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Autologous Bone Marrow Stem Cell Therapy Shows Functional Improvement in Hemorrhagic Stroke

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ABSTRACT

In hemorrhagic stroke, damage to the brain tissue is inevitable and no effective treatment for functional improvement is currently available except neurorehabilitation. Stem cell therapy is a rapidly growing field and has recently opened new avenues for brain repair strategies. We present a case study of a 69-year-old female treated with stem cell therapy for right-sided hemiplegia caused due to left thalamic hemorrhagic stroke. Inspite of regular physiotherapy, the patient had constant residual neurodeficit, one year after the stroke, which was severely incapacitating. In view of the same, the patient was given intrathecal autologous bone marrow derived stem cell therapy as part of the neuroregeneration and rehabilitation therapy (NRRT) along with rehabilitation. After the therapy, patient showed functional as well as neurological improvements (cognition and motor strength) without any side effects. There is accumulating experimental data showing the benefits of cell transplantation on functional recovery after hemorrhagic stroke. This case study supports the concept of neuroregeneration with bone marrow stem cells as a novel strategy having great therapeutic potential. However, large clinical studies are needed to further investigate autologous bone marrow stem cell therapy in addition to neurorehabilitation for treating the disability in hemorrhagic stroke.

Keywords: Hemorrhagic stroke, bone marrow stem cells, autologous transplantation, neuroregeneration, rehabilitation

Stroke is the leading cause of mortality and significant morbidity in India (prevalence of approximately 0.5%) and worldwide.[13] It is ranked as the sixth leading cause of DALY (disability-adjusted life years) in 1990 and projected to rank fourth by 2020. Hemorrhagic stroke, of all strokes, is a major cause of serious long-term disability and the survivors of ischemic insults have no effective treatment available other than neurorehabilitation. To repair the human brain after hemorrhagic stroke may seem unrealistic because of the loss of many different neuronal cells. One of the most encouraging approaches has been restorative therapy using stem cell replacement in the ischemic areas.[2] Apart from their individual impact, research shows that exercise enhances the effect of stem cells by helping the mobilization of local stem cells and encouraging angiogenesis. Hence, the concept of neuro-regenerative rehabilitation therapy (NRRT) endeavors to combine the impact of neuroregeneration and rehabilitation for a better therapy outcome. Although, evidence of the beneficial effects of stem cells in animal stroke models is growing, there is lack of enough clinical data.[3] Our case study is an effort towards this direction.

CASE STUDY

We present a 69-year-old female patient with history of hemorrhagic infarct, a year ago, leading to right-sided hemiplegia with impaired cognition, speech as well as bladder and bowel function. Magnetic resonance imaging (MRI) revealed left thalamic bleed with intraventricular extension. Patient received standard treatment for the same and had a ventriculoperitoneal (VP) shunt in place. She also underwent neuro-rehabilitation for one year. Then, on our pre-stem cell treatment evaluation, patient was hypertonic with spasticity of Grade 1 (According to Modified Ashworth Scale). She was hyperreflexic with reduced sensations over right-half of the body and had muscle power of Grade 2/5 in right upper and lower limb and Grade 5/5 strength on the left-half of her body. She was impaired cognitively with affection of orientation in time, place and person, along with

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hemineglect of right side of her body and emotionally labile. Functionally, she was dependent on the caregiver for all her activities of daily living (ADLs). Stroke Rehabilitation Assessment of Movement (STREAM) score was 19. Functional Independence Measure (FIM) score was 39 with severe affection in areas of self-care, sphincter control, mobility and social cognition. She was given autologous bone marrow stem cells (BMSCs) intrathecally, since she had exhausted all other treatment options.

METHODS

The NRRT has been designed and the patients are selected for the therapy-based on the inclusion criterion as per the World Medical Associations Helsinki declaration.[4] The NRRT is approved by the Institutional Committee for Stem Cell Research and Therapy (IC-SCRT). Granulocyte colony-stimulating factor (G-CSF) (300 μg) injections were administrated subcutaneously, 48 hours and 24 hours prior to the bone marrow aspiration. The G-CSF administered before the transplantation helped in stimulation of $CD34^+$ cells and also in survival and multiplication of the stem cells. Bone marrow (100 ml) was aspirated from the iliac bone and mononucleocytes (MNC) were obtained after density gradient separation. Viable count of the isolated MNCs was taken and checked for $CD34^+$ by fluorescence-activated cell sorting (FACS) analysis. A total of 50 x 10^6 MNC were then injected intrathecally in L_4-L_5 using a lumbar puncture needle and catheter.[14] Stem cell therapy was followed by neurorehabilitation including regular physiotherapy, occupational therapy and counseling to reduce her impairment and improve functionality. The patient showed progressive improvements after the therapy as mentioned below.

