



## Cell Therapy for Traumatic Brain Injury: Opportunities and Pitfalls

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### ABSTRACT

Today, stem cell transplantation is a hot topic in scientific circles as a novel therapeutic approach to repair the structure and function of central nervous system. The safe and neuroprotective effects of cell therapy in models and traumatic brain injury patients were evaluated in many experimental and clinical studies in recent decade and somewhat promising results were provided to the scientific community. Nevertheless, there are still obstacles in translating experimental studies in the laboratory into clinical practice that should not be overlooked. In this review study, a brief explanation is provided about biological events and endogenic neurogenesis and angiogenesis after TBI; the performance of transplanted cells in restoration of damaged neurons; the role and potential use of mesenchymal stem cells as adult stem cells preferred in cell transplantation and clinical trials ever conducted in this area; features of cell transplant candidates who will most benefit from transplantation, the type of and proper time for cell transplantation, optimal method for conducting transplant to deliver cells to the brain, and the best dose for effectiveness of transplantation. Finally, the various neuroimaging techniques are discussed, which are used to track and evaluate the survival and implantation of transplanted cells.

**Keywords:** Trauma, Nervous System; Brain Injuries; Neurogenesis; Angiogenesis; Mesenchymal Stem Cells; Cell Grafting; Cell Tracking

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### Introduction

About a million people suffer from traumatic brain injury (TBI) every year in the world (1). TBI injuries are divided into primary and secondary categories. Primary injuries occur due to mechanical force and cause rupture of and pressure on nerves and vessels, and are not

preventable, but secondary injuries are often caused by ischemia and inflammation, are potentially affected by treatment and are preventable to some extent (2,3). Despite all interventions, permanent injuries occur in most cases leading to destructive consequences due to limited potential of CNS

neurons for repair and regeneration. TBI is one of the main causes of permanent mental and motor disabilities among individuals under 45 years (4). Despite significant progresses which resulted in successful surgical treatment of traumatic brain lesions, some patients are faced with permanent mental and physical problems (5). It seems that these outcomes are due to cascade changes in gene expression and secretion of neurochemical factors damaging neurons that occur during secondary injuries and remain for months and even years (6-8). Ischemia plays an important role in TBI pathogenesis. Pathophysiological responses after TBI are very complicated and involve multiple mechanisms, including excitotoxicity, damages caused by free radicals and inflammation (9), which ultimately lead to neural impairment and neuron death (10,11). The brain's response to injury appears in the form of recapitulation and expression of fetal factors and proteins such as synaptophysin and vascular endothelial growth factor (VEGF). These proteins involved in angiogenesis and brain development are abundant in the lesion area (12).

### ***Endogenic neurogenesis and angiogenesis after traumatic neural injury***

Neurogenesis occurs in some areas of the adult mammalian brain, such as the subventricular zone (SVZ) and the subgranular zone (SGZ) of the dentate gyrus of the hippocampus and olfactory bulb (13,14). Neural progenitors residing in these zones can replace lost neurons due to acute injuries. Vascular system in adults' brain, which is stable under normal conditions and is activated in response to pathological conditions such as neuron lesions, remodels in the form of angiogenesis by mature

endothelial cells (capillary growth in vessels) and endothelial progenitor cells (EPC), which strongly contribute to angiogenesis. The angiogenesis that occurs through the secretion of growth factors such as fibroblast growth factor (FGF) and VEGF by endothelial cells is supported by EPCs (15,16). Neurogenesis and angiogenesis are linked together by vascular production of stromal-derived factor 1 (SDF1) and angiotensin 1 (Ang1) (17). After injury, activated endothelial cells of cerebral vessels secrete SDF1. This factor is an attractant for CXCR4 receptor which is expressed in neuroblasts (18,19). Thus, instead of migrating to olfactory bulb, SVZ neuroblasts deviate from their migratory path to reach the ischemic boundary zone (IBZ) where angiogenesis occurs (20). After migration, SVZ neuroblasts differentiate into mature neurons and glial cells in IBZ (17,18). Active angiogenesis is observed after 3-4 days of brain lesions in human (23). It has been found that endogenic angiogenesis and neurogenesis mediate the improvement of functional and neurological outcomes in all animal models (24-29). Studies show that injured brain can be stimulated by external stimulants, so endogenic angiogenesis and neurogenesis processes can be strengthened. Therefore, neurogenesis and angiogenesis can be induced by cell therapy or pharmacological agents (30-32).

