Stem Cell Therapy in Stroke: A Review Literature

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ABSTRACT

Stroke is an important cause of death in the world and disability world-wide especially in developed countries. Following acute phase of stroke, some procedures and medical treatment such as thrombolytic agents has been recommended; nevertheless many patients have enduring deficits. Thus, there is a realistic need to develop treatment strategies for reducing neurological deficits. However, the stem cell (SC) therapy could arrange an alternative intervention for disease modifying therapy. In this article, we present a brief review of different methods of SC therapy in stroke patients and discuss the results with different cell types and routes of administration.

Keywords: Clinical, stem cell, stroke, treatment, trials

Review Article

INTRODUCTION

Stroke is an important cause of death in the world and disability worldwide especially in developed countries.[1] It has two sub-types, hemorrhagic and ischemic and the latter make up the majority of all strokes, almost 80% of the total[2] susceptibilities of neurons in the brain to injuries such as ischemia leading to difficult treatment of suffered patients from the involved diseases.[3]

Following acute phase of stroke, some procedures and medical treatment such as thrombolytic agents has been recommended; nevertheless many patients have enduring deficits.[4] Thus, there is a realistic need to develop treatment strategies for reducing neurological deficits. On the other hand,[5] in stroke, damage process is acute and restricted in time, also multiple cell types including, endothelial and neural cells has been lost therefore, the brain may be more ready to transplantation than in other neurologic diseases.

However, the stem cell (SC) therapy could arrange an alternative intervention for disease modifying therapy.[5]

In this article, we present a brief review of different methods of SC therapy in stroke patients and discuss the results with different cell types and routes of administration.

Mechanism of tissue repair

Application of SC therapy in stroke has been discussed for its indecisive mechanism of action and lack a specific intention.[6,7] Some purposed mechanisms for this approach are incorporation

into the host brain to replace within the damaged host tissue however, limited evidences exist; also it has been confirmed that acute cell delivery could reduce lesion size and inhibits apoptosis suggesting a significant role for cell-induced neuroprotection and immunomudolatory effects that could down-regulate many inflammatory and immune responses in transplanted host as well as vascular repair for promoting endothelial proliferation in the peri-infarct region.[8-12]

According to covered mechanism within SC, two strategies are presented to diminish an ongoing degenerative process or immunological attack. One is the transplantation of SCs to supply new neurons into the infracted brain by the activation of intrinsic neural stem cells (NSCs) or delivery of extrinsic SCs such as embryonic stem cells (ESCs) and induce pluripotent stem (iPS) cells derived neural cells. The second approach is usage of SCs by preparing immunomodulatory and neuroprotective support in transplanted graft.[6,7]

Endogenous neurogenesis

It was already reported that two restricted regions of the adult mammalian brain including the subgranular zone (SGZ) and subventricular zone (SVZ) of the lateral ventricle are as a rich source of NSCs involving in the neurogenesis process.[13,14] NSCs of the SGZ can proliferate and differentiate mainly into neuronal cells under ischemic condition that potentially present in the human. Usage of granulocyte-colony stimulating factor (G-CSF) is a notable example, which is routinely used in hematological malignancies to activating endogenous SCs for transplantation.[15] In rodent models of stroke, G-CSF has been demonstrated to be beneficial,[16,17] by inducing improvement of cell proliferation of the SGZ and enhancement of SC mobilization and residency to brain.[16] This hopefully results in animal models opened a noble vision for transplantation in Phase I/II clinical trials in stroke.[18-21] Although, it is uncertain that G-CSF acts as a neuroprotective or neuroregenerative effectors in post-stroke patients.

Exogenous neurogenesis

Up to now, the following sources have been examined for brain repair: ESCs and iPSs derived neural cells, NSCs or other SCs originated from different tissues, e.g., bone marrow (BM).

