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Stem cells therapy for patients with stroke

Stroke represents the second leading cause of death worldwide. Moreover, it is the most common cause of physical disability in adults [1].

Ischemic stroke accounts for approximately 85% of all stroke events. Thrombosis and embolism of the intracranial artery is the main cause of ischemic stroke. Very few therapeutic options are currently available for the treatment of ischemic stroke. All of them aimed at rapid vessel recanalization and neuroprotection. Unfortunately, limited success in clinical practice is achieved by different approaches for protection the brain from ischemic damage. As a result, a large number of stroke survivors are left with severe disabilities.

In addition, the only pharmacological treatment approved for acute ischemic stroke is recombinant tissue plasminogen activator (tPA). However, using of tPA is limited by the time window of 4 to 5 hours after acute ischemic stroke. During this period of time the tPA therapy is effective for restoration the brain function. Thus, the tPA is appropriate for only 2% to 4% patients[2]. Also, tPA doesn't affect the mortality rate as well as it prevents disability in only six patients per 1000 ischemic strokes[3]. Actually, there is no particular treatment which can repair lost brain function.

Stem cells therapy is a new perspective option and alternative for conventional treatment of stroke. In general, stem cells exhibit neuroprotective properties through production of growth and trophic factors, stimulation of endogenous neurogenesis, angiogenesis and synaptogenesis as well as modulation of neuroinflammation. In more details it is considered that the microenvironment of damaged tissues produces factors that attract stem cells to the site of injury and enhance their differentiation into desired cells. Thus, stem cells promote tissue regeneration by differentiating into the injured cells[4]. It is important to notice that stem cells secrete neurotrophins such as brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor, which promote to anatomical and functional recovery of the ischaemic brain[5,6]. Moreover, brain-derived neurotrophic factor reduces spasticity due to its ability to affect neuronal excitability and synaptic transmission as well as upregulate a potassium chloride co-transporter KCC2 which maintains activation of inhibitory receptors[7,8]. In addition brain-derived neurotrophic factor attenuates microvascular permeability disturbances, blood cerebrospinal fluid barrier breakdown, blood–brain barrier breakdown and therefore brain oedema[9]. Glial cell line-derived neurotrophic factor also ameliorates brain oedema[10]. Anti-oedematous effect of neurotrophins contributes to reduction of lesion size in the brain. Also, stem cells possess immunomodulatory properties. They limit the local inflammatory response due to inhibition of microglia and macrophages activation. In addition, they impair T-lymphocyte maturation[11]. Indeed, in the presence of stem cells immature or partially immature antigen presenting cells was showed to be produced. These cells turn off T cells leading to down-regulation of activated immune cell reactivity and thus reducing tissue damage[12].

Encouraging results were obtained in controlled clinical trial in which the safety, feasibility and efficacy of autologous mesenchymal stem cells(MSCs) therapy in patients with chronic stroke were researched. Twelve patients diagnosed with stroke 3 months to 1 year ago were enrolled in the study. All of them were divided into two groups. Patients in first group were infused intravenously autologous mesenchymal stem cells. The second group was control. During 8 weeks all patients had received physiotherapy. The follow-up period was 6 months. No mortality or adverse reaction associated with stem cells therapy was observed. Also, the clinical, laboratory and radiological evaluations did not reveal any cell-related complications, stroke recurrence and structural changes in imaging during the 6-month follow-up period. The scores of Fugl Meyer scale for upper limbs were increased in the stem cell treated patients in compare with control group. The power of wrist and hand muscles was found to increase. Moreover, a decrease of tone in spastic muscles, a lower pain threshold and a better functional performance were observed in MSCs group. The obtained data have indicated that mesenchymal stem cells therapy is safe and feasible for the treatment of stroke patients[13].

Two years later the same research group published the results of controlled clinical trial in which safety, feasibility and efficacy of autologous MSCs therapy of stroke patients were proved on a larger sample size. Forty patients with diagnosed stroke were included in the study. They were allocated in two groups. The first experimental one included patients who were infused stem cells. The second group was control. Eight weeks of physiotherapy was administered to all forty patients. The follow-up period was 6 months. Significant improvement of modified Barthel Index was observed in the stem cell group indicating amelioration of performance in activities of daily living. Also, no side effects associated with stem cell therapy was reported. Thus, stem cell therapy of stroke patients is safe as well as it helps in functional recovery [14].

The long-term safety and efficacy of MSCs using in the treatment of patients with ischemic stroke were evaluated in clinical trial which was conducted by Lee J.S. et al. It was a controlled randomized, observer-blinded clinical study in which fifty two patients with ischemic stroke who had severe and persistent deficits were recruited. All of them were randomly allocated to one of two groups. The first group included the patients who were injected intravenously autologous MSCs. The second one was control. The follow-up period was 5 years. No any significant side effects were noticed following MSCs treatment. It is important to mention that the mortality rate in the MSC group was lower than in the control group. Also, functional recovery was more frequently observed in the MSCs group. The modified Rankin Scale scores were significantly improved in patients who received MSCs[15].

In 2011 Honmou O. et al. reported the results of clinical trial in which feasibility and safety of autologous MSCs using in the treatment of stroke patients were assessed. Twelve patients with ischaemic grey matter, white matter and mixed lesions were enrolled in the study. Autologous mesenchymal stem cells were delivered intravenously. The follow-up period was 1 year. No any central nervous system tumors, abnormal cell growths or neurological deterioration were observed in any of the patients following stem cell infusion. Also, it is necessary to mention that there was no evidence for venous thromboembolism, systemic malignancy or systemic infection associated with stem cell therapy. It was noticed that mean lesion volume which was detected by magnetic resonance imaging was reduced by more than 20% post-cell infusion. Also, there was improvement in National Institutes of Health Stroke Scale (the NIHSS) score in all patients demonstrating functional amelioration which was maintained for 1 year in all patients[16].

In 2014 Jeong H. et al. published the results of a systematic review and meta-analysis of clinical trials in which stem cell therapy was used for the treatment of stroke. Fourteen clinical studies were included in a review. It was demonstrated that stem cell therapy significantly improved behavioral and functional capacity of patients with stroke. Moreover, the 5.7 points reduction in the NIHSS was observed reflecting amelioration of stroke symptoms. It is necessary to mention that increase of the scores in NIHSS by 1 point leads to decrease the likelihood of favorable outcome by 17%[17,18].

In conclusion, as established by various clinical trials using of autologous stem cells in stroke patients was safe. Also, available data have showed that stem cell therapy leads to considerable improvement of behavioral and functional capacity of patients with stroke as well as promote to more rapid functional recovery. Moreover, it decreases the mortality rate of stroke patients.

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