### ***Neuroregeneration through stem cells implant***

Unfortunately, most randomized phase III clinical trials were not much effective for neuroprotective pharmacological treatments. Although, at the present, neuroprotective treatment is the main strategy to ameliorate the acute TBI, various clinical studies have not confirmed the effectiveness of this

therapeutic strategy and evidences have not shown significant clinical improvement (33,34). Therefore, in recent years attitudes have been directed toward neurorestorative approaches (30,35-37). For this reason, in recent years, extensive studies have been conducted in the field of cell therapy for TBI, some of which produced almost favorable results (38,39), but there are significant obstacles in this context. Evidence from preclinical and clinical studies was promising for researchers and clinicians about stem cell transplantation as a safe and effective treatment for brain injuries such as stroke (40-42) and TBI (43). This new and exciting approach not only is directed to the prevention of secondary cascade injuries and neuronal protection, which is also the goal of all conventional therapeutic approaches, but also tries to actually repair brain lesions (44). Fundamentally, stem cells possess potential ability to develop into various cell lines. Cell therapy for brain lesions is based on two important principles: first, proliferation and differentiation of transplanted cells into phenotypes of cells in the lesion location and second, secretion of neural growth factors that induce neurogenesis in regeneration areas of the brain such as nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF) (45). Reports suggest that after transplant of stem cells to the nervous system, these cells express neuronal [neuronal nuclear antigen (NeuN)] and glial [glial fibrillary acidic protein (GFAP)] markers (46). Histological studies confirm the induction of neurogenesis by stem cells after their transplant with presence of the neurosphere groups in the lesion areas. The migration of these neurosphere groups is directed by astrocyte

projections arising from the ventricular area (47).

### ***The mechanism of mesenchymal stem cells after grafting***

Although embryonic stem cells and embryonic tissues are appropriate sources for cell therapy, their clinical use has some limitations including ethical issues and an increased risk of developing tumor and antigenicity (48). It seems that among the types of adult stem cells, bone marrow mesenchymal stem cells (MSC) are more useful for the treatment of central nervous system lesions. MSCs possess the potential to differentiate into cellular phenotype of three germinal layers, and special attention is given to its therapeutic use. There is much evidence supporting clinical benefits of MSC transplant in the treatment of diseases that are characterized by neuronal death, such as multiple sclerosis (MS) (49-52), amyotrophic lateral sclerosis (ALS) (53-55), Parkinson's disease (56) and other neurological lesions such as stroke (41,57) and spinal cord injuries (SCI) (58). The ability of these cells in systemic transplant and crossing the blood-brain barrier and also their migration properties to the lesion area and the possibility of genetic manipulation, and availability of these cells, all have made them a good candidate for cell therapy (43). Systemic transplant of these cells is associated with up-regulation of neural growth factors and cytokines that are important in returning brain physiological conditions and the repair of damaged brain tissue (59,60). Systemic transplant of these cells 24 hours after injury in rats had increased the number of labeled cells by BrdU (Bromodeoxyuridine) in the

subventricular zone and hippocampus two weeks after transplant (30). They were found to increase precursors of oligodendrocytes in the white matter of the brain (61,62). These cells exert their neuroprotective role by secreting neurotrophic factors, which were described earlier. Growth and neurotrophic factors secreted by MSCs may contribute to synaptogenesis and the increase in dendritic tree in lesions. They strengthen contralateral nerve fiber sprouting in ischemic hemisphere and increase endogenous structural plasticity in the brain. An increase in dendritic spines was observed in the ipsilateral and contralateral hemisphere (60). Gliosis is a major obstacle in neurons regeneration after injury. Transforming growth factor- $\beta$  (TGF $\beta$ ) is an important factor in the prevention of gliosis and scar tissue in the brain (63), which is secreted by MSCs and helps brain tissue repair (64-66). Studies show that after TBI, neuronal apoptosis in penumbra around the lesion is reduced by transplant of MSCs; researchers believe that this effect is due to the secretion of growth factors by stem cells. MSCs also stimulate main parenchymal cells to secrete growth factors. This neuroprotective mechanism occurs through reducing the size of penumbra in case of acute phase transplant i.e. within 48 hours after injury (67-69). Another effect of cell therapy is to reduce the inflammation caused by brain damage. Implant of MSCs will lead to reduced number of leukocytes migrating to the brain and down-regulation of the genes related to immune and inflammatory responses and will change the balance of responses from pro-inflammatory to anti-inflammatory. Stem cells prevent the proliferation of T cells and modulate the induction of T cells with release of cytokines and immunosuppressed factors (70,71).