Embryonic stem cells and iPSs cells

In 1998, ESCs were first originated from the inner cell mass of blastocysts.[22] These cells can be differentiated by various methods into neural progenitor cells.[23] In animal model, ESCs cells derived neural cells could survive in stroke lesions of brain, and differentiated into mature neurons.[15] However, there are potential concerns following ESC application. ESCs have the ability of unlimited growth in culture, which could be associated with a high-risk of teratoma formation and ethical concerns about destruction of human fertilized eggs. IPS were established in 2007[24] and it can be provided by delivering a cocktail of four transcription factors including, c-myc, Sox 2, oct 4 and k1f4, also known as yamanaka factors into human skin fibroblasts. It has been confirmed that IPS cells could be differentiated into various type of neurons.

Despite lack of ethical problem of these cells, high teratoma-forming properties of IPS cells is a critical problem and nowadays techniques that develop the efficiency of reprogramming have been advanced which are less invasive for generating iPSs.[25]

NEURAL STEM CELLS

NSCs are one of the sub-types of adult SCs, which are particularly found in the brain of both fetal and adult mammals with ability of differentiation to three major central nervous system (CNS) cell types: Neurons, astrocytes and oligodendrocytes.[26,27] Unlike ESCs and fetal NSCs, adult NSCs could be used without ethical problem.[28] However, there are some major obstacles in clinical application. The source of NSCs is most importantly problem and appropriate source of human NSCs has to be determined. NSCs separated from adult brain as neurospheres and create neurons under differentiating conditions *in vitro*.[29,30] It has been indicated that delivery of intravenously or intraparenchymal NSCs could improve functional recovery in rodent models of stroke.[31,32]

Cell lines

Some SC lines from rodent CNS and human tissues have been introduced as another transplantation source. Immortalized cell line "NT2" a neuronally committed human teratocarcinoma

cell line is an example, which is originated from a human testicular germ cell tumor.[33] Another cell line, the "MHP 36 cells" of murine NSCs have been shown to decrease infarct volume and improve functional outcome after transplantation.[34] Recently, the production of immortalized cell lines of human fetal NSCs has been introduced HB1.F3 is one of them which have been showed a potential ability for differentiation to neurons and widespread migration from the site of injection to other anatomical locations in a mouse model of stroke.[34]

Other stem cells

There are two SC populations with distinct progenies within adult BM, hematopoietic stem cells (hSCs) and mesenchymal stem cells (MSCs). MSC could differentiate into cartilage, fat, bone, and muscle and some studies showed differentiation capacity for transformation to neural-like cells *in vitro*[35] and *in vivo*[36] (in spite of the evidences that this trans-differentiation is rare) There are several useful advantages of clinical application of MSCs including; easily obtained from BM, the potential of autologous transplantation, no need for immunosuppressive regimes, lack the ethical issues associated with embryonic- and fetal-derived cells and are less susceptible to malignant changes and genetic abnormalities[8,25]

In rodent models of stroke, MSC transplantation through Intravenous, intra-arterial, and intra-cerebral routes have shown a beneficial effect on functional improvement.[37-39]

Strong immunomodulatory effects of MSCs on the host immune system and secretion a number of trophic factors such as vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor supporting this idea that these cells presented as an excellent candidates for therapeutic treatment in the adult CNS.[29]

In addition, the use of hSCs for BM transplantation is well-investigated. Systemically or intra-cerebral transplantation of CD34+ cell (including populations of hematopoietic and endothelial stem and progenitor cells) resulted in evidence of reduced infarct size and progression of functional recovery in animal model.[15]

Delivery route for exogenous cell therapy

Another important point in SC transplantation is the route of cell implantation. However, it is difficult to find an optimum time for transplantation, because many studies used distinct models of stroke, cell types, methods of cell delivery, and outcome measurements to evaluate efficacy. Transplantation time was optimized based on the used cell type and their mechanism of action. Acute delivery should be better considered, if major target in treatment was concentrated on neuroprotective mechanisms, but sub-acute delivery would be recommended if the main goal was planned on repair mechanisms.[40]

Indeed, administration route of delivery may also order the timing of transplantation intravascular delivery may be ideal in early time window of 24 h out to a month after stroke onset. In contrast, intraparenchymal injection of cells would be chosen when the initial inflammatory response has ceased and this condition may permit better engraftment.[25,29,30]

In the other hand, every route of administration has safety issues. Intravenous delivery as a systemic route is less invasive approach than injection into the brain; but it raises concerns about microemboli formation.[26] It seems that the use of immunosuppression in intravenous SCs transplantation had no improvement result on behavioral outcomes in pre-clinical studies.