RESULTS

Cognition

Prior to stem cell therapy, there was total neglect of right-half of body and immediately after the stem cell therapy, awareness of the right side of the body was present and the patient tried to use it for functional activities. Emotionally, she was less labile and crying spells had reduced significantly. She had increased attention span, with ability to participate in conversations and read the clock and tell time accurately. She could identify colors, weeks and months of the year and was well-oriented in time and place along with improvements in her comprehension and memory skills.

Motor System

She could move her right upper extremity voluntarily. Improvement in gross as well as fine motor activity was observed. Tightness/spasticity/clawing of right hand had reduced and could open and close her fist. Strength in her upper extremity had grossly improved from Grade 2 to 3++. Strength in her right lower limbs had improved from Grade 2 to 3++. Also, spasticity in her muscles had reduced significantly with near normal voluntary control.

Activities of Daily Living

Independently she can now tie a knot, cut vegetables, peel peas and pick up coins and marbles with her right hand, transfer from bed to wheelchair and vice versa, stand up from chair and remain standing for about 10 minutes with an assistive device. On the bed, she could shift and roll independently. On reassessment her FIM[6] had increased from 39 to 84 with major improvements seen in sections of self-care activities, transfer skills, social cognition and communication. STREAM[7] score improved from 19 to 53, with an overall improvement in voluntary movements/activities using the right side of the body.

DISCUSSION

In hemorrhagic stroke, the ultimate aim of any therapeutic strategy is to achieve maximum possible restoration of normal function. Stem cell therapy is a cellular approach that has the potential to induce all of the neurorestorative processes essential for facilitating recovery of neurological function.[5] Stem cells are undifferentiated cells that retain the capacity to proliferate and produce generations of progenitor cells, which can differentiate into virtually all cell types of the body in response to the proper stimuli.[8] The main rationale to employ stem cell therapies in stroke patients is to replace infarcted brain tissue in a way that lost neurons are replaced and there is re-establishment of a functional neuronal circuitry with proper nerve conduction. It has been observed that the transplanted stem cells can act as biological mini pumps releasing a missing transmitter or secrete growth factors which can stimulate plastic responses, improve the survival and function of host neurons and restore synaptic connection by providing a local reinnervation and neuronal replacement.

The stem cells can become integrated into existing neural and synaptic networks, and re-establish functional afferent and efferent connections.[10,13]

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The nonregenerative trait of the injured adult brain has been challenged in recent years and neural plasticity has been observed experimentally in both global and focal brain ischemia in animal models. There are several sources of stem cells that may be useful in hemorrhagic stroke, embryonic stem cells derived from the inner cell mass of preimplantation embryos, neural stem cells found in specific regions of brain, bone marrow, umbilical cord blood and adipose tissue.[1]

In our case study, BMSC were chosen as they are easily accessible through the aspiration of the bone marrow, can be isolated from patients themselves thereby bypassing the ethical problems and can easily be administered to the patients for autotransplantation.

The MNCs obtained from bone marrow, comprises of a variety of cells like hematopoietic stem cells, tissue specific progenitor cells, mesenchymal stromal cells and specialized blood cells in different stages of development. They produce trophic factors in host tissue after transplantation, which is beneficial for tissue protection and restoration, along with a potential to differentiate into local cells in response to environmental signals and cues. They are also known to home onto the site of injury and promote angiogenesis. In a study by Lee et al, cells of human neural stem cells (NSC) line, transplanted into the brain of mice after intracerebral hemorrhage (ICH), gave rise to both neurons and astrocytes and induced behavioral recovery in the rotarod and limb placing tests.[8]

In another study, human BMSCs transplanted in rats after ICH, showed formation of new neuronal connections and significantly improved neurological function was found one week after transplantation.[12] Behavioral recovery in the beam-walking test was observed in the groups of rats that received intra-arterial and intraventricular delivery of BMSC in a study by Zhang and coauthors,[15] who used cells of rat origin. Autologous mesenchymal stem cells have been widely used in the clinical trials in brain injury diseases such as multiple sclerosis, glioma and recently with stroke.[11,10] In our case study, autologous bone marrow stem cell transplantation was given intrathecally to a hemorrhagic stroke patient as part of the NRRT.