Determining the most effective time for reducing inflammation by stem cells is very important as inflammation plays a dual role, in the acute phase is a harmful mediator of cell death, but in chronic phase is useful for removing the dead neurons debris and remodeling of neurovascular unit. So, the long-term reduction of inflammation may not be beneficial (72). Increased angiogenesis in the penumbra during the first few days after brain injury is associated with neurological improvement in patients. The ability of MSCs in increasing the levels of angiogenesis factors such as FGF, VEGF and chemo-attractant factors such as SDF-1 is through direct secretion of these factors or induction of expression in these factors, which are very important for stimulation of vascular endothelial cell proliferation (angiogenesis) and mobility and homing of endogenic endothelial progenitors (vasculogenesis). Studies show that angiogenesis occurs only in the penumbra by stem cells and does not happen in healthy tissue. CXCR4 receptor is expressed on the surface of MSCs and interaction of SDF-1/CXCR4 plays an important role in compressing these stem cells in the lesion. MSCs therapeutic benefits in transplantation are attributed to their ability to differentiate into neurons and are more related to their ability as trophic generators in improvement of neurogenic function through angiogenesis, synaptogenesis and neurogenesis and axonal remodeling and immunomodulatory role (60,73,74). These cells suppress glutamatergic toxicity by down-regulation of glutamatergic receptors and inhibition of these receptors, and protect neurons (75). Genetic manipulation of MSCs with increased expression of growth factors provides a rich and improved source for cell therapy in central nervous system lesions

(76). Promising results have been shown for cell therapy in central nervous system trauma (77). In a study, bone marrow MSCs and granulocyte stimulating growth factor (GCSF) were used to improve neurological function in TBI models and the results indicated that both therapeutic approaches led to significant improvement in neurological function compared to the control group (78). In a similar study on TBI model, six-week rats were treated by intravenous injection of human umbilical cord matrix MSCs in tail vein at day after creating the model, and their neurological function was assessed and compared before the injury and after treatment with a control group. The results showed significant improvement in the group treated with stem cells compared to the control group. The functional recovery began one week after treatment with stem cells and persisted for six weeks after injury (79). In both recent studies, the immunohistochemical BrdU survey of the brain sections showed the mesenchymal cells labeled with BrdU in the border of injury on the last day of treatment. This proves that the intravenously implanted MSCs will have sufficient homing. However, there are no definitive standards on the clinical use of MSCs and successful translation of stem cell transplantation from basic research to clinical application stage is always faced with some limitations, which must be overcome on those to achieve satisfactory results. Here are a few examples on clinical trials of stem cell transplantation for TBI. In the study of Zhang et al. in 2008, six TBI patients aged 30 to 50 years who had a Barthel index score less than 40 in the initial evaluation after damage and were surgery candidates for cranial correction entered in the clinical trial phase I with written consent and autologous transplantation of bone