Intra-arterial (intra-carotid) administration is preferred to intravenous delivery, avoiding of first pass effect resulting in better crossing of cells into the brain.[15] Intraparenchymal transplantation is more invasive, moreover this cavity characterized as an inflammatory environment without trophic support. Facilitation of graft survival in the cavity will be supported by delivered cells within a scaffold shield.[26]

OUTCOME MEASUREMENT

Most of the clinical trials in stroke has focused on motor function measurements such as the Modified Rankin scale and the Barthel index and can neglect significant recovery of other improvement scales.[29,30] Due to different variety of clinical manifestations of stroke we could not describe a definite outcome scales for evaluating of disease recovery. Cramer *et al*. have suggested that in clinical trials "modality specific outcome measures" are more appropriate for evaluation of disease remission.[41] This method indicates that the specific outcome measurement should be suitable to proper patients, for example in patients with upper extremity motor weakness, specific

motor function tests such as the Fugl-Meyer and in aphasic patients, specific aphasia scales should be considered.

In addition, the distribution of the brain lesion, and monitoring of survival, migration, and function of SCs in host brain will be evaluated by non-invasive imagines, magnetic resonance imaging, bioluminescence imaging, and positron emission tomography.[14] Rueger *et al*. presented that *in vivo* mobilization of endogenous NSCs in the SVZ after stroke could be measured by positron emission tomography.[42]

CLINICAL TRIALS

Cell-based therapies open a promising view in the treatment of stroke. In 2007, researchers and members of the National Institutes of Health had been arranged a meeting with clear recommendation for facilitation of the translational progression of cellular therapies from animal studies to clinical trials that was named "Stem Cell Therapies as an Emerging Paradigm in Stroke [STEPS]." In following, a second meeting was organized that called "STEPS 2" in 2010. At this meeting, new recommendations were classified to create a novel guideline for future researching plan based on treatment with SCs.[43]

Hicks *et al*.[44] discussed about effectiveness of cell therapies in 69 different non-clinical studies of stroke. As regards the significant discrepancies between animal models and human stroke, some queries including, safety procedures, optimal cell dose, source and delivery route, need for immunosuppressant should be clearly clarified before leading SC therapy studies in humans.

In the first reported clinical trial in 12 patients with basal ganglia infarct, human neuronal cells (NT2N cells) were transplanted stereotactically. In a follow-up with positron emission tomograghy scans, in 6 of 11 patients after 6 months, increasing of fluorodeoxyglucose at the transplanted site was observed. Other patients showed improvement in the European Stroke Scale (ESS).[45] This trial was conducted a Phase II randomized clinical trial to test safety, feasibility and effectiveness of transplantation for ischemic or hemorrhagic basal ganglia stroke for eight patients. Patients were recruited to two cell doses (seven patients per group) administration or a non-surgical group (n = 4). A single seizure was observed in one patient the day after the surgery and a patient experienced a subdural hematoma 1 month after engraftment. The primary outcome ESS had no improvement but some secondary outcome measures such as Stroke Impact Scale, Everyday Memory Scores, and Action Reach Arm Test were significantly developed in the transplanted group during 6 months. In this study, the feasibility of neuronal cells transplantation was confirmed.[46]

In a small Phase I trial, fetal porcine cells intra-cerebrally were injected in five patients with basal ganglia infarcts, but the food and drug adminstration stopped the trial because adverse effects were observed in two patients. Neurological worsening 3 weeks after the intervention was observed in one patient and a patient experienced one seizure attack 1 week after transplantation.[47]

Bang *et al*. started a study to indicate the efficacy of MSC transplantation in stroke patients. Five patients were recruited for intravenously transplantation of autologous MSCs with ischemic stroke at 5-9 weeks after the stroke onset. No side-effect was observed just after transplantation in patients. At 1 year follow-up, Barthel index and modified Rankin score showed a non-significant trend toward better scores in treated patients and a clinically feasible and relatively safe procedure was confirmed.[48] However, this study due to missing appropriate follow-up and treatment analysis has a potentially bias.