After the therapy the patient showed improvement functionally due to better cognition, voluntary control and motor strength, as stated above and evident from improvements in FIMS as well as STREAM scores. The patient was not recovering with neuro-rehabilitation alone for one year and that the patient showed functional improvement, only after addition of stem cell therapy suggests that BMSC played a significant role by various mechanisms as stated above.

CONCLUSION

Autologous intrathecal transplantation of BMSCs fully circumvents the problem of immune rejection and bears no ethical concerns. Intrathecal transplantation is a noninvasive and most importantly a safe method for bone marrow stem cell transplantation without any major side effects. In view of experimental data, the patient was treated with autologous bone marrow stem cells as a last resort to improve functionality thereby decreasing her disability.

Post stem cell therapy, along with continued neurorehabilitation, the patient showed functional and neurological improvements which were progressive in nature. This case study represents one of the earliest clinical data on intrathecal delivery of autologous bone marrow derived stem cells showing functional improvement in hemorrhagic stroke, supporting laboratory experimental data. Further large clinical studies are needed to investigate functional improvement by autologous bone marrow stem cell therapy in addition to neurorehabilitation for treating the disability in hemorrhagic stroke.

SUGGESTED READING

1. Andres RH, Guzman R, Ducray AD, Mordasini P, Gera A, Barth A, et al. Cell replacement therapy for intracerebral hemorrhage. Neurosurg Focus 2008;24(3-4):E16.
2. Bliss T, Guzman R, Daadi M, Steinberg GK. Cell transplantation therapy for stroke. Stroke 2007;38 (2 Suppl):817-26.
3. Chen J, Li Y, Wang L, Zhang Z, Lu D, Lu M, et al. Therapeutic benefit of intravenous administration of bone marrow stromal cells after cerebral ischemia in rats. Stroke 2001;32(4):1005-11.
4. Carlson RV, Boyd KM, Webb DJ. The revision of the Declaration of Helsinki: past, present and future. Br J Clin Pharmacol 2004;57(6):695-713.
5. Dharmasaroja P. Bone marrow-derived mesenchymal stem cells for the treatment of ischemic stroke. J Clin Neurosci 2009;16(1):12-20.
6. Hamilton BB, Laughlin JA, Fiedler RC, Granger CV. Interrater reliability of the 7-level functional independence measure (FIM). Scand J Rehabil Med 1994;26(3): 115-9.
7. Daley K, Mayo N, Wood-Dauphinée S. Reliability of scores on the Stroke Rehabilitation Assessment of Movement (STREAM) measure. Phys Ther 1999;79(1):8-19; quiz 20-3.

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8. Lee HJ, Kim KS, Kim EJ, Choi HB, Lee KH, Park IH, et al. Brain transplantation of immortalized human neural stem cells promotes functional recovery in mouse intracerebral hemorrhage stroke model. Stem Cells 2007;25(5):1204-12.
9. Lipska K, Sylaja PN, Sarma PS, Thankappan KR, Kutty VR, Vasan RS, et al. Risk factors for acute ischaemic stroke in young adults in South India. J Neurol Neurosurg Psychiatry 2007;78(9):959-63.
10. Mohyeddin-Bonab M, Mohamad-Hassani MR, Alimoghaddam K, Sanatkar M, Gasemi M, Mirkhani H, et al. Autologous in vitro expanded mesenchymal stem cell therapy for human old myocardial infarction. Arch Iran Med 2007;10(4):467-73.
11. Tandon PN. Transplantation and stem cell research in neurosciences: where does India stand? Neurol India 2009;57(6):706-14.
12. Seyfried D, Ding J, Han Y, Li Y, Chen J, Chopp M. Effects of intravenous administration of human bone marrow stromal cells after intracerebral hemorrhage in rats. J Neurosurg 2006;104(2):313-8.
13. Wiltrout C, Lang B, Yan Y, Dempsey RJ, Vemuganti R. Repairing brain after stroke: a review on post-ischemic neurogenesis. Neurochem Int 2007;50(7-8):1028-41.
14. Yoon SH, Shim YS, Park YH, Chung JK, Nam JH, Kim MO, et al. Complete spinal cord injury treatment using autologous bone marrow cell transplantation and bone marrow stimulation with granulocyte macrophage-colony stimulating factor: Phase I/II clinical trial. Stem Cells 2007;25(8):2066-73.
15. Zhang H, Huang Z, Xu Y, Zhang S. Differentiation and neurological benefit of the mesenchymal stem cells transplanted into the rat brain following intracerebral hemorrhage. Neurol Res 2006;28(1):104-12.