marrow MSCs was conducted by local and IV methods. Local transplant was conducted by direct injection of  $10^7$ - $10^9$  cells during brain surgery and intravenous transplant 4 to 12 days after the first implant by systemic infusion of  $10^8$ - $10^{10}$  cells. Three and six months after transplantation, evaluation of neurological function showed significant improvement compared to baseline. No immediate or delayed toxicity was observed from cell transplantation in patients, except one patient who experienced epilepsy in the first two months after transplantation that was controlled with phenytoin (38). Another phase I trial was conducted by Charles et al. in 2012 on 10 children 5 to 10 years with severe TBI and ICP less than 40 without long-term hypoxic ischemic signs in MRI and without pulmonary contusion and coagulopathy. Within 48 hours, children underwent autologous transplantation of  $6 \times 10^6$  bone marrow mononuclear stem cells per body weight (kg) through intravenous infusion. Transplant-related toxicity was evaluated every day for 21 days. Functional outcome was evaluated by Glasgow Outcome Scale (GOS), the intelligence by Wechsler Intelligence Scale, and recall auditory verbal learning test and structural changes in the brain by MRI, 1 and 6 months after transplant. The results of this study showed the safety of cell transplantation. In MRI images, no change was observed in the volume of white and gray matter in the brain and there was no increase in CSF volume. All patients survived and no transplant-related toxicity was reported. Six months after transplantation, 70% of children had good functional outcome and 30% had moderate disability (80). A phase I clinical trial NCT02028104 has been conducting since 2010. The study aims to evaluate the effects

of intrathecal autologous transplantation of bone marrow mononuclear stem cells on clinical symptoms of traumatic injuries and disability rate scale (DRS) and SF-8 scale, 6 months after transplantation in patients with chronic TBI ( age ranged between 6 months and 65 years). The results of this study have not been reported yet.

### *Contributing elements which are effective in the results of grafting*

Ambiguity in the most appropriate source of stem cells, the time, type and method of transplant and the therapeutic dose of cells are considered the most important obstacles to grafting. Further clinical trials are needed to respond to them. Although clinical trials have shown promising results of autologous stem cells transplantation in TBI (38,39,80) and other neurological lesions such as stroke (41,57,81-83), neurodegenerative diseases (52,84,85), intracerebral hemorrhage (86) and spinal cord injuries (87,88), proliferated and stored heterologous cells are available. In addition to being available in different doses and there is no need to extract them from the bone marrow and proliferate them, but immune system response and rejection of transplantation are an important issue that should be considered in using the heterologous cells (89). The time required for cell proliferation in order to be transplanted is an important issue i.e. autologous MSC should be extracted from the bone marrow, processed and then proliferated according to therapeutic dose that needs to several weeks, makes them less possible to be used in acute or subacute conditions (80). Cell transplantation rout is a limiting variable in cell therapy. Various studies have been conducted in this regard. In direct implant of cells, there is a possibility for transplantation

of many cells (90). Intralesional implant through brain surgery is an invasive method and there is a possibility of further damage to the damaged tissue, more importantly, the stability of patient's condition is required, therefore, it is less possible to perform it in acute phase. Intracranial implant is not concordant to bio-distribution, besides this, leads to form a mass of cells, which in turn disrupts normal tissue (82). Because of presence an inflammatory environment without trophic supports in the lesion cavity (91), the survival of transplanted cells in the lesion area may require them to be encapsulated or placed on a scaffold inside the cavity. This technique is based on the phenomenon of biological adaptation of matrix with transplanted cells (92-94). Some studies have used intra-arterial method, in which more purposeful implantation is provided. Moreover, there is no large degree of pulmonary first-pass effect (95,96) and a larger number of cells are transferred to the brain (97). In a study, 21% of cells were found in MCA (98). An important issue is the risk of embolism and blockage in the brain arteries; cases of sudden death after the procedure have also been reported (99). The intravenous method is more reliable than other methods, but it causes cell adhesion and creates microemboli, on the other hand, there is homing probability in other organs except the brain (100). Its advantage over intracranial procedure is its non-invasive nature. Tracking these cells by SPECT technique suggests the distribution of cells in many organs (97). A negative point of this method is a high percentage of pulmonary first-pass effect (101). Studies show that the diameter of the cells has a critical role in being trapped in pulmonary capillaries. The average thickness of cells is 15-19



