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Research Report

# Umbilical cord mesenchymal stem cell transplantation significantly improves neurological function in patients with sequelae of traumatic brain injury

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ABSTRACT

The aim of this study was to investigate the effects of transplantation with umbilical cord mesenchymal stem cells in patients with sequelae of traumatic brain injury (TBI). The study hypothesis was that umbilical cord mesenchymal stem cell transplantation could safely and effectively improve neurological function in patients with sequelae of traumatic brain injury. Forty patients with sequelae of TBI were randomly assigned to the stem cell treatment group or the control group. The patients in the stem cell treatment group underwent 4 stem cell transplantations via lumbar puncture. All patients of the group were also evaluated using Fugl-Meyer Assessments (FMA) and Functional Independence Measures (FIM) before and at 6 months after the stem cell transplantation. The patients in the control group did not receive any medical treatment (i.e., neither surgery nor medical intervention), and their FMA and FIM scores were determined on the day of the visit to the clinic and at 6 months after that clinical observation. The FMA results demonstrated an improvement in upper extremity motor sub-score, lower extremity motor sub-score, sensation sub-score and balance sub-score in the stem cell transplantation group at 6 months after the transplantation ($P<0.05$). The FIM results also exhibited significant improvement ($P<0.05$) in the patient self-care sub-score, sphincter control sub-score, mobility sub-score, locomotion sub-score, communication sub-score and social cognition sub-score. The control group exhibited no improvements after 6 months ($P>0.05$). All in all,

Abbreviations: TBI, traumatic brain injury; FMA, Fugl-Meyer Assessment; FIM, Functional Independence Measure; UCMSCs, umbilical cord mesenchymal stem cells; MSCs, mesenchymal stem cells; PT, physical therapy; OT, occupational therapy; WHO, World Health Organization; GCS, Glasgow Coma Scale; DMEM, Dulbecco's modified Eagle's medium; GDNF, glial cell line-derived neural factor; BDNF, brain-derived neurotrophic factor; SDF-1, stromal-derived factor 1

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the study results confirmed that the umbilical cord mesenchymal stem cell transplantation improved the neurological function and self-care in patients with TBI sequels. Umbilical cord mesenchymal stem cell transplantation may be a potential treatment for patients with sequelae of TBI. Further research, including a multicenter and large sample size prospective randomized clinical trial, will be required to define definitively the role of umbilical cord mesenchymal stem cell transplantation on sequelae of TBI.



## 1. Introduction

Umbilical cord mesenchymal stem cells (UCMSCs) display strong self-renewal and differentiation abilities. When induced by chemical and neurotrophic factors, UCMSCs can differentiate into bone, cartilage, fat, muscle and vascular endothelial cells or even neural cells and glial cells with secretory functions (Fan et al., 2011; Koh et al., 2008; Secco et al., 2008; Troyer and Weiss, 2008; Wu et al., 2007; Zhang et al., 2010). The major cell types used in animal experiments and in clinical treatment are neural stem cells (Itoh et al., 2011; Pardal and Lopez-Barneo., 2012), bone marrow mesenchymal stem cells (Cheng et al., 2010; Chernykh et al., 2011), umbilical cord mesenchymal stem cells (Liao et al., 2009; Yang et al., 2008; Zanier et al., 2011), embryonic stem cells (Cui et al., 2011; Palmgren et al., 2012; Ronaghi et al., 2010) and umbilical cord blood stem cells (Ali et al., 2011; Dasari et al., 2009). UCMSCs have many advantages compared with other cell types, including the following: (1) the wide range of sources and the ease of their collection, storage and transport; (2) no risk of allograft rejection; (3) no ethical controversy (Romanov et al., 2003).

Therefore, mesenchymal stem cells (MSCs) are used in a wide range of applications, such as the treatment of traumatic brain injury, Parkinson's disease, neuromyelitis optica or diabetic renal injury among others (Lu et al., 2012; Park et al., 2012; Shi et al., 2012; Xiong et al., 2011).

Traumatic brain injury (TBI) is one of the many serious diseases that threaten human life and health. TBIs are caused primarily by traffic accidents, collisions with hard objects and falling from high places (Hu et al., 2012; Wu et al., 2008; Zhao and Wang, 2001). With improving medical technology, the survival rate of patients with TBIs has increased significantly. However, the majority of those who survive suffer from varying types of disabilities, such as body motor dysfunction, language and communication difficulties, mental problems and psychological and social cognitive defects. All of these disabilities affect the patients' studies, work and daily life seriously (Andelic et al., 2009; Jaracz and Kozubski, 2008). The current typical treatment for TBI includes surgery or conservative symptomatic treatment during early stages and physical therapy (PT) and occupational therapy (OT) during late stages. Stem cell therapy for TBI remains at the stage of animal experimentation (Chuang et al., 2012; Tu et al., 2012). Studies have indicated that active rehabilitation exercises during the first year after TBI can restore in part the damaged nerve function (Al-Jarrah et al., 2009). However, the current typical rehabilitation protocols have little benefit for patients with TBIs that have existed for more than one year. This study investigated the clinical treatment effects of transplantation of UCMSCs in patients with sequelae of TBI that had been sustained more than one year previously. The study aims to certify the additional compensation of neurological recovery providing by the migration and differentiation of stem cells or the neurotrophic factors.

## 2. Results

### 2.1. *FMA scoring*

#### 2.1.1. *Baseline FMA scores of the patients in both groups*

The upper extremity motor sub-score of the stem cell transplantation group and the control group were $16.60 \pm 11.70$ and $15.95 \pm 9.63$, respectively, and the lower extremity motor sub-score were $12.75 \pm 6.25$ and $14.80 \pm 8.54$, respectively. The sensation sub-score were $15.75 \pm 7.25$ and $14.15 \pm 9.22$, respectively. The balance sub-score were $5.40 \pm 3.19$ and $6.05 \pm 3.89$, respectively, and the total scores of the two groups were $50.50 \pm 21.80$ and $50.95 \pm 25.48$, respectively. The differences between the two groups were not statistically significant ($P > 0.05$; Table 1).

#### 2.1.2. *Comparison of the FMA scores before and at 6 months after stem cell transplantation*

The motor sub-scores of upper and lower extremity, the sensation and balance sub-scores at baseline and 6 months after stem cell transplantation are presented in Table 1. Statistically significant improvements after transplantation were observed in the upper extremity motor sub-score ($P < 0.001$), the lower extremity motor sub-score ($P < 0.05$), the sensation sub-score ($P < 0.05$), the balance sub-score ($P < 0.001$), and the total FMA score ($P < 0.001$; Table 1).

#### 2.1.3. *Comparison of the FMA scores in the control group at baseline and at 6 months*

The motor sub-scores of upper and lower extremity, the sensation and balance sub-scores at baseline and at 6 months in the control group are presented in Table 1. Statistical analyses revealed that, in the control group, there were no significant differences between timepoints in the upper extremity motor sub-score, lower extremity motor sub-score, sensation sub-score, balance sub-score or in the total scores ($P > 0.05$). In addition, there were no changes in the lower extremity motor sub-score or in the sensation sub-score between baseline and 6 months (Table 1).