Lee *et al*. transplanted MSCs intravenously in 52 patients with ischemic stroke an open-label, observer-blinded clinical trial[49] and followed by a pilot clinical trial using intravenous injection of MSCs that was performed into 12 patients with ischemic stroke 36-133 days after stroke. They concluded that intravenous injection of autologous MSCs could be a safe and effective management for ischemic stroke. Furthermore, no proved clinical trial in its clinical efficacy is present.[50]

Three additional clinical trials are currently ongoing to investigate the role of hSCs therapy in ischemic stroke with different methods of delivery. These researches utilized autologous CD34+ cells in acute as well as chronic ischemic stroke patients. The results will be announced in the future.[15]

Other clinical trial was carried out by Rabinovich *et al.*[51] Human fetal cells were transplanted into the subarachnoid space of ten patients with ischemic or hemorrhagic stroke. They didn't have precise conclusion about its efficacy due to lack of outcome measurements.

Man *et al.* in 2006[52] designed intravenous injection of human umbilical cord blood stem cells to evaluate the improvement in post-stroke patients and no side-effects were reported. At 3 months follow-up, Fugl-Meyer Assessment and Barthel Index were significantly better in transplanted patients and a clinically feasible and relatively safe procedure was concluded. Moreover in this study, control group was not designed.

Yang *et al*. in 2005[53] carried out a clinical trial based on intrathecal injection of ESC derived NSC in 26 patients. Improvement at ESS and Bartel Index were indicated in 23 patients. Despite lack of control group in this design, no adverse effects were observed except a transient fever in four patients. Recently, a Phase I trial was planned using NSC line, to be injected stereotactically in ischemic patients (ReNeuron, UK).[54]

At last, Due to small sample size and the lack of double-blinded controls in most of these clinical trials, it is difficult to get exact conclusion. Only in one year follow-up Kondziolka *et al*. and Bang *et al*. studies, there was no report of teratoma formation but for rejecting of tumorigenic potential hypothesis, the long-term follow-up is needed.[28]

There are many challenges of translating animal studies on SC therapies to the clinical trial and an important advance for the future is best incorporation into the whole neurological system of the recipients for a full clinical recovery; something, which is recently being more focused on in most of the studies.[8]

MENSTRUAL BLOOD CELLS FOR STROKE

Firstly the existence of SCs in the endometrium was reported over 30 years ago.[55] High proliferating potential in these cells could be described with monthly shedding of the superficial layers. Stromal stem cells that obtained from menstrual blood were expanded and presented clonogenic and multipotentiality properties *in vitro*.[56] Moreover, menstrual blood stem cells (MenSCs) expressed markers of pluripotency, such as Oct-4, SSEA-4, something like presented in ESCs. There are several advantages in clinical application of MenSCs including: Increased availability in autologous transplantation, lack of ethical conflicts and low immunogenicity due to the lack of MHC class II expression, immunomodulation properties and secretion of neurotrophic factors such as VEGF and angiogenic properties and finally differentiation capacity and express neural markers (MAP 2 and Nestin) *in vitro*. For these characteristic, MenSCs are suggested as a restorative therapy for post-stroke patients aiming to rehabilitation and functional improvement.[57,58]

Tissue repair and functional improvement of menstrual blood cell administration have been confirmed in animal model. Borlongan *et al*. reported functional stabilization after MenSCs transplantation in the 12 months follow-up, without adverse events presentation.[59] The safety aspects of MenSCs administration was investigated by only clinical study.[60] Four patients with multiple sclerosis were recruited to intrathecal injections; also one patient received an extra-intravenous injection. These preliminary data proposed feasibility of MenSCs application but further studies by this novel SC type should be planned for more confirmation.

CONCLUSIONS

According to previously published papers, more advanced investigations should be performed for confirmation of SC transplantation efficacy for stroke. We don't exactly know, whether this procedure can progress functional outcome in these patients. Large and well-designed trials should be planned in stroke patients for getting appropriate decision about application of SC in clinical approach[61] (Finally, this intervention has not proved in human yet and unresolved questions including, type of cell type, cell numbers to be delivered, best time of treatment, optimum route of delivery must be clarified in this issue.[15]

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