micrometer, while the diameter of pulmonary capillaries is 5-9 micrometer. Also, using Sodium Nitroprusside will reduce pulmonary first pass effect because of its pulmonary vasodilation effect (102). Bang et al. reported adverse complications of intravenous implantation of mesenchymal stem cells (41). In a South Korean study, a 260-week follow-up of patients suffered from ischemic stroke who underwent intravenous stem cell therapy showed no more complications compared to the control group (57). The intravenous method is more suitable for large lesions and leads to widespread distribution of cells around the ischemic region (43). The therapeutic benefits of MSC transplantation are determined mainly by the homing rate in the lesion, although the homing mechanism is very complicated and is still unclear. It should be considered that the efficiency of cells homing in the lesion is associated with the distance between the lesion and administration of cells and frequency of administration and is less dependent on the number of transplanted cells (38). The time of cells transplantation in various studies is considered due to the type of damage in the central nervous system in the acute, subacute and chronic phases. Based on the type of stem cell used, the time varied from 3 days after the injury in the acute phase for transplantation of stem cells derived from blood and bone marrow (78,79,103) to more than 3 weeks in chronic phase for transplantation of neural stem cells (104 106). The optimal time for transplantation is different due to the type of stem cell and their mechanism of action. If therapeutic strategy is focused on neuroprotection mechanisms, transplantation should be performed in the acute phase. But if treatment aims to strengthen endogenic repair mechanisms such

as plasticity and angiogenesis, transplantation is more common in acute phase and in the first few weeks after injury (107). The implantation route contributes to determining the optimum time for transplantation; if intravenous method is used, transplantation should be quickly performed in the acute phase because cells benefit from inflammatory signals for implantation in the lesion in acute phase (108,109). Meanwhile, it is better to perform intracerebral implantation later because the initial inflammatory responses will be subsided and the cells survival will increase (91). The location of lesion is also an important factor in determining the treatment results. Significant improvements have been reported in striatal (103,108,110) and cortical lesions (111) as a result of cell therapy. Lesion size should not be very large; in this case, there will be no significant improvement (112). It should be noted that most clinical trials were conducted with small sample sizes and aimed to evaluate the degree of safety and transplantation tolerance and not the effect of transplantation on improving the outcome, so it is difficult to conclude about the efficiency of the cell transplantation.

### *The methods of tracking transplanted cells*

There are a series of non-invasive methods for monitoring, tracking and evaluating the survival of transplanted cells that can use them in clinical studies, such as Magnetic Resonance Imaging (MRI) (113), Bioluminescence Imaging (BLI) and Positron Emission Tomography (PET) techniques (114). Labeling cells with nanoparticles such as Super-Paramagnetic Iron Oxide (SPIO) provides the possibility to explore cells with MRI technique; however, grafting survival cannot be evaluated by this method as SPIO

is reduced by proliferation of cells (115). BLI has resolved this problem. To use this technique in the evaluation of transplanted cells' survival, luciferase reporter gene should be transferred into the cells before transplantation. After injection of D-luciferin, cells can be detected by determining the characteristics of the emitted photons. Since this method depends on the enzyme activity, it provides the possibility of evaluating the viability of transplanted cells (116). Instead, it provides a low-resolution two-dimensional image and down-regulation of luciferase will give a false negative result (117). Transplanted cells in which a PET reporter gene is placed are detectable by PET techniques (118). The PET detection threshold is much more sensitive than MRI, but lower spatial resolution and the lack of anatomical information are the disadvantages of this method (117). In the PET scan, increased uptake of fluorodeoxyglucose (FDG) more than 10% suggests increased activity in the targeted area (119,120), but this may be due to other causes such as inflammation or local cells activity (121,122). Rey et al. suggested that the combination of these techniques be used as the strengths of each technique compensate for the weaknesses of the other ones (123). Jacob et al. used the combination of PET and BLI in a clinical trial on glioma patients (124).

## Conclusion

Based on the evidence from preclinical and clinical studies, it can be concluded that transplantation of adult mesenchymal stem cells has a high potential to become a standard approach as an effective therapeutic approach for rehabilitation of patients with TBI. Nevertheless, there are fundamental questions, the most important of which

include the optimal time of transplantation and the best route for cells delivery, a suitable dose of cells, and suitable patients for candidate of transplantation. So, more studies should certainly be conducted in the future to answer these questions to find the most effective method and protocol for the potential application of this approach in the standard treatment of TBI. Finally, it should be said that a close cooperation is needed between neuroscientists and neurosurgeons and neurologists to achieve a specific framework for TBI treatment through cell transplantation.

## Conflict of Interest

No Conflict of Interest

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