up period. During the 12-week follow-up period, the most common acute adverse event was wound pain from the surgical procedure (n = 9), followed by headache (n = 4), dizziness (n = 3), and postoperative delirium (n = 3). There was no dose-limiting toxicity.
Discussion: Administration of hUCB-MSCs into the hippocampus and precuneus by stereotactic injection was feasible, safe, and well tolerated. Further trials are warranted to test the efficacy.
Clinical Trial Registration: ClinicalTrial.gov identifier NCT01297218 and NCT01696591.

Keywords: Alzheimer's disease; Mesenchymal stem cell; Stereotactic injection; Hippocampus; Precuneus

1. Introduction

Alzheimer's disease (AD) dementia is a neurodegenerative disease that results in progressive dementia. Currently, no approved disease-modifying treatments are available for AD. Mesenchymal stem cells (MSCs) are multipotent stem cells that are capable of self-renewal and differentiation into various cell types when cultured under appropriate

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*Corresponding author. Tel.: +82-2-3410-3591/-3599; Fax: +82-2-3410-0052.

E-mail address: dukna@naver.com

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conditions [1]. However, it is known that MSCs are less likely to differentiate into neurons when injected into the brain. Rather, MSCs secrete various cytotropic factors that may exert beneficial effects in AD mice through various mechanisms such as reducing amyloid burden, decreasing inflammation,or increasing endogenous neurogenesis [2–4]. Several human clinical trials have suggested that MSCs are effective in slowing down the course of neurodegenerative diseases such as Parkinson's disease [5], multiple system atrophy [6], and amyotrophic lateral sclerosis [7,8]. However, to the best of our knowledge, there has been no clinical trial that has attempted to treat human AD using MSCs.

Given the lack of an effective regimen for AD dementia, more innovative treatments are needed to effectively alter the course of the disease. There has been little evidence regarding the ability of MSCs, injected either intraarterially or intravenously, to penetrate through the blood-brain barrier for engraftment into the brain parenchyma of AD dementia patients. Thus, to test the therapeutic potentials of MSCs, we directly transplanted MSCs into the brains of human AD patients using stereotactic surgery because the most effective route of delivering MSCs into a targeted structure may be through direct implantation. Indeed, a recent phase 1 clinical trial reported that the stereotactic injection of nerve grow factor into the nucleus basalis of Meynert of AD dementia patients is both feasible and well tolerated [9].

In the present study, we targeted the hippocampus and precuneus as injection sites because they are areas that are predominantly affected during the earlier phases of AD dementia. According to pathologic and imaging studies, the precuneus is where amyloid start to accumulate in the course of AD [10,11] and the hippocampus is where neurofibrillary tangles begin to aggregate during the progression of AD [12]. Consistent with these data, recent functional neuroimaging studies have suggested a central role of the precuneus in memory [13] and that decreased hippocampus-precuneus functional connectivity is an early sign of AD [14]. Furthermore, the hippocampus and precuneus undergo atrophy in the early stages of AD dementia [15].

MSCs can be isolated from the umbilical cord blood, which have been widely used in various clinical settings [16–18]. Establishing the safety and feasibility of a surgical method to effectively deliver human umbilical cord blood–derived MSCs (hUCB-MSCs) into the hippocampus and precuneus would represent an important milestone in advancing the application of this novel treatment for AD dementia. Therefore, the aim of this study was to evaluate the safety and tolerability of surgical stereotactic injection of hUCB-MSCs into the bilateral hippocampus and right precuneus and to assess the maximum tolerated dose. We also investigated the potential efficacy of hUCB-MSCs in AD patients using cognitive measurements and imaging markers.

2. Methods

2.1. Study design

This was an open-label, single-center, phase 1 clinical trial performed at Samsung Medical Center. The first three AD dementia patients received a low dose (a total of 3.0×10^6 cells, 1.0×10^6 in each side of the hippocampus and 1.0×10^6 in the right precuneus) of hUCB-MSCs. After we confirmed that there were no serious adverse events, additional six AD dementia patients were selected to receive a high dose (a total of 6.0×10^6 cells, 2.0×10^6 in each side of the hippocampus and 2.0×10^6 in the right precuneus) of hUCB-MSCs via the same route. We injected MSCs into only the right precuneus to compare the change in amyloid burden level in the MSC-treated right precuneus with that in the untreated left precuneus. This trial was registered at ClinicalTrial.gov (ClinicalTrial.gov number NCT01297218 for 12 weeks of follow-up; NCT01696591 for extended follow-up of 24 months). We obtained written informed consent from every patient or their legally authorized representatives in cases of impaired capacity. This study was approved by the Institutional Review Board of Samsung Medical vCenter.

2.2. Participants

Eligible patients were aged 50–75 years, fulfilled the criteria for probable AD dementia according to the National Institute of Neurological and Communicative Disorders Stroke and AD and Related disorders Association [19], and had a mini-mental state examination (MMSE) score between 10 and 24. Patients with neurologic diseases other than AD dementia were excluded, as were those with one or more of the following conditions: severe white matter hyperintensities on fluid-attenuated inversion recovery (FLAIR) images at baseline, which were defined as a cap or band (periventricular white matter hyperintensities) $\geq$10 mm, and deep white matter lesions (deep white matter hyperintensities) $\geq$25 mm as modified from the Fazekas ischemia criteria [20]; major psychiatric disorder; history of stroke within 3 months of enrollment; hepatic, renal, hematologic, or active pulmonary disorder; history of alcohol abuse; and/or underlying malignancy. Patients were required to have been on a stable dose of acetylcholinesterase inhibitors or memantine for at least 60 days before enrollment, and the same dose of medication was continued throughout the study. Nine patients who met the mentioned criteria were also evaluated for amyloid burden using ^{11}C-labeled Pittsburgh compound B (PiB) positron emission tomography (PET) as well as the downstream neuronal degeneration biomarker using [^{18}F]fluoro-2-deoxy-D-glucose (FDG) PET and structural brain magnetic resonance imaging (MRI). All nine patients were positive for amyloid (standardized uptake value ratio [SUVR] $\geq$1.5), had decreased FDG uptake in the temporoparietal